CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s000

<u>MEDICAL REVIEW(S)</u>

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Complete Response Review Addendum

Sponsor Safety Reporting
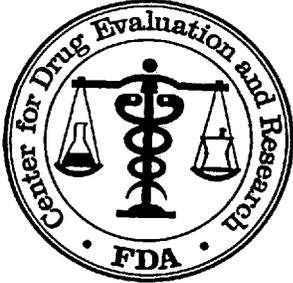
Submissions: NDA 22-433 and IND 65,808 SD 632

Drug: ticagrelor (Brilinta™)

Indication: reduce the rate of thrombotic events in patients with acute coronary syndromes (ACS)

Sponsor: AstraZeneca

Review date: June 8, 2011

Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

On April 20, 2011, we met with AstraZeneca (AZ) staff to discuss progress on the reviews of the complete response for NDA 22-433. Because my review and that of the IND reviewer, Dr. Martin Rose, had suggested significant problems with AZ's handling of serious adverse events (SAEs), I added to the end of the agenda a discussion of these problems. The minutes for the meeting filed on May 19, 2011, summarize that discussion as follows:

> "There was some discussion regarding the applicant's internal procedures for handling of adverse event reporting. Dr. Marciniak asked why the applicant had not expedited the reporting of serious and unexpected adverse events in two PLATO subjects, one an out-of-hospital arrest with seizure in a patient with subsequent in-hospital AV block and the other a subject hospitalized with headache and an unspecified abnormality on cerebral scans. For both patients the investigator discontinued study drug because of the serious adverse event (SAE). The applicant replied that the investigator had indicated that the SAEs were unrelated to study drug and that it was company policy to accept investigator determination of relatedness. Dr. Marciniak noted that under FDA's new reporting rule it is the applicant's responsibility to determine relatedness of serious unexpected adverse events, although that was not clear at the time of reporting. Dr. Rose raised a question regarding a recent initial reporting of an AV block SAE. He asked why the name and address of the reporter were marked as private. The applicant commented that under German law they are limited in the information they can gather. Dr. Marciniak asked why the listing of prior AV block AEs included with the SAE report for this patient (see Figure 2) listed no prior AV block adverse events (AEs). The applicant responded that the listing only included AEs submitted post-marketing."

FIGURE 2 (from filed minutes)

AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850- 5437

Mfr. Rep. #: 2011SE19562

Date: 14-APR-2011

LISTING OF PRIOR SAFETY REPORTS
SUBMITTED TO IND # 65,808

ADVERSE EVENT: Atrioventricular block
                  (all preferred and included coded terms)

Manufacturer Report #   FDA Submission Date   Protocol Number   Country of Origin
No safety reports have been previously submitted to the IND for this adverse event.

The minutes above neither convey completely and accurately my remarks at the meeting nor the seriousness of the problems with handling of AEs by AZ. I had submitted the following draft statements for inclusion in the minutes:

> "There was some discussion regarding the applicant's internal procedures for handling of adverse event reporting. Dr. Marciniak asked why the applicant had not expeditely reported the serious and unexpected adverse events in two PLATO patients, one an out-of-hospital arrest with seizure in a patient with in-hospital AV block and the other a patient hospitalized with headache and an unspecified abnormality on cerebral scans. For both patients the investigator discontinued study drug because of the SAE. Neither SAE was adjudicated. The applicant replied that the investigator had indicated that the SAE was unrelated to study drug and that it was its policy to use the investigator's determination of unrelatedness. Dr. Marciniak noted that it was ultimately the applicant's responsibility to determine unrelatedness, not just the investigator's. Dr. Rose asked regarding a recent initial reporting of an AV block SAE why the name and address of the reporter were marked as privacy. The applicant commented that under German law they are limited in the information they can gather. Dr. Marciniak asked why the listing of prior AV block AEs included with the SAE report for this patient (see Figure 2) listed no prior AV block AEs. The applicant responded that the listing only included AEs submitted post-marketing. Dr. Marciniak commented that, particularly for a newly marketed drug, post-marketing AEs should be evaluated in the context of all knowledge regarding AEs, not just post-marketing reports, and that the listing was misleading."

I did not quote the FDA's new reporting rule regarding the two PLATO SAEs or state that the sponsor's responsibility for determining relatedness of SAEs was "not clear at the time of reporting" as the filed minutes state. To the contrary, I asserted that under both ICH E2A, the guidance in effect during the conduct of PLATO, and the new reporting rule it was and is the sponsor's ultimate responsibility for determining relatedness.

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The applicable statement from E2A is the following:

> "All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs."

The 21 CFR 312.32 has the following regulatory requirements (emphasis added):

> "(b) Review of safety information. The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

> "(c)(1) IND safety reports. The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after **the sponsor determines that the information qualifies for reporting** under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section."

The final rule establishing this regulation provides this clarification:

> "The sponsor must continue to evaluate the evidence and use its judgment to determine whether an adverse event meets the definition of suspected adverse reaction and qualifies for expedited reporting under § 312.32(c)."

Note the "continue" in the statement above. AZ consistently maintained at the meeting and in its response to questions I submitted regarding NDA cases that it relies upon the investigator determinations. AZ appears not to understand its responsibilities regarding SAE reporting.

Similarly, AZ's analyses of the AEs are inadequate and misleading. The 21 CFR 312.32 continues with the following requirement:

> "In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information."

Note the "all IND safety reports" in the above requirement. The draft guidance from September 2010 for safety reporting has several clarifications that the sponsor is required

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to consider all information relevant to the safety of the drug from all sources. Among the clarifications it explains the previous CFR requirement as follows:

> "Sponsors should evaluate a suspected adverse reaction in the context of other related reports or adverse events, including those that occurred in pre- and postmarket studies."

Note that the sponsor reported in Figure 2 (from the filed minutes) above that no atrioventricular (AV) block AEs had been filed to the IND for ticagrelor. No AV block AEs would be astounding because AV block is a recognized AE for ticagrelor because of ticagrelor's adenosine-like effects. I counted six SUSARs submitted to the IND for PLATO alone with AV block listed as the primary AE and I noted AV block reported on other SUSARs having a different primary AE, such as heart failure. AZ's explanation for not listing any prior AV block AEs because it only listed AEs submitted post-marketing is contrary to 21 CFR 312.32, the reporting law in effect at the time of submission of this AV block SUSAR. (The CFR changes were effective March 28, 2011.)

AZ's inadequate analysis of SUSARs is not limited to the AV block SUSAR. I scanned other SUSARs submitted recently to the IND and quickly identified the following similar problems:

- AZ's "Listing of Prior Safety Reports Submitted to IND 65,808" dated 11-APR-2011 (supporting document 630) for "Non-cardiac chest pain (all preferred and included coded terms)" lists one prior AE from the US from 2008. An investigator reported this SUSAR for protocol D5132C00001, so apparently AZ did include one prior IND SUSAR. However, even in the PLATO submissions I note another SUSAR for "precordial pain" with negative enzymes and ECG. Furthermore, for the 11-APR-2001 report, the investigator recorded the SUSAR as "NON CARDIAC CHEST PAIN/ DYSPNOE/ STRANGE FEELING IN THE HEAD/ DIZZINESS" and "spontanious sinusbradycardia 38 beats per min". AZ's analysis notes that "Dyspnea and dizziness are well described for ticagrelor" and that "a causal or contributory role for ticagrelor with these events cannot be excluded" but does not elaborate upon the chest pain or bradycardia. This minimizing analysis is disturbing because AZ has claimed that dyspnea and bradycardia are mild and rarely lead to discontinuation.

- AZ's "Listing of Prior Safety Reports Submitted to IND 65,808" dated 14-APR-2011 (supporting document 632) for "Rectal cancer (all preferred and included coded terms)" lists no prior AEs for this SUSAR on protocol D5132C00001 detected because of lower GI bleeding. I found related SUSARs of coecal cancer and colon cancer for PLATO. The site of the colon cancer was not specified but, because one treatment was a suppository, was likely low. The bleeding started day 2, so AZ's analysis of this SUSAR as unrelated because of the short latency period is reasonable.

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- AZ's "Listing of Prior Safety Reports Submitted to IND 65,808" dated 19-APR-2011 (supporting document 634) for "Lower gastrointestinal haemorrhage (all preferred and included coded terms)" similarly lists no prior AEs, not even the SUSAR from 14-APR-2011. This patient died from ventricular fibrillation at the time of the bleeding but AZ did not analyze the more severe event. There are, not surprisingly for a platelet inhibitor, several GI bleed SUSARs reported for PLATO.

Some might argue that the individual SUSARs as in these examples are impossible to interpret individually. However, all of them fall into the "(C)" category described in the CFR: "(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group." For this category the analysis of prior AEs is critical. Regardless, these examples represent AZ's handling of SUSARs. AZ's approach is noninformative such that from AZ's presentations we—and investigators, DSMBs, and IRBs—can not glean an understanding of the adverse event profile of ticagrelor. We can not have confidence that investigators understand how to evaluate and handle AEs for ticagrelor.

AZ's problems with AEs are not limited to its handling of SUSARs. AZ's handling of AEs in PLATO in general was also inadequate. The two SAEs that were the justifications for the discussion at the April 20, 2011, meeting are good examples of other problems. I have reproduced below, for ease of reference, the descriptions of them from my review of AZ's complete response:

- A ticagrelor patient had a PCI with stent on day 1 followed by hypotension and mild pulmonary edema. On day 2 he suffered bradycardia and complete AV block treated with a temporary pacemaker and resolving by day 6. On day 12 he was rehospitalized for "syncope((b) (6)   )before hospitalization, Ventricular tarchycardia, seizure,v-fib and Asystole after hospitalization"; ticagrelor was discontinued. Treatment included CPR, cardioversion, and an IABP. AZ did not report this event as a SUSAR nor was it submitted for adjudication as a possible cardiac ischemic event. After queries AZ did not provide any other clinical details regarding this event other than the minimal information quoted above. His last visit was on day 42 but AZ counts him as completing the study through day 391 without an endpoint.

- A ticagrelor patient had an AE of headache starting on day 1 and then was rehospitalized on day 10 with left foot weakness; ticagrelor was discontinued. After imaging an SAE was reported as "left anterior sylvian fissure abnormality". The investigator's verbatim description is not ominous but also does not define what the abnormality is: "headache pre-existing, routine MRI showed abnormality, pt hospitalized MRI showed abnormality, CT confirmed, CTA confirmed abnormality but no bleed, aneurysm." AZ did not report this event as a SUSAR nor was it submitted for adjudication as a possible stroke. After queries

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AZ did not provide any other clinical details regarding this event beyond the minimal information quoted above.

Please see my review of the complete response for a detailed discussion of these two, and other, problematic AE reports. For this review two observations regarding them are germane: (1) The minimal information collected regarding these SAEs is unacceptable. For the first case above AZ should have explored the possibility of drug-induced block (syncope, asystole) and drug-induced seizure (seizure is another adenosine-related effect) by soliciting more information; for the second case AZ should have resolved the ambiguous diagnosis of "left anterior sylvian fissure abnormality" by obtaining the scan and angiography reports. (2) Both are potential endpoints as well as SUSARs yet AZ did not submit the events for adjudication. AZ's inadequate handling of AEs also implicates the validity of the endpoint ascertainments in PLATO.

My review of AZ's complete response includes summaries of 24 such problem cases from those I identified after reviewing case report forms (CRFs) for only about 3.7% of the cases. While with the latter small sample I found more than 24 problematic cases, with 24 problematic cases among 3.7% checked one would expect 644 problematic cases if all cases were reviewed. This estimate does ignore the fact that the sample was not random, but I selected CRFs for review for efficacy considerations, not for safety.

One of the cases is particularly egregious: AZ reported unblinding 389 PLATO cases for potential expedited SUSAR reporting. I queried AZ regarding 26 patients who had been so unblinded but for whom AZ did not distribute SUSAR reports. For one of these patients AZ responded that they had not distributed a SUSAR because the patient had been "Unblinded to clopidogrel". When I queried AZ why this latter patient was unblinded to clopidogrel but was assigned to ticagrelor in all NDA data sets, AZ responded that "it has been determined that this subject was unblinded in GRand to ticagrelor (treatment A) and due to a transcription error the study treatment was entered into Sapphire as clopidogrel." A documented error rate of 1 in 389 (upper 95% confidence limit 1.4%!) for misidentifying treatment is completely unacceptable. If we don't have confidence that we know what treatment the patient received, how can we trust any safety—or efficacy—statistics?

A final example (not included in my CR review because I encountered it when perusing the SUSARs after filing the review) illustrates all the previously mentioned problems (i.e., inadequate data collection, inadequate analysis, and failure to adjudicate potential endpoints) as well as an additional one (late reporting of SUSARs):

- A ticagrelor patient in PLATO developed moderate right sided weakness on the morning of day 263. The patient had visits on days 266, 376, and 404 prior to the submission of a SAE report of this event on day 558 submitted to the IND as a 15-day report on day 565. The report states that "The event was ongoing at the time of reporting" and "Company Clinical Comment: Right sided weakness has not been associated with study drug. A diagnosis of transient ischaemic attack is mentioned. The investigator has not explained why the event is considered to be related to study drug. The patient has underlying vascular disease,

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hyperlipidaemia, hypertension and diabetes, which all increase risk of cerebrovascualr events." A follow-up report on this event states that "Diagnostic investigations: suspected transient ischaemic attack but has not been cofirmed[(b)(6)] [(b)(6)] Brain CT was negative for ischaemic stroke," "At the time of reporting the patient was gradually recovering, but has not totally recovered," and "Company Clinical Comment: Hemiparesis has not been associated with study drug. A diagnosis of transient ischaemic attack was suspected but not confirmed. The patient was receiving ASA as well as study drug. The investigator considered the event to be possibly due to study drug and probably due to inadequate antiplatelet dose. The patient has underlying vascular disease, hyperlipidaemia, hypertension and diabetes, which all increase risk of cerebrovascular events." Despite the stated suspicion that this event was a cerebrovascular event AZ did not submit the event for adjudication and counts the patient as event free through day 376. (NB: Hemiparesis persisting 10 months after onset is NOT a transient ischemic attack.)

Finally, AZ's problems with AE handling in PLATO were not limited to study conduct issues. Recording of bleeds was incomplete by design. If an investigator checked on the AE form that an event was a bleed and checked that "Bleed is related to a procedure and does not represent an adverse event", then he could not enter the severity of the bleed (minimal, minor, major, etc.) and he was not to complete the rest of the AE form. The AE form states boldly "NB: Per protocol bleeding associated with a procedure should not be reported as an AE if it is expected for the procedure." There is no guidance on the form about what is "expected" for the procedure. On the AE form there is also a "CABG related" checkbox in line with the "Bleed is related to a procedure ..." checkbox and the minimal, minor, major, etc. severity checkboxes. However, for CABG-related bleeds the investigator was to complete the rest of the AE form. In addition, the eCRF system automatically created a bleed event form for all CABG forms.

For a "better" platelet inhibitor but with a "faster" offset (ticagrelor compared to clopidogrel), one would expect more percutaneous procedural bleeds (because of the better platelet inhibition during and immediately following the procedure) but fewer CABG-related bleeds (because of faster offset since CABG is usually delayed after $P2Y_{12}$ inhibitor discontinuation.) PLATO's design appears to have sacrificed consistency and completeness of recording of bleeding events in order to minimize ticagrelor's disadvantage (more percutaneous procedural bleeds) and maximize the potential advantage (fewer CABG-related bleeds.) Percutaneous procedural bleeds were likely underreported because some investigators may have "expected" some PCI patients to develop femoral puncture site hematomas or even retroperitoneal bleeds—and we can not detect this underreporting. We can not have confidence from PLATO data that we understand the bleeding risks associated with ticagrelor.

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Recommendations

The problems I have documented with AZ's handling of AEs have two implications: (1) AZ must improve its handling of AEs; and (2) Both safety and efficacy results from PLATO are suspect such that we need results from another trial to justify approval. I present specific recommendations for both implications below.

Handling of AEs

1. We, including other FDA Divisions, should examine other AZ NDA and IND submissions to determine the prevalence of the AE reporting problems. AZ has defended its unacceptable practices (e.g., accepting investigator judgments about causality without formulating a second opinion, analyzing only post-marketing AE reports) as company policy and not as specific practices for PLATO or ticagrelor. Hence these problems are relevant to all AZ submissions.

2. AZ must improve its AE handling in the following ways:

   a. AZ must collect information adequate for characterizing SAEs such that a clinician can understand the nature of the AE and how it should be treated. Because of the wide variety of AEs I admit that the adequacy of characterization is a judgment call for which I can not provide more specific general guidance. For specific cases I can be more specific, e.g, for the "left sylvian fissure abnormality" short descriptions of the abnormality on scans and angiography are needed. Adequate characterization of the AEs is the most critical improvement needed both for the issues regarding AE handling and for having confidence in trial results.

   b. AZ must analyze all of the serious events associated with one episode, e.g., for a case above with syncope, ventricular arrhythmias, seizure, and asystole after discharge from an ACS hospitalization complicated by complete AV block AZ should have addressed all events and potential mechanisms. In another case discussed in my review of AZ's complete response AZ submitted a SUSAR for AV block but did not specifically address subsequent SAEs of thrombocytopenia and peripheral ischemia leading to bilateral amputations.

   c. AZ must analyze AEs, whether reported from a trial or post-marketing, in view of all safety information available. Pre-marketing safety data are relevant to post-marketing reports—as are post-marketing reports to post-marketing clinical trials.

   d. AZ must comply with all AE reporting requirements of 21 CFR 312.32. In reality complying is not onerous because the revised regulation, compared to the prior version, relaxes reporting requirements for

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individual cases. I would interpret several of the cases AZ did report as SUSARs as not requiring expedited reporting under the revised version, e.g., I would judge the rectal cancer to be not related to study drug because of the very short latency and the lower GI bleeding to be relevant only in an aggregate analysis.

3. We should consider placing on hold ticagrelor clinical trials or other AZ trials in the IND phase.   I judge the problems with AE reporting that I have documented in this review to be serious. I am not confident that AZ is protecting adequately the safety of patients in its trials. Placing one or more trials on hold would force AZ to address these problems expeditiously and facilitate confirmation that AZ has addressed the problems.

New Ticagrelor Trial Prior to Approval

I have outlined in my CDTL review of the original NDA submission the general requirements for a new ticagrelor trial. I recommend that the new trial be completed and successful prior to approval to address outstanding efficacy and safety issues with ticagrelor. I itemize below the requirements for the new trial related to safety reporting.

4. The design must not exclude "expected" bleeds. The trial must capture all bleeds greater than "minimal", i.e., not requiring intervention or treatment or discontinuation of treatment.

5. AZ must collect adequate information for characterizing the AEs as described under 1.a. above.

6. AZ must count discontinuations of treatment or study following an AE as discontinuations for the AE unless the site records explicitly another reason for the discontinuation other than withdrawal of consent or investigator decision. We will discuss with AZ and agree upon the criteria for determining "following an AE."

7. AZ must submit for blinded, independent adjudication as endpoints all AEs that could potentially be events. The threshold for submitting events for adjudication must be low.

8. As discussed in my review of the complete response, AZ must capture and include in the NDA submission the original descriptions of all AEs as reported by the sites. AZ must not "inactivate" or "soft delete" AE records but must submit the original records with variables indicating the "inactivation" or "soft deletion" and categorizing the reason for inactivation or deletion. "In error" alone is not an adequate categorization for a deletion. "In error because entered for wrong patient (see patient xxx)" or "Entered on wrong form – see form yyy" are acceptable.

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/s/

THOMAS A MARCINIAK
06/08/2011

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Review of Complete Response

NDA: 22-433

Drug: ticagrelor

(Brilinta™)

Indication: reduce the rate of thrombotic events in patients with acute coronary syndromes (ACS)

Sponsor: AstraZeneca.

Review date: May 14, 2011

Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

Recommendation and Conclusions

I recommend that ticagrelor not be approved for use in acute coronary syndromes (ACS) until the results of a second study confirm safety and efficacy in ACS. AstraZeneca (AZ) submitted the ticagrelor NDA on November 13, 2009. The initial reviews, in addition to noting inconsistencies in the results, revealed a striking discrepancy by region in the efficacy results in the large, international PLATO trial: Ticagrelor was inferior to clopidogrel in the US but superior to clopidogrel outside of the US (OUS). AZ proposed that the differential results were the consequence of differential aspirin (ASA) dosages in the US and OUS. The Cardiovascular and Renal Drugs Advisory Committee (AC) reviewed the submission at its July 28, 2010, meeting. While the AC members were not convinced that the differential ASA dosing explained the differential US/OUS outcomes, they nevertheless voted 7:1 recommending approval. The Office of Drug Evaluation I issued a complete response letter on December 16, 2010, requesting additional analyses of ASA dosing. AZ submitted its response on January 18, 2011. That response and inconsistencies and irregularities in the study results are the focus of this review.

My recommendation not to approve is a change from my recommendation in my CDTL memo. I formerly recommended approval for ACS patients excluding STEMI patients undergoing early percutaneous coronary intervention (PCI). After being assigned as the primary efficacy reviewer for the complete response and completing a more intensive review of the application, I now conclude that there are sufficient problems with PLATO data quality such that, at best, the US results are representative of ticagrelor's efficacy, i.e., ticagrelor is inferior to clopidogrel in efficacy and safety. Ticagrelor appears to perform less well than clopidogrel in patients undergoing early PCI, the preferred approach for STEMI patients and common practice in the US for other ACS patients. The interaction between ticagrelor and early PCI is more consistent than the interaction between ticagrelor and ASA for the most compelling endpoint, i.e., mortality—as are interactions between ticagrelor and statin use and diabetes and ASA. The data do not confirm a ticagrelor-ASA interaction. I recommend confirmation of efficacy and safety in ACS by a second study in the US in invasively managed patients, correcting all of the PLATO deficiencies and addressing all of the critical unanswered questions.

I summarize the data supporting denying approval below—but please also see my original CDTL memo for additional discussion of many of these problems. Because I believe that too much emphasis has been placed upon the *post hoc*, wildly post-randomization, and erratically defined ASA dosages, I provide the details of the other problems with PLATO first, also addressing ASA dosage when relevant. I include my comments on the pharmacology-toxicology and statistical reviews along with my additional discussion of ASA dosage last.

General Analytical Issues

Before reviewing the data, there are three general analytical issues to understand:

1. Censoring. AZ, for its time-to-event analyses, used censoring dates for patients without the event of interest based on the last study visit date for the "completers" but projected based on either a future planned visit date plus 30 days for withdrawals or upon the last dispense date plus 90 days for patients who continued on study medication after a "last" visit. How inappropriate the AZ censoring rules are is illustrated by the following two patients:

   - A patient was randomized to ticagrelor and then was allegedly immediately dropped because of not eligible (criterion 13 "investigator opinion", no explanation given) and allegedly did not receive study drug. The patient then had angiography, possibly angioplasty, and a CABG as well as an assortment of SAEs including acute hepatic failure, rhabdomyolysis, and an "unspecified neurologic problem" post CABG that could be a stroke. All of the SAEs and procedures were dropped from the study data sets because study drug allegedly was not given. There is no valid reason for dropping them from the data sets. While these events are excluded from the safety set by AZ's non-ITT definition of the safety set, I have also argued for, and use routinely, ITT analyses of safety for common events (but not including rare events such as rhabdomyolysis and acute hepatic failure.) However, a more compelling argument for not dropping the events is that the patient should be and was included in the ITT primary efficacy analysis. There was no follow-up on possible endpoint events. There was no further follow-up after the initial hospitalization until the patient was reported alive by a phone call on day 375, no other details. In short, there is no non-mortality endpoint follow-up on this patient yet the AZ censoring day is day 391, completed study with no endpoints.

   - Another ticagrelor patient on day 3 had the following SAE recorded: "during planned pci the cardiologist wanted to know the treatment because the rca artery was thrombosed on a long distance the patient got 3 stents back to back --the patient was unblinded." Ticagrelor was discontinued but neither the unblinding nor the PCI were recorded in the study data sets. The patient had no visits after day 31 but was reported alive by phone call on day 325 with no other details. The AZ censoring day is day 301, completed study with no endpoints.

These censoring abominations were not uncommon. For example, PLATO includes three other patients dropped allegedly because of ineligibility by criterion 13, investigator opinion. These other three are also ticagrelor patients. For only one of them was an explanation recorded for the ineligibility and only this patient has follow-up visits recorded. The other two, like the first patient above, are simply counted as endpoint free to day 391. Poor follow-up and inappropriate censoring were not limited to the ticagrelor group: 43 patients (24 ticagrelor and 19 clopidogrel) had a last visit on day 1 but nonetheless AZ counted them as completing the study without endpoints.

I censor the two patients in the bulleted examples above at the day of their last visit (day 1 for the first patient and day 31 for the second), counting them as endpoint free. While I am suspicious that they were not endpoint free, the missing data in PLATO precludes concluding otherwise—but it also precludes having confidence that the reported PLATO results reflect reality.

In general I censor patients not having endpoints within the study period at the earlier of the day of their last good cardiovascular (CV) follow-up or their end of study day. I base the end of study day on this statement from AZ's Statistical Analysis Plan: "Patients who withdraw from study participation prior to their last scheduled visit date will be assigned a notional last scheduled visit date which is 180, 270, or 360 days following their randomisation date, based on the specific cut-off dates of 18JAN2008 and 18APR2008. Any events that are reported before or on those dates + 30 days will be used in the primary efficacy analysis." I use 210, 300, and 390 days as end of study days regardless of whether patients had visits or events after these study days.

COMMENT: While I assert that the censoring days I propose are more appropriate than AZ's for time-to-event analyses, it makes little difference whether mine or AZ's censoring days are used. Events, not censoring days, are the critical elements for determining statistical significance. Unfortunately correcting the censoring days does not eliminate the critical problem with this poor PLATO follow-up: Many of the early dropouts, like the examples discussed above, likely represent missed events and informative censoring biasing the results.

2. Primary endpoint definition. As I discussed in my CDTL memo, AZ counted bleeding deaths as CV deaths. While including bleeding deaths is reasonable for the primary endpoint (PEP) to estimate a net benefit, excluding non-CV bleeds (i.e., to use a more typical major adverse cardiovascular event (MACE) endpoint) is more appropriate for an endpoint to explore antithrombotic efficacy effects or the effects of ASA upon increasing thrombotic events. Hence I exclude gastrointestinal bleeding and other non-CV bleeding deaths but include non-traumatic intracranial hemorrhage deaths (i.e., hemorrhagic strokes). Additionally, AZ counted all unknown deaths as CV deaths, again reasonable for a PEP for net benefit. To minimize noise and to avoid rewarding poor follow-up, I count sudden unknown deaths as CV deaths but exclude completely unknown deaths. Conversely, AZ counted "multiorgan failure" deaths as non-CV regardless of the initiating event. I count multiorgan failure deaths as CV if the

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initiating event was CV, e.g., heart failure, and as non-CV if the initiating event was not CV, e.g., sepsis. Finally, AZ ignored 39 deaths (22 ticagrelor, 17 clopidogrel) occurring in patients reported in patients not having a PEP and withdrawing consent but having data in the case report forms (CRFs) regarding the deaths. I counted these deaths. In this review I reference AZ's primary endpoint as AZ's primary endpoint (or AZ's PEP) and the endpoint excluding bleeding deaths as the MACE endpoint.

3. Adjudication. In performing my review I checked adjudication packages for 622 patients (293 clopidogrel and 329 ticagrelor). With rare exceptions I judged that the DCRI adjudications were appropriate, with my disagreements almost invariably limited to cases with equivocal data. Hence, in addition to the AZ endpoints and the site-reported events, I will present statistics using the adjudications except for the few disagreements, for the endpoint definition variations described under 2 above, and for additional events not submitted by AZ for adjudication.

    I do note several limitations to concluding that the adjudications are accurate representations of the trial results. All suspicious events must be submitted for adjudication and the adjudication packages must be complete and accurate for the adjudications to be representative and correct. Simply not submitting an event eliminates the possibility of an endpoint. Furthermore, even with submission, a missing biomarker or symptom duration makes an adjudication equivocal or negative. The problem of missing trial data was ignored in the endpoint definitions, e.g., the definition of an MI requires "Elevation of myocardial necrosis biomarkers typical of acute MI" without allowing for missing biomarkers. If biomarkers were not done or not reported, then adjudication of an MI was impossible. Inclusion or exclusion of biomarker values in adjudication packages is subject to manipulation that is impossible to detect.

    Even if the adjudication were done correctly, recording of it could be confounded. I found three examples of the latter:

    - A patient had an adjudicated MI within 24 hours of CABG. However, the adjudicated date and time were recorded as ███████ (b) (6) despite the facts that all hospital documents and data sets record the CABG as ████ (b) (6) ████ the biomarker rises were on ██████ (b) (6) and ██████ (b) (6) ████ and the date of randomization was ██████ (b) (6). AZ did not count the MI.

    - Another patient had an adjudicated MI within 24 hours of CABG with the recorded year wrong (2005 instead of 2007). AZ did not count the MI.

    - A third patient has a triggered MI adjudicated as starting at the time of angioplasty (████ (b) (6) ████) although the biomarker rises began late that day. The event appears not to have been counted because the arbitrary start time was later than the randomization time (11:47). However, the first study drug administration was at 11:40, prior to the PCI start time and prior to the randomization time.

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All three of these erroneous date recordings that eliminated endpoints are ticagrelor patients. While AZ expressed agreement regarding the errors, AZ refused to correct its endpoint assignments because "Censoring rules for the inclusion of events were laid out in the Statistical Analysis Plan prior to the PLATO study database being locked on 20 April 2009." I count these patients as having AZ primary endpoints.

Ticagrelor-ASA Interaction Is Not Significant in PLATO Short Term Results but Other Interactions Are

The most striking PLATO result was the reported long term mortality benefit. PLATO provides much less substantial evidence of short term benefits and beneficial effects on thrombotic events. This combination of results is inconsistent with those of all earlier platelet inhibitor ACS trials, which have shown strong short term benefits and smaller or no later benefits particularly regarding mortality. The ticagrelor-ASA interaction is not significant for the short term results and not significant for mortality results regardless of short or long term. The short term results and mortality results demonstrate that three other interactions are more important and creditable than the ticagrelor-ASA interaction. These interactions are the following:

1. Diabetics appear to benefit from higher ASA dosage regardless of treatment arm.

2. Ticagrelor interacts favorably with statins—or inappropriate restriction of statin dosages was detrimental to clopidogrel patients in PLATO.

3. Ticagrelor patients undergoing early PCI fare worse than clopidogrel patients.

The short term, i.e., 30-day, results are likely more useful for exploring mechanistic issues, such as the effects of ASA dosage, than the long term results for the following reasons: In prior ACS antiplatelet trials the major differences in outcomes have always been most dramatic in the first 30 days (see the Section 7.1.3 in my CDTL Review.) The majority or a substantial portion of the endpoints occur in the first 30 days; PLATO is no exception, with about 50% of the MACE endpoints and 43% of the deaths occurring within the first 30 days. Another advantage of short term is that there are fewer ASA dosage changes and missing dose records, making ASA dosage estimates less problematic (although even these short term ASA dosages are substantially post-randomization.) Similarly, there are fewer problems with study drug interruptions or discontinuations. Finally, for PLATO there is an even more cogent argument for scrutinizing the short term results: PLATO long-term follow-up was poor as I summarize under 3.c. above, with 19% having questionable CV follow-up for the entire study period. For 30-day follow-up the rate of questionable CV follow-up is not good (about 3.4%) but it is substantially lower such that we should have more confidence that any inferences regarding results or mechanisms are real and not artifacts of informative censoring.

AZ bases its arguments regarding ASA dosages on Cox regression models limited to study drug, ASA dosage, and region factors and their interactions. When one analyzes clinically relevant baseline factors for PLATO, one finds that there are several other interactions between ticagrelor and other factors that are equally or more significant than the ASA interaction—particularly for short term results and for mortality. When

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modeling it is preferable to use full models utilizing all contributory covariates and cofactors rather than cherry-picking a limited number. For PLATO I argue that using full models is particularly appropriate because of the study design issue I discussed in my CDTL Review, Section 7.1.6.1.1: PLATO was multiple studies rolled into one, combining STEMI with NSTEMI, invasive with non-invasive management, and clopidogrel pre-treatment with no clopidogrel treatment—with US vs. OUS and high ASA dose vs. low ASA dose forced in by the results. If one tries to analyze PLATO with a traditional subsetting, tabular approach, one ends up with a huge table with small numbers in many of the cells, e.g., Table 3 in my CDTL Review. For PLATO I suggest that a multivariable Cox regression analytical approach is more appropriate than subsetting.

For the Cox regressions below I have included baseline cofactors identified based on availability in PLATO, on clinical knowledge regarding risk predictors in other ACS and coronary heart disease trials, and on significant results in PLATO regressions. I have included all cofactors satisfying these criteria with the following exceptions: body weight and histories of MI, stroke, heart failure, peripheral vascular disease, and renal impairment. The latter are significant cofactors in many Cox regressions of PLATO endpoints but I have omitted them to simplify the regressions. They do not interact with ticagrelor use, ASA use, region, or the other cofactors; including them does not change the observations I note below. I did retain in the regressions age (always one of the most significant covariates for CV risk) and baseline creatinine clearance (rather than body weight because clearance is both a risk factor and a surrogate for body size and drug clearance). I imputed values for 2 missing ages as the mean age for the same sex patients at the same site and for creatinine clearance using the Stata multiple imputation procedure.

For ASA dosage I use dichotomous ASA dosage factors ($<$ or $\geq$ 300 mg) that I generated specifically for each endpoint type and for 30 day censoring. I based these ASA dosage factors on all available ASA records including loading doses, counted no ASA records as zero dosage, and selected the modal ASA dosage administered prior to the endpoint or the last CV follow-up day (for MACE) or vital status follow-up day (for mortality) or day 30, whichever is earliest.

I have included interaction terms that have been identified as of interest, i.e., the ticagrelor-ASA interaction, and others that are significant (or close to significant) in some analyses. I have omitted interaction terms that are statistically insignificant, e.g., diabetes does not appear to interact significantly with treatment arm. In general the interactions significant in the more extensive models are also significant in more limited models omitting the non-interacting factors.

I show the variable names for the Cox regressions in Table 1. I show the 30-day Cox regression results for the MACE primary endpoint (see 3 above) in Table 2, for 30-day mortality in Table 3, and for 30-day CV mortality in Table 4. For completeness I also show the 30-day Cox regression results for the sponsor's PEP in Table 5. I do not recommend using the latter because of the definitional limitations discussed in 3 above and the endpoint ascertainment errors discussed throughout this review and in my CDTL Review.

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Table 1: Variable Names for Cox Regressions

Variable	Description
angpci	angiography or PCI at any time during study
angpci30d	angiography or PCI within 30 days
angpcilt24h	angiography or PCI within 24 hours of randomization
ageimp	age in years (2 ages imputed)
asaaz30ge300	AZ's median ASA dosage ≥300 mg, 30 day PEP censoring, 0 mg imputed for missing
asad30ge300	modal ASA dosage ≥300 mg, 30-day mortality censoring
asabldmajge300	modal ASA dosage ≥300 mg, major bleed censoring
asabldminge300	modal ASA dosage ≥300 mg, minor or greater bleed censoring
asabm30ge300	modal ASA dosage ≥300 mg, 30-day major bleed censoring
asabm3ge300	modal ASA dosage ≥300 mg, 3-day major bleed censoring
asadge300	modal ASA dosage ≥300 mg, mortality full study censoring
asaf30ge300	modal ASA dosage ≥300 mg, FDA MACE 30-day censoring
asafge300	modal ASA dosage ≥300 mg, FDA MACE full study censoring
azmonitor	regions monitored by Astra Zeneca
cabg	any CABG during study
clpearly	clopidogrel early, i.e., pre-study
crcl0imp	baseline creatinine clearance mL/min (800 imputed values)
diabhx	baseline history of diabetes
ecgstemi	ST elevation at presentation
gibldhx	baseline history of gastrointestinal bleed
med55ge300	median55 (AZ ASA dosage excluding loading) ≥300 mg
pcin	number of PCIs done during the study
proclt24h	PCI within 24 hours of randomization – "early PCI"
smoker	current smoker at baseline
statin0	baseline statin use
statinon	statin use on study
strkhx	baseline history of stroke
ticagrelor	ticagrelor arm (vs. clopidogrel arm)
us	United States
wtimp	weight in kilograms (56 weights imputed)

Note: In the Cox regressions two variable names separated by a "#" sign indicate the interaction term between the two variables. For example "ticagrelor#us" is the interaction term for ticagrelor use in US patients. The "1 1" in the regression tables is Stata's notation for indicating that the interaction term is for ticagrelor=1 and US==1, i.e., ticagrelor arm patients in the US.

Table 2: Cox Regression for MACE through Day 30

```
No. of subjects =        18624                Number of obs   =      18624
No. of failures =          941
Time at risk    =       525178
                                              LR chi2(16)     =     428.60
Log likelihood  =   -9001.7444               Prob > chi2     =     0.0000

------------------------------------------------------------------------------
         _t | Haz. Ratio  Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
1.ticagrelor |   1.145151   .1743938    0.89   0.373     .8496389    1.543446
        1.us |    .502205   .1017354   -3.40   0.001     .3376345    .7469909
             |
 ticagrelor# |
          us |
         1 1 |   .9307677   .2579514   -0.26   0.796     .5406805    1.602293
             |
      ageimp |   1.019971   .0041731    4.83   0.000     1.011825    1.028183
     crcl0imp |   .9914044   .0013482   -6.35   0.000     .9887656    .9940503
    1.smoker |   1.298124    .132621    2.55   0.011     1.062562    1.585908
             |
     smoker# |
  ticagrelor |
         1 1 |   .7959762   .1134646   -1.60   0.109     .6019539    1.052536
             |
    ecgstemi |   1.247253   .0933839    2.95   0.003     1.077019    1.444393
1.asaf30~300 |   4.730446    .695238   10.57   0.000     3.546502    6.309631
             |
asaf30ge300# |
  ticagrelor |
         1 1 |   1.296615   .2434855    1.38   0.167     .8973618    1.873503
             |
     1.diabhx |    1.41656   .1110109    4.44   0.000     1.214868    1.651736
             |
      diabhx# |
  asaf30ge300 |
         1 1 |   .4919138   .0958589   -3.64   0.000     .3357499    .7207125
             |
    1.statin0 |   1.017497   .1123623    0.16   0.875     .8194734    1.263372
             |
     statin0# |
  ticagrelor |
         1 1 |   .7478474   .1142871   -1.90   0.057     .5542825    1.009008
             |
  1.proclt24h |    .771617   .0767042   -2.61   0.009     .6350185    .9375992
             |
   proclt24h# |
  ticagrelor |
         1 1 |   1.146748   .1528746    1.03   0.304     .8830659    1.489165
------------------------------------------------------------------------------
```

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Table 3: Cox Regression for All Cause Mortality through Day 30

```
No. of subjects =         18624            Number of obs    =      18624
No. of failures =           416
Time at risk    =        545479
                                           LR chi2(16)      =     444.52
Log likelihood  =     -3861.147            Prob > chi2      =     0.0000

------------------------------------------------------------------------------
         _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
1.ticagrelor |   1.057227   .2157592     0.27   0.785     .708688    1.577182
        1.us |   .4795989   .1478548    -2.38   0.017    .2620973    .8775942
             |
 ticagrelor#|
         us |
         1 1 |   .5404665   .2577112    -1.29   0.197    .2122704    1.376094
             |
      ageimp |   1.024989   .0062916     4.02   0.000    1.012731    1.037395
     crcl0imp |   .9837055   .0021406    -7.55   0.000     .979519    .9879099
     1.smoker |   1.477069   .2214706     2.60   0.009    1.100962     1.98166
             |
     smoker#|
  ticagrelor |
         1 1 |   .6532846   .1448116    -1.92   0.055    .4230768    1.008755
             |
     ecgstemi |   2.138221   .2354551     6.90   0.000     1.72314     2.65329
1.asad30~300 |   5.989711   1.243281     8.62   0.000    3.987699    8.996825
             |
asad30ge300#|
  ticagrelor |
         1 1 |   1.327698   .3587579     1.05   0.294    .7818004    2.254773
             |
     1.diabhx |   1.85421   .2104352     5.44   0.000    1.484416    2.316126
             |
     diabhx#|
 asad30ge300 |
         1 1 |   .3429358   .1010806    -3.63   0.000    .1924511    .6110901
             |
    1.statin0 |   .7978949   .1188927    -1.52   0.130    .5958129    1.068517
             |
    statin0#|
  ticagrelor |
         1 1 |   .5551043   .1170701    -2.79   0.005    .3671625    .8392491
             |
  1.proclt24h |   .4826154   .0717725    -4.90   0.000    .3605904    .6459342
             |
  proclt24h#|
  ticagrelor |
         1 1 |   1.885937   .3843366     3.11   0.002    1.264911    2.811863
------------------------------------------------------------------------------
```

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Table 4: Cox Regression for CV Mortality through Day 30

```
No. of subjects =        18624              Number of obs   =      18624
No. of failures =          760
Time at risk    =       545479
                                            LR chi2(16)     =     569.65
Log likelihood  =   -7168.7844              Prob > chi2     =     0.0000

------------------------------------------------------------------------------
         _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
1.ticagrelor |   1.085404    .1648271     0.54   0.589     .8059903    1.461683
        1.us |   .3537394    .1048937    -3.50   0.000     .1978236    .6325408
             |
 ticagrelor#|
         us |
         1 1 |    1.78096     .675329     1.52   0.128     .8470012    3.744765
             |
      ageimp |   1.022217    .0046649     4.82   0.000     1.013114    1.031401
     crcl0imp |   .9855022    .0015751    -9.14   0.000     .9824198    .9885942
     1.smoker |   1.191491    .1393998     1.50   0.134     .9473344    1.498573
             |
     smoker#|
  ticagrelor |
         1 1 |   .7345064    .1245597    -1.82   0.069     .5268007    1.024106
             |
     ecgstemi |    1.83369    .1499112     7.42   0.000     1.562201     2.15236
1.asad30~300 |    3.68683    .6951476     6.92   0.000     2.547769    5.335144
             |
asad30ge300#|
  ticagrelor |
         1 1 |    1.11797    .2754085     0.45   0.651     .6898259    1.811845
             |
    1.diabhx |    1.83976    .1476174     7.60   0.000     1.572038    2.153076
             |
     diabhx#|
 asad30ge300 |
         1 1 |   .3434552    .0906442    -4.05   0.000     .2047492    .5761265
             |
    1.statin0 |   .8437862    .0964421    -1.49   0.137     .6744392    1.055655
             |
    statin0#|
  ticagrelor |
         1 1 |   .7046395    .1133465    -2.18   0.030     .5140968    .9658041
             |
  1.proclt24h |   .4888136    .0553632    -6.32   0.000     .3915037    .6103104
             |
   proclt24h#|
  ticagrelor |
         1 1 |   1.313278     .201161     1.78   0.075     .9726892    1.773125
------------------------------------------------------------------------------
```

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Table 5: Cox Regression for AZ Primary Endpoint through Day 30

```
No. of subjects =        18624                Number of obs   =      18624
No. of failures =          949
Time at risk    =       525056
                                              LR chi2(16)     =     268.97
Log likelihood  =    -9159.4768               Prob > chi2     =     0.0000

------------------------------------------------------------------------------
        _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+------------------------------------------------------------------
1.ticagrelor |   1.097508   .1633335     0.63   0.532     .8198421    1.469215
      1.us |    .773324    .1624099    -1.22   0.221     .5123846    1.167151
           |
 ticagrelor#|
        us |
       1 1 |   1.186216   .3485477     0.58   0.561     .6668897    2.109957
           |
    ageimp |   1.018419   .0041564     4.47   0.000     1.010305    1.026598
    crcl0imp |   .9903033     .001352    -7.14   0.000     .9876569    .9929567
   1.smoker |    1.31643   .1319864     2.74   0.006     1.081572    1.602285
           |
    smoker#|
  ticagrelor |
       1 1 |   .7835548   .1116519    -1.71   0.087     .5926227    1.036002
           |
   ecgstemi |   1.279829   .0957754     3.30   0.001      1.10523     1.48201
1.asaaz3~300 |   2.348385   .4562568     4.39   0.000     1.604698    3.436729
           |
asaaz30ge300#|
  ticagrelor |
       1 1 |   .9852037    .256556    -0.06   0.954     .5913783    1.641295
           |
   1.diabhx |   1.314342   .0986093     3.64   0.000      1.13461    1.522546
           |
    diabhx#|
asaaz30ge300 |
       1 1 |    .692425   .1625902    -1.57   0.118     .4370185    1.097099
           |
   1.statin0 |    .989374   .1060719    -0.10   0.921     .8018668    1.220728
           |
    statin0#|
  ticagrelor |
       1 1 |   .7512663     .11372    -1.89   0.059     .5584016    1.010744
           |
  1.proclt24h |   .7676661   .0750636    -2.70   0.007     .6337829    .9298315
           |
   proclt24h#|
  ticagrelor |
       1 1 |   1.175491   .1565192     1.21   0.225     .9054818    1.526014
------------------------------------------------------------------------------
```

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COMMENT: I summarize what these Cox regressions of short term results show as follows:

- *The interaction term for ticagrelor and region is insignificant in all regressions. For short term results there is no major US vs. OUS discrepancy that requires explanation.*

- *The interaction term for ticagrelor and ASA dosage is insignificant in all regressions. The short term results do not support worst outcomes with higher ASA dosage in ticagrelor patients alone. While one can argue that the fewer numbers of short term events than long term reduces the power to detect a real difference, note that four other interactions are significant for these short term results—one of them related to ASA dosage.*

- *The interaction term for history of diabetes and ASA dosage is significant for MACE and 30-day all cause and CV mortality; it is only insignificant for the AZ PEP with the AZ ASA dosage, although the point estimate is similar. Note that high ASA dosage is beneficial in diabetics. Diabetics are a sizeable minority in ACS trials, comprising about 25% of the PLATO population. Diabetics comprised a higher percentage of the US patients (33%) than OUS (24%).*

  That higher ASA dosage may be beneficial in diabetics is consistent with a growing body of evidence that diabetics show reduced responsiveness to ASA inhibition of platelet aggregation. The reduced responsiveness is likely responsible for the observations that diabetics fare less well with angioplasty than non-diabetics such that CABG is preferred for diabetics. The TRITON investigators published a paper entitled "Greater Clinical Benefit of More Intensive Oral Antiplatelet Therapy with Prasugrel in Patients with Diabetes Mellitus in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38." They allege that "It has been known for decades that platelets from patients with DM are characterized by increased reactivity." They did not address ASA dosage in their paper. If higher ASA dosage is confirmed as an important factor in achieving better outcomes in diabetics, then that result may be the most important lesson from the PLATO trial. Regardless, the PLATO ASA-diabetes interaction makes it impossible to recommend labeling for ticagrelor: Should all patients receive low dose ASA, as AZ is proposing? Or should diabetics receive high dose ASA? Or is it some other combination of factors that should determine ASA dosage? We need another trial, preferably with random assignment of ASA dosages but minimally with control of ASA dosage.

- *The interaction term for ticagrelor and statin use at baseline is almost statistically significant for the MACE endpoint, highly statistically significant for 30-day mortality, and significant for CV mortality. That ticagrelor and statins may interact on outcomes is not surprising: Statins have definite CV outcome benefits. Ticagrelor increases exposure of CYP3A4-metabolized statins such as simvastatin and atorvastatin. However, the clinical interaction seen in PLATO appears stronger for all statins than for CYP3A4-metabolized statins, but note that about 70% of patients were on a CYP3A4-metabolized statin (predominantly*

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simvastatin and atorvastatin) while only an additional 8% were on some other statin. Discriminating reliably between statin effects and CYP3A4-metabolized statin effects in PLATO is impossible. It is unexpected that, if this does represent the effects of the PK interaction, the effects are discernible within 30 days.

The reported all-cause mortality in PLATO is almost statistically significantly lower with ticagrelor at 30 days (p = 0.058) and highly statistically significant in the available full trial results. While the mortality trend was also favorable to ticagrelor in the US at 30 days, the lean was negative for mortality in the available full trial results; the trend and lean are more consistently negative in the other regions not monitored by AZ. That the mortality benefit appears to be explained by an interaction with statins does not negate entirely the value of the suggested mortality benefit. While one should question whether the benefit would still be manifest with appropriate statin dosing, this latter question is a hypothesis for testing and not an established fact.

- *The interaction term for ticagrelor and PCI within 24 hours of randomization is statistically significant for 30-day mortality with ticagrelor showing relative worse mortality with early PCI (hazard ratio 1.9). This negative interaction is the reason why my recommendation for approval in my original CDTL Review excluded STEMI patients undergoing early PCI. Note that early PCI patients were more likely to receive higher dosage ASA treatment, explaining some of the presumed ticagrelor-higher ASA dosage interaction. The apparent ticagrelor-early PCI detrimental interaction is major reason why I believe ticagrelor should not be approved in the US until this interaction is refuted: Early PCI is the practice for most ACS patients, particularly STEMI patients, in the US.*

- *Current smokers fared worse but there is some suggestion that they fared better on ticagrelor. There has evidence presented in the medical literature that smoking induces some CYP enzymes responsible for producing the clopidogrel active metabolite such that clopidogrel platelet inhibition is enhanced. The PLATO results suggest some other effect for ticagrelor.*

As I have documented above, there is little evidence for a ticagrelor-ASA interaction in the short term results. On the contrary, the short term results provide strong evidence for ticagrelor interactions with statins and with early PCI and for higher ASA dosage and beneficial results in diabetics. The statins and the early PCI interactions are not post hoc as is the ticagrelor-ASA interaction: I proposed analyzing them to the primary efficacy reviewer prior to the NDA receipt because of the known ticagrelor-statin PK interactions and because of previous trials separating out invasive management from non-invasive. Given that the ticagrelor-ASA interaction is post hoc and wildly post-randomization, I assert that the ticagrelor-statin, ticagrelor-early PCI, and diabetes-ASA interactions deserve more attention and credibility than the ticagrelor-ASA interaction.

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Ticagrelor-ASA Interaction Is Not Significant for PLATO Long Term Mortality but Other Interactions Are

The short term regression analyses may be criticized that the unadjusted results, for treatment effect alone, are marginally significant at best (mortality, AZ PEP) and completely insignificant for the FDA MACE. This criticism does not apply to long term all cause mortality, for which I calculate a hazard ratio for ticagrelor of 0.81 and a P value by Cox regression of 0.001 (using my censoring dates and counting all deaths including ones excluded by AZ.) I show the mortality rates in Table 6.

Table 6: Tabulation of All Cause Mortality Rates through Study End by Treatment, Region, and ASA Dosage

	OUS		US	
	low ASA	high ASA	low ASA	high ASA
clopidogrel	5.6%	18.8%	2.9%	4.4%
ticagrelor	4.3%	20.1%	4.3%	4.8%

COMMENT: Table 6 suggests a therapeutic role for low dose ASA--combined with clopidogrel to achieve the lowest mortality rates as in PLATO for this combination. Table 6 also suggest that the two regions are extremely heterogeneous for ASA dosage effects and likely reasons for high ASA dosing: Note the extremely high mortality rates in both groups OUS with high ASA dosing.

For long term mortality the interactions between ticagrelor and US and ticagrelor and ASA (whether my ASA dosage or AZ's) are statistically insignificant. There is a significant interaction between ticagrelor and regions monitored by AZ as shown in Table 7.

Table 7: Cox Regression for All Cause Mortality through Study End by Regions Monitored by Astra-Zeneca

```
No. of subjects =        18624                Number of obs   =      18624
No. of failures =          966
Time at risk    =      192762.6
                                              LR chi2(3)      =      20.33
Log likelihood  =    -9384.6668               Prob > chi2     =     0.0001


------------------------------------------------------------------------------
        _t | Haz. Ratio  Std. Err.      z    P>|z|    [95% Conf. Interval]
-----------+------------------------------------------------------------------
      1.rx |   1.201463   .1906998    1.16   0.248    .8802479    1.639893
 1.azmonitor |   1.421402   .1790775    2.79   0.005    1.110394    1.819521
           |
rx#azmonitor |
       1 1 |   .6215354   .1081135   -2.73   0.006    .4419802     .874035
------------------------------------------------------------------------------
```

The more extensive Cox regression models shown in Table 8, for all cause mortality, and Table 9, for CV mortality, are inconclusive regarding a significant interaction between ticagrelor and AZ monitoring.

Table 8: Cox Regression for All Cause Mortality through Study End, Full Model

```
No. of subjects =         18624              Number of obs   =      18624
No. of failures =           966
Time at risk    =       5783449
                                             LR chi2(16)     =     833.49
Log likelihood  =    -8978.1455              Prob > chi2     =     0.0000

------------------------------------------------------------------------------
         _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
1.ticagrelor |   1.281734   .2563622     1.24   0.215     .8660589    1.896918
 1.azmonitor |   1.400226   .1900451     2.48   0.013     1.073172    1.826952
            |
 ticagrelor#|
   azmonitor |
        1 1 |    .7467569   .1395898    -1.56   0.118     .5176852    1.077191
            |
      ageimp |   1.026404   .0041764     6.40   0.000     1.018251    1.034622
     crcl0imp |   .9834529   .0014113   -11.63   0.000     .9806906    .9862229
    1.smoker |   1.338285   .1344782     2.90   0.004     1.099044    1.629603
            |
     smoker#|
  ticagrelor |
        1 1 |    .7431647   .1107241    -1.99   0.046     .5549636    .9951891
            |
     ecgstemi |   1.789831   .1295712     8.04   0.000     1.553069    2.062685
 1.asadge300 |   3.919459   .6330966     8.46   0.000     2.855844    5.379201
            |
  asadge300#|
  ticagrelor |
        1 1 |    1.269798   .270347      1.12   0.262     .836583    1.927348
            |
    1.diabhx |   1.856621   .131458      8.74   0.000     1.616047    2.133009
            |
     diabhx#|
   asadge300 |
        1 1 |    .347709   .0816178    -4.50   0.000     .2194892    .5508314
            |
    1.statin0 |   .8699148   .0885744    -1.37   0.171     .7125374    1.062052
            |
    statin0#|
  ticagrelor |
        1 1 |    .6920502   .1013462    -2.51   0.012     .5193794    .9221265
            |
   1.proclt24h |   .4656041    .046049    -7.73   0.000     .3835584    .5651998
            |
  proclt24h#|
  ticagrelor |
        1 1 |    1.40815   .1924657     2.50   0.012     1.077226    1.840734
------------------------------------------------------------------------------
```

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Table 9: Cox Regression for CV Mortality through Study End, Full Model

```
No. of subjects =        18624              Number of obs   =      18624
No. of failures =          749
Time at risk    =       5783449
                                            LR chi2(16)     =     595.02
Log likelihood  =    -6997.2079             Prob > chi2     =     0.0000

------------------------------------------------------------------------------
        _t | Haz. Ratio  Std. Err.      z    P>|z|    [95% Conf. Interval]
-----------+------------------------------------------------------------------
1.ticagrelor |   1.45466   .3322471    1.64   0.101    .9297055    2.276028
 1.azmonitor |  1.516585   .2427372    2.60   0.009    1.108224    2.075419
             |
  ticagrelor#|
    azmonitor|
         1 1 |  .7194593   .1540644   -1.54   0.124    .4728579    1.094666
             |
      ageimp |   1.02145   .0046781    4.63   0.000    1.012323    1.030661
     crcl0imp|  .9850102   .0015781   -9.43   0.000     .981922    .9881081
    1.smoker |  1.175775   .1381047    1.38   0.168    .9339924    1.480148
             |
     smoker# |
   ticagrelor|
         1 1 |  .7483548   .1273371   -1.70   0.088    .5361304    1.044587
             |
     ecgstemi|  1.934316   .1581642    8.07   0.000    1.647885    2.270534
 1.asadge300 |  4.001564   .7435573    7.46   0.000    2.780113    5.759665
             |
  asadge300# |
   ticagrelor|
         1 1 |  1.386531    .330081    1.37   0.170    .8695413    2.210898
             |
    1.diabhx |  1.796729   .1454593    7.24   0.000    1.533102    2.105688
             |
      diabhx#|
    asadge300|
         1 1 |  .3323002   .0882953   -4.15   0.000    .1974051    .5593748
             |
    1.statin0|  .8326293     .09768   -1.56   0.118    .6615961    1.047877
             |
     statin0#|
   ticagrelor|
         1 1 |  .6807493   .1121594   -2.33   0.020    .4928835    .9402214
             |
  1.proclt24h|  .4659644    .052888   -6.73   0.000    .3730262    .5820577
             |
   proclt24h#|
   ticagrelor|
         1 1 |  1.346328   .2074475    1.93   0.054    .9953929     1.82099
------------------------------------------------------------------------------
```

Table 8 and Table 9 also confirm that the same factors significant for short term mortality remain significant for long term mortality, whether all cause mortality or CV mortality. That the results differ little for all cause mortality and CV mortality should not be surprising because the majority of the deaths were clearly CV, about 77%. The significant interactions are diabetes and higher ASA dosage (with higher ASA dosage better), baseline statin use and ticagrelor, and early PCI and ticagrelor.

Reviewers unfamiliar with multivariable Cox regressions have difficulty understanding these more complicated models. The diabetes-ASA interaction does not involve ticagrelor; some have criticized the statin interaction as clinically implausible. Hence I include in Table 10 a simplified Cox regression including only the treatment, US, ASA, and early PCI factors and their interactions.

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Table 10: Simplified Cox Regression for All Cause Mortality through Study End

```
No. of subjects =          18624              Number of obs   =      18624
No. of failures =            966
Time at risk    =       5783449
                                              LR chi2(7)      =     226.82
Log likelihood  =    -9281.4769              Prob > chi2     =     0.0000

------------------------------------------------------------------------------
         _t | Haz. Ratio  Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
1.ticagrelor|   .7000522   .0587847    -4.25   0.000     .5938181    .8252917
       1.us |   .3181973   .0738608    -4.93   0.000     .2018893    .5015099
            |
 ticagrelor#|
         us |
        1 1 |   1.343841   .4280386     0.93   0.353     .7198202    2.508832
            |
1.asadge300 |   3.725315   .6167479     7.94   0.000     2.693032    5.153288
            |
 ticagrelor#|
   asadge300|
        1 1 |   1.206999   .2829398     0.80   0.422      .76238    1.910918
            |
1.proclt24h |   .4559005   .0421603    -8.49   0.000     .3803239    .5464954
            |
 ticagrelor#|
   proclt24h|
        1 1 |   1.324477   .1792131     2.08   0.038     1.015944     1.72671
------------------------------------------------------------------------------
```

Note that neither the ticagrelor-US or ticagrelor-ASA interactions are significant while the ticagrelor-early PCI interaction is. Hence it is justifiable to eliminate the former interactions from the regression to arrive at a model including only treatment and early PCI as shown in Table 11.

Table 11: Cox Regression of Treatment and Early PCI for All Cause Mortality through Study End

```
No. of subjects =          18624              Number of obs   =      18624
No. of failures =            966
Time at risk    =       5783449
                                              LR chi2(3)      =     112.26
Log likelihood  =    -9338.7615              Prob > chi2     =     0.0000

------------------------------------------------------------------------------
         _t | Haz. Ratio  Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
1.ticagrelor|   .7283743   .0591887    -3.90   0.000     .6211333    .8541309
 1.proclt24h|    .460096   .0423773    -8.43   0.000     .3841035    .5511231
            |
 ticagrelor#|
   proclt24h|
        1 1 |   1.329167   .1791547     2.11   0.035     1.020584    1.731054
------------------------------------------------------------------------------
```

There appears to be a statistically significant negative interaction between ticagrelor and early PCI. While for the entire study population it is not clear that ticagrelor is actually worse than clopidogrel with early PCI, the US results suggest that ticagrelor might be inferior as shown in Table 12 for all cause mortality and in Table 13 for CV mortality.

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Table 12: Tabulation of All Cause Mortality Rates through Study End by Treatment, US Region, and Early PCI

	all PLATO		US only	
	no early PCI	early PCI	no early PCI	early PCI
clopidogrel	7.8%	3.7%	6.1%	2.3%
ticagrelor	5.7%	3.6%	5.2%	4.1%

Table 13: Tabulation of CV Mortality Rates through Study End by Treatment, US Region, and Early PCI

	all PLATO		US only	
	no early PCI	early PCI	no early PCI	early PCI
clopidogrel	5.8%	2.8%	3.1%	1.4%
ticagrelor	4.6%	2.9%	4.1%	3.2%

In these analyses examining the relationships between ticagrelor, PCI, and outcomes I use whether there was an early PCI rather than the invasive intent variable allegedly captured by the IVRS at randomization. I use early PCI because patients need optimal platelet inhibition if angioplasty is done and not because the investigator is contemplating angioplasty or CABG. While early PCI can be criticized as post-randomization, the decision to perform PCI appears to have been made very early, e.g., 93% of the patients who had PCIs within the first 24 hours had their PCIs within the first 10 hours. In various reviews I have used 10, 12, and 24 hours as cutoffs with little differences in the inferences from the differing cutoffs; I use 24 hours in this review because our cardiologists have suggested to me that 24 hours is the cutoff used by US cardiologists to define early PCI. Twenty-four hours is also statistically a good cutoff because it roughly bisects the study population: about 51% of patients (62% US, 50% OUS) had a PCI within 24 hours.

Invasive intent is less informative than early PCI, particularly in the US. US investigators recorded that they intended to manage 94% of patients invasively; with 6% intent for medical management that subgroup is too small for any statistical inferences. Furthermore, in the US about 35% of patients intended to be managed invasively did not have a PCI within 24 hours. OUS investigators were less aggressive (70% invasive management intent) but OUS intent is also less discriminatory than early PCI and about 31% of OUS patients intended for invasive management did not have a PCI within 24 hours. Finally, invasive intent has its share of anomalies: 9 patients who the investigator reported to be medically managed already had a PCI within the 24 hours prior to randomization.

COMMENT: All of the Cox regressions of mortality, whether all cause or CV, suggest similar conclusions. There is no interaction between ticagrelor and ASA dosage. The strongest interaction appears to be between diabetes and ASA, with diabetics benefitting from higher ASA dosage. Ticagrelor and early PCI is associated with slightly greater mortality. Conversely, either ticagrelor and statin use is associated with slightly lower mortality or clopidogrel and reduced statin dosage is associated with slightly higher

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mortality. Smokers also may benefit from ticagrelor. Whether there is an interaction between ticagrelor and monitoring by AZ is unclear.

The interactions between ticagrelor and statins and ticagrelor and early PCI share related failures in trial design and data collection:

- *AZ had identified the PK interaction between ticagrelor and statins prior to starting PLATO such that they proposed restricting the dosages for some statins regardless of trial arm. While we agreed to this restriction in advance, I believe that agreement was a mistake and that other options for handling the statin interaction should have been implemented. Regardless, despite implementing the statin restriction AZ failed to collect data on statin dosages and failed to collect adequate data on lipid levels in PLATO (see my CDTL Review Section 7.1.6.1.2 for the documentation of this problem.) Hence we lack the data to evaluate the statin interaction. The lower hazard ratio for the interaction term between ticagrelor and baseline statin use could be artifact, ticagrelor boosting statin levels for a beneficial impact, the inappropriate restriction of statin dosages in clopidogrel patients producing a detrimental impact for them, or some other unknown interaction. We have no reliable PLATO data to evaluate these possibilities.*

- *To understand the interaction between ticagrelor and early PCI we need to have accurate recordings of the times of platelet inhibitor administrations (both study drug and pre-study clopidogrel) and of PCI. However, AZ failed to collect the timing of pre-study clopidogrel and AZ failed to collect accurately the times of initial study administration, first PCI, and randomization. For 725 patients the first study drug time is prior to the randomization time (for only 1 patient AZ verified that study drug was administered prior to randomization.) For 335 patients the PCI time is prior to randomization (either protocol violations or time errors.) For 730 patients the study drug time is after the PCI (either contrary to the study intent or time errors.) With the available PLATO data we can not define better the interaction between ticagrelor and early PCI.*

Table 12 *and* Table 13 *also illustrate well the dilemma that has plagued the interpretation of PLATO: Mortality and CV mortality are strikingly lowest in the US—for clopidogrel. Similarly, regarding ASA dosage, mortality is lowest in the US—for US and low dose clopidogrel.*

My two final conclusions for the short term results and mortality data are the following: (1) All of the focus upon ASA dosage, while ignoring the other interactions, has impeded the understanding of ticagrelor activity. (2) There are many PLATO deficiencies as well as critical outstanding issues such that a confirmatory trial is mandatory.

Pre-Study Clopidogrel Is Inconsistent with the Proposed Labeling

PLATO allowed enrollment of patients pre-treated with clopidogrel, including loading doses. About half of the patients in each arm received non-study drug clopidogrel. However, determining the impact of non-study drug clopidogrel use is impossible because PLATO did not capture the timing of it. While allowing baseline clopidogrel use

has been defended as more representative of the real world than excluding patients treated with it, allowing baseline clopidogrel also produces the problem of extrapolating trial results: Half of the PLATO study population is not relevant to the proposed label, which does not specify pre-treatment with clopidogrel.

AZ alleges that ticagrelor is a faster, better platelet inhibitor than clopidogrel. Hence the study design that should optimize the chances for ticagrelor beating clopidogrel is to enroll clopidogrel-naïve ACS patients and randomize them to the two drugs; ticagrelor's faster onset should be advantageous in optimizing outcomes. For the other faster, better platelet inhibitor (prasugrel) its pivotal trial TRITON adopted this latter design. TRITON showed the most impressive short term benefit in the patients who we believe have the greatest need for faster, better platelet inhibition, i.e., STEMI patients undergoing early PCI. Why might AZ not have chosen the better study design for PLATO? PLATO results suggest that ticagrelor is inferior to clopidogrel for patients undergoing early PCI. While *in vitro* results may suggest that ticagrelor is the better, faster platelet inhibitor, the PLATO study design suggests that AZ did not have confidence that the *in vitro* results translated into a clinical advantage. PLATO results in the early PCI subgroup appear to confirm this lack of confidence.

AZ did not collect data on the timing of administration of pre-study clopidogrel. Lacking these data (and good data on early timings as described elsewhere in this review) we can not analyze whether pre-study clopidogrel use interacted with ticagrelor use or describe the impact.

Poor PLATO Follow-up Precludes Confidence in the Long Term Results

PLATO follow-up was poor. While PLATO was a short CV outcomes study with fewer than 60% of the patients needing follow-up of at least 360 days, about 19% of patients alive at the end of study did not have a visit with vitals signs on or after the earliest study completion date (19.7% ticagrelor vs. 18.1% clopidogrel.) The excess number of ticagrelor patients without vitals signs follow-up and without an AZ primary endpoint (148) exceeds the difference in AZ primary endpoint (147). The excess number of ticagrelor patients lacking final vital signs and the MACE endpoint (141) greatly exceeds the difference in MACE endpoints (87). When the rate of missing data exceeds the endpoint difference, one must be concerned about the validity of any conclusions. While vital status follow-up was better (3.1% missing for ticagrelor vs. 2.6% for clopidogrel), vital status follow-up was not uncommonly limited to a checkbox that the patient was alive by phone on some date months after the last site visit. See also my CDTL Review Section 7.1.6.2.

Lack of Robustness of PLATO Superiority with Failure in the US Makes a Confirmatory Study Mandatory

Ticagrelor superiority to clopidogrel in PLATO was not robust. Besides failure in the US, superiority was only evident in the adjudicated results. For site-reported MACE the p value is 0.12. With checking of 3.7% of cases and correcting <1% of the endpoint assignments, the P value increases from <0.001 (AZ's PEP) to 0.027 (MACE with corrections). If the two outlier favorable-to-ticagrelor countries (Hungary and Poland)

are excluded, the ticagrelor MACE benefit is remote from statistical significance (P > 0.3). If all outlier countries, favorable and unfavorable to ticagrelor (Hungary, Poland, and the US), are excluded, the ticagrelor MACE benefit is also statistically insignificant (P = 0.078). Considering only the US the MACE endpoint is statistically significant (P = 0.03)—with the hazard ratio 1.43 unfavorable to ticagrelor. Mortality was also unfavorable in the US (hazard ratio 1.2) although not statistically significantly so. In the US subpopulation of PLATO clopidogrel was superior to ticagrelor.

Higher Rates of Other Thromboembolic and Ischemic Events with Ticagrelor Are Inconsistent with Lower MI Rates

While ticagrelor allegedly overall produced lower MI rates than clopidogrel in PLATO (although not in the US), virtually all other arterial thromboembolic and peripheral ischemic adverse event rates as reported by the sites were higher with ticagrelor than with clopidogrel as shown in Table 14.

Table 14: Rates of Patients with Site-Reported Peripheral Thromboembolic and Ischemic Adverse Events (except MI) in PLATO

adverse event	clopidogrel	ticagrelor	RR*
gastrointestinal ischemia	0.08%	0.04%	0.6
peripheral ischemia	0.82%	1.05%	1.3
claudication	0.43%	0.56%	1.3
amputation	0.10%	0.14%	1.4
pulmonary embolism	0.30%	0.44%	1.5
renal ischemia	0.00%	0.04%	
retinal ischemia†	0.06%	0.09%	1.3

* RR = relative risk ticagrelor:clopidogrel; †not adjudicated as strokes in PLATO

The one exception to higher peripheral thromboembolic and ischemic AE rates with ticagrelor is the rare gastrointestinal ischemia event; conversely, the rarest category (renal ischemia) was only reported for ticagrelor. The other relative risk estimates are reasonably consistent, i.e., 1.2-1.5. Note also that the relative risk for strokes (which I did not include in Table 14 because strokes were adjudicated separately in PLATO—and strokes may not be deemed "peripheral") is about 1.2 by both adjudicated and site-reported events. Rates of site-reported thromboembolic and ischemic adverse events, excluding MI, are higher with ticagrelor than clopidogrel in PLATO.

The following case demonstrates that these events could be extremely serious but were minimized: A patient with MI symptoms was hospitalized, randomized and started on ticagrelor, and underwent PCI with two right coronary stent placements. Following PCI on day 1 she developed bradycardia, advanced AV block, and hypotension treated with a temporary pacemaker until day 3, and ticagrelor was not withdrawn. She developed dyspnea on day 3 and thrombocytopenia (92,000) and gangrene on day 4 (she had a history of peripheral vascular disease) and was unblinded on day 4. Ticagrelor was stopped on day 6 because of thrombocytopenia (44,000) reported by the investigator related to ticagrelor and clopidogrel was given from days 7 to 14. She subsequently had an amputation of the right leg on day 13 and of the left leg on day 26. AZ reported the AV block as a SUSAR, which mentions the right leg amputation once and states that it

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"was captured as another case in safety database." The site reported gangrene as an SAE and it was adjudicated as an arterial thrombotic event. However, the SAEs reported by the site for the amputations were "inactivated" as "Data entered in error" more than 6 months after the events and initial data entry. They do not appear in the AZ NDA tabular listings or in the EVTLOG.XPT AE SAS dataset. AZ did not report them, the gangrene, or the thrombocytopenia separately as SUSARs.

These site-reported thromboembolic and ischemic adverse event rates are inconsistent with the adjudicated arterial thrombotic event rates: The adjudicated arterial thrombotic event rate (acute events with imaging confirmation) favor ticagrelor, i.e, 0.21% to 0.36%, RR 0.56. Many site-reported peripheral thromboembolic and ischemic events were not adjudicated, i.e., 128 ticagrelor patients with events not adjudicated vs. 88 clopidogrel patients. The reverse is true for events not reported as AEs but adjudicated as potential arterial thrombotic events, 14 ticagrelor vs. 25 clopidogrel. The differential submission-for-adjudication rates likely explain the discrepancy between site-reported and adjudicated event rates. I judge that the site-reported rates in PLATO reflect more accurately ticagrelor activity. I find it incongruous that ticagrelor had lower MI rates but higher rates for all other thromboembolic and ischemic events.

Data Collection and Reporting of Ticagrelor Events Was Flawed

Minimization of ticagrelor adverse events, as I document above for a patient with bilateral amputations, was not rare in PLATO. The following two cases also illustrate this problem:

- A ticagrelor patient had a PCI with stent on day 1 followed by hypotension and mild pulmonary edema. On day 2 he suffered bradycardia and complete AV block treated with a temporary pacemaker and resolving by day 6. On day 12 he was rehospitalized for "syncope (b) (6) before hospitalization, Ventricular tarchycardia, seizure,v-fib and Asystole after hospitalization"; ticagrelor was discontinued. Treatment included CPR, cardioversion, and an IABP. AZ did not report this event as a SUSAR nor was it submitted for adjudication as a possible cardiac ischemic event. After queries AZ did not provide any other clinical details regarding this event other than the minimal information quoted above. His last visit was on day 42 but AZ counts him as completing the study through day 391 without an endpoint.

- A ticagrelor patient had an AE of headache starting on day 1 and then was rehospitalized on day 10 with left foot weakness; ticagrelor was discontinued. After imaging an SAE was reported as "left anterior sylvian fissure abnormality". The investigator's verbatim description is not ominous but also does not define what the abnormality is: "headache pre-existing, routine MRI showed abnormality, pt hospitalized MRI showed abnormality, CT confirmed, CTA confirmed abnormality but no bleed, aneurysm." AZ did not report this event as a SUSAR nor was it submitted for adjudication as a possible stroke. After queries AZ did not provide any other clinical details regarding this event beyond the minimal information quoted above.

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We discussed these cases with AZ at a meeting and AZ stated that, despite ticagrelor being discontinued in each case because of the SAE, AZ did not report the cases as SUSARs because it was AZ's policy to rely upon the investigators' determinations of relatedness to study drug. In a written response AZ conveyed that it did not inform the DSMB specifically about these cases because the DSMB was "independent."

COMMENT: Note, however, that AZ did not submit the thrombocytopenia SAE in the case I describe above with bilateral amputations despite the investigator reporting it as related to study drug. Regardless, as I conveyed to AZ at the meeting, it is the sponsor's responsibility to make final determinations regarding the relatedness of SAEs for expedited reporting purposes. Furthermore, I find the limited data collection highly disturbing for these two patients who had SUSARs and potential endpoints. This pattern of failing to report and submit for adjudication suspicious events is the precise pattern I have seen with other problematic NDA submissions. I present other problematic cases later in this review.

Ticagrelor is Less Safe than Clopidogrel

Despite the evidence for underreporting of ticagrelor AEs, the available data are sufficient to conclude that ticagrelor is less safe than clopidogrel. Please see the primary safety reviewer's review for a more detailed discussion of ticagrelor safety issues. I show in Table 15 the non-thromboembolic AEs with rates differing between ticagrelor and clopidogrel.

Table 15: Non-Thromboembolic Adverse Event Rates by Patient Differing between Ticagrelor and Clopidogrel in PLATO

adverse event	clopidogrel	ticagrelor	RR*
bradycardia	4.04%	4.36%	1.1
dyspnea	8.78%	14.49%	1.6
bleeds			
intracerebral hemorrhage	0.22%	0.44%	2.0
GI bleed	2.90%	3.58%	1.2
SAE bleed	3.15%	3.95%	1.3
minor bleed or worse†	7.02%	8.91%	1.3
major bleed or worse†	3.19%	3.85%	1.2
gynecomastia	0.03%	0.19%	6.0
ventricular tach/fib	3.25%	2.94%	0.9

* RR = relative risk ticagrelor:clopidogrel; †not CABG-related

COMMENT: Bradycardia (and AV block and sinus arrests), dyspnea, and gynecomastia are AEs unique to ticagrelor among platelet inhibitors. While the PLATO data do not confirm that they are substantial problems, I remain concerned that the underreporting of AEs may have concealed some significant problems—two of the underreported SAEs I describe above both began with in-hospital AV block. The one class of AEs that appears to have lower rates with ticagrelor is ventricular arrhythmias. This observation, if real, could contribute to the lower reported death rate with ticagrelor. However, underreporting could also play a role for this observation.

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Non-CABG related bleeding rates were higher with ticagrelor. Hazard ratios of most types of bleeds ranged 1.2 to 1.3. The rates of intracerebral hemorrhages, however, were about double with ticagrelor compared to clopidogrel.

On the other hand, bleeding rates with CABG were only slightly higher for clopidogrel (relative risk about 1.05-1.1) while there was no clear difference in CABG bleeds by days since last study drug despite the alleged faster offset for ticagrelor (see the primary safety review.) This latter fact suggests that we do not understand completely the relationship between drug levels or in vitro tests and clinical effects for this new class of drug. I also do not consider it contradictory to have lower efficacy and more bleeding with ticagrelor: For a reversible inhibitor with greater variability in inhibition throughout the day, we might see more bleeding (at the peaks) and more thrombotic events (at the troughs.)

Bleeding Rates Do Not Support a Differential Contribution of ASA to Platelet Inhibition for Ticagrelor vs. Clopidogrel but Ticagrelor Has More Bleeding

AZ, to explain the alleged ticagrelor-ASA interaction regarding efficacy, proposes that ASA does not contribute to platelet inhibition with ticagrelor because of ticagrelor's superior platelet inhibition. AZ proposes that higher dosage ASA does enhance the weaker platelet inhibition achieved with clopidogrel. If AZ's hypothesis is true then we would expect enhancement of bleeding with clopidogrel and higher dosage ASA. Hence I analyzed the bleeding events similar to AZ's and my Cox regression analyses of CV outcomes. For the ASA dosages for bleeding I did execute one variation: We believe that we understand the mechanism of increased bleeding with platelet inhibition. We presume that bleeding is directly related to the platelet inhibition and subsides when platelet inhibition ceases. Hence I analyzed the ASA dosages in the ten days (average platelet life) prior to the event. I show the results of these Cox regressions below.

For the unadjusted results, i.e., only treatment as a factor, ticagrelor is associated with higher bleeding rates: hazard ratio 1.3 for minor or worse non-CABG bleeding, $P < 0.0001$; hazard ratio 1.2, $P = 0.012$ for major or worse. The risk factors (i.e., associations between baseline factors and the analyzed event) are different for bleeding than for CV outcomes, as would be expected. The ones that are significant in PLATO are predominantly ones that seem reasonable clinically, e.g., age, renal dysfunction, history of GI bleeding, early clopidogrel use. Males appear to be at lower risk of bleeding while diabetics and patients with a history of stroke are at higher risk. I show the Cox regression for non-CABG-related minor or worse bleeding in Table 16 and for major or worse bleeding in Table 17.

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Table 16: Cox Regression for Non-CABG-Related Minor or Worse Bleeding

```
No. of subjects =        18624              Number of obs   =      18624
No. of failures =         1474
Time at risk    =      5176287
                                            LR chi2(16)     =     780.93
Log likelihood  =    -13925.67              Prob > chi2     =     0.0000

------------------------------------------------------------------------------
        _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+------------------------------------------------------------------
1.ticagrelor |   1.331708    .0792808     4.81   0.000     1.185044    1.496525
      1.us |   1.467219    .6466224     0.87   0.384     .6185277     3.48041
           |
 ticagrelor#|
        us |
       1 1 |   .8277493    .1825409    -0.86   0.391     .5372619    1.275298
           |
    ageimp |   1.020876    .0032533     6.48   0.000      1.01452    1.027273
      male |    .803604    .0452502    -3.88   0.000     .7196341     .897372
   crcl0imp |   .9919641    .0010972    -7.29   0.000      .989816    .9941168
    gibldhx |   1.721566    .2803473     3.34   0.001     1.251153    2.368847
   1.strkhx |   1.706255     .270851     3.37   0.001     1.250041    2.328969
           |
    strkhx#|
 ticagrelor |
       1 1 |   .5904865    .1393681    -2.23   0.026     .3717982    .9378054
           |
   1.diabhx |   1.259176    .0793591     3.66   0.000     1.112859    1.424732
1.asabldmi~0 |   5.897198    .7602078    13.77   0.000     4.580546    7.592312
           |
    diabhx#|
asabldmi~300 |
       1 1 |   .5551964    .0866343    -3.77   0.000     .4089055    .7538246
           |
ticagrelor#|
asabldmi~300 |
       1 1 |   1.128324    .1816366     0.75   0.453      .823016     1.54689
           |
   clpearly |   1.239904    .0657879     4.05   0.000      1.11744    1.375789
   1.angpci |   1.954607    .1863459     7.03   0.000     1.621469     2.35619
           |
  angpci#us |
       1 1 |    .317512    .1365067    -2.67   0.008     .1367119    .7374182
------------------------------------------------------------------------------
```

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Table 17: Cox Regression for Non-CABG-Related Major or Worse Bleeding

```
No. of subjects =         18624              Number of obs    =       18624
No. of failures =           649
Time at risk    =       5386818
                                             LR chi2(16)      =      440.70
Log likelihood  =    -6089.9424              Prob > chi2      =      0.0000

------------------------------------------------------------------------------
        _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+------------------------------------------------------------------
1.ticagrelor |  1.247935    .111969     2.47   0.014     1.046693    1.487869
      1.us |  2.058825    1.141413     1.30   0.193     .6945651    6.102753
           |
ticagrelor#|
        us |
       1 1 |  .8894621    .2847843    -0.37   0.714     .4748902    1.665949
           |
    ageimp |  1.029267    .005034     5.90   0.000     1.019447    1.039181
      male |  .7119266    .0592003    -4.09   0.000     .6048581    .8379477
   crcl0imp |  .9910619    .0016948    -5.25   0.000     .9877458    .9943892
   gibldhx |  1.974879    .4503903     2.98   0.003     1.263036    3.087914
  1.strkhx |  1.930285    .4221671     3.01   0.003     1.257354    2.963366
           |
     strkhx#|
 ticagrelor |
       1 1 |  .5390068    .1811267    -1.84   0.066     .2789705     1.04143
           |
   1.diabhx |  1.440057    .1324731     3.96   0.000     1.202475    1.724578
1.asabldma~0 |  5.911776   1.177106     8.92   0.000     4.001598    8.733786
           |
     diabhx#|
asabldma~300 |
       1 1 |  .3988599    .0977683    -3.75   0.000     .2467029    .6448614
           |
ticagrelor#|
asabldma~300 |
       1 1 |  1.247407    .311107      0.89   0.375     .7650957    2.033763
           |
   clpearly |  1.352241    .1087297     3.75   0.000     1.155079    1.583058
  1.angpci |  1.776426    .2426562     4.21   0.000     1.359173    2.321772
           |
  angpci#us |
       1 1 |  .2634636    .1412537    -2.49   0.013     .0921205    .7535029
------------------------------------------------------------------------------
```

Note that in Table 16 and Table 17 I did include a post-randomization factor in the regressions, the variable angpci indicating a coronary angiography or PCI at any time during the study. I believe angpci is appropriate despite being post-randomization because coronary angiography and PCI are not used to treat bleeding. Regardless, the regressions are similar if I substitute the closer to baseline variable angiography or PCI within the first 24 hours.

Bleeding rates are clearly higher with ticagrelor, i.e., hazard ratios 1.2 to 1.3. Higher ASA dosage is also associated with more bleeding, but for these analyses including PCI-related bleeds ticagrelor does not appear to interact with ASA dosage. Diabetics, on the other hand, do seem to show lower rates of bleeding with increased ASA dosages than non-diabetics as might be expected from their decreased platelet responsiveness to ASA.

The US was associated with lower rates of both minor and worse and major bleeding particularly in association with a procedure. One possible explanation is that US

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practitioners tend to delay giving P2Y$_{12}$ inhibitors until after they elucidate the coronary artery anatomy by angiography, a delay that likely also reduces catheter insertion-related bleeding. However, note that procedure-related bleeding likely was not recorded reliably in PLATO—see my discussion under PLATO Study Design, Conduct, and Submission Problems Destroy Confidence in the Validity of the Results, Recording of bleeds was incomplete. US investigators may have considered more procedure-related bleeds to be "expected" than OUS investigators and hence failed to record the "expected" ones.

About 57% of the major non-CABG bleeds occurred within the first 30 days while 75% of the patients having angiography or PCI had one within the first 24 hours, 97% within the first 30 days. Hence I analyzed early major bleeding rates in relationship to angiography and PCI. I show the Cox regression for major bleeding within 30 days in Table 18 and for major bleeding with 3 days in patients not having CABG or a PCI later than day 1 in Table 19.

Table 18: Cox Regression for Non-CABG-Related Major or Worse Bleeding through Day 30

```
N No. of subjects =          18624              Number of obs   =      18624
No. of failures =            371
Time at risk    =         529753
                                                LR chi2(16)     =     348.54
Log likelihood  =   -3463.4949                  Prob > chi2     =     0.0000

------------------------------------------------------------------------------
        _t | Haz. Ratio  Std. Err.      z    P>|z|    [95% Conf. Interval]
-----------+------------------------------------------------------------------
1.ticagrelor |   1.1497   .1415155    1.13   0.257    .9032565    1.463384
      1.us |  1.259047   .7223845    0.40   0.688    .4089411    3.876351
           |
ticagrelor#|
        us |
       1 1 |   .835486   .3494276   -0.43   0.667    .3680771    1.896442
           |
    ageimp |  1.027946   .0066051    4.29   0.000    1.015082    1.040974
      male |   .536453   .0579638   -5.76   0.000    .4340695    .6629856
   crcl0imp |  .9907323   .0022357   -4.13   0.000     .98636     .995124
   gibldhx |  1.594617   .5397175    1.38   0.168    .8214044    3.095679
  1.strkhx |  1.931549    .542205    2.35   0.019    1.114204     3.34847
           |
    strkhx#|
 ticagrelor|
       1 1 |   .64173   .2681831   -1.06   0.288    .2828979     1.45571
           |
  1.diabhx |  1.507959   .1893407    3.27   0.001    1.178995    1.928711
1.asabm30g~0 |    5.734   1.316717    7.61   0.000    3.655894    8.993356
           |
    diabhx#|
asabm30ge300 |
       1 1 |  .4022727   .1156053   -3.17   0.002     .229035    .7065441
           |
 ticagrelor#|
asabm30ge300 |
       1 1 |  1.488305   .4159341    1.42   0.155    .8606129    2.573806
           |
1.angpci~24h |  1.863176   .2304037    5.03   0.000    1.462153    2.374187
           |
 angpcilt24h#|
        us |
       1 1 |  .3089478   .1697757   -2.14   0.033    .1052266    .9070782
           |
   clpearly |  1.628078   .1746672    4.54   0.000    1.319334    2.009074
------------------------------------------------------------------------------
```

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Table 19: Cox Regression for Major or Worse Bleeding through Day 3, Patients with or without a PCI Day 1 but No CABG or Subsequent PCI through Day 3

```
No. of subjects =          17326          Number of obs   =      17326
No. of failures =            198
Time at risk    =          51380
                                          LR chi2(14)     =     268.28
Log likelihood  =   -1796.7192            Prob > chi2     =     0.0000

------------------------------------------------------------------------------
         _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
1.ticagrelor |   1.021005    .183703     0.12   0.908     .7175904    1.452711
        1.us |   2.694739   2.269022     1.18   0.239     .5173551    14.03605
             |
ticagrelor#  |
         us  |
         1 1 |   1.054318   .5704331     0.10   0.922     .3651182    3.044456
             |
      ageimp |   1.016159   .0086518     1.88   0.060     .9993426    1.033259
        male |   .4140924   .0613686    -5.95   0.000     .3097055    .5536632
     crcl0imp |  .9882566   .0030365    -3.84   0.000     .9823231    .9942259
      strkhx |   1.650173   .4781308     1.73   0.084     .9351848     2.9118
    1.diabhx |   1.602647   .3016914     2.51   0.012     1.108161    2.317784
1.asabm3ge~0 |   5.41614    1.407695     6.50   0.000     3.25429     9.014123
             |
     diabhx# |
  asabm3ge300|
         1 1 |   .3686947   .1270771    -2.89   0.004     .1876227    .7245168
             |
ticagrelor#  |
  asabm3ge300|
         1 1 |   1.632011   .5206835     1.54   0.125     .8732775    3.049959
             |
1.angpci~24h |   4.156474   .9488947     6.24   0.000     2.657061    6.502024
             |
angpcilt24h# |
         us  |
         1 1 |   .1275971   .1006355    -2.61   0.009     .0271957    .5986618
             |
    clpearly |   1.514105   .2216086     2.83   0.005     1.136506    2.017159
------------------------------------------------------------------------------
```

The short term bleeding results are consistent with the long term bleeding results. They do demonstrate the risk of doing an invasive procedure more clearly and that the procedure-associated risk appears to be lower in the US—or US sites reported procedure-related bleeds less frequently. The relationships between diabetes, ASA dosage, and bleeding are very consistent.

COMMENT: These data do not support AZ's ticagrelor-ASA interaction hypothesis. Higher dose ASA is associated with more bleeding for both clopidogrel and ticagrelor. If anything the bleeding rates are worse with ticagrelor and higher dose ASA rather than being worse with clopidogrel as AZ's ticagrelor-ASA interaction hypothesis predicts. These analyses do confirm that, for bleeding, ticagrelor is less safe than clopidogrel.

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PLATO Study Design, Conduct, and Submission Problems Destroy Confidence in the Validity of the Results

PLATO had many study design and conduct problems and its NDA submission has also been problematic. I have discussed some of these problems in my CDTL Review and others elsewhere in this review. The following is a consolidated list, with numbers in parentheses referencing the section numbers from my CDTL Review:

- PLATO was multiple studies in one attempting to address excessively heterogeneous populations (7.1.6.1.1). Addressing this heterogeneity is the justification for using the multivariable Cox regressions in this review.

- PLATO recommended inappropriate restrictions on statin dosages, failed to collect statin dosages, and failed to collect lipid levels on most patients. (7.1.6.1.2) Note that there is a significant favorable interaction between ticagrelor and baseline (or on study) statin use. While some reviewers have questioned the clinical plausibility of this interaction and (like any non-randomized association) the correlation could be spurious, I believe that the interaction can not be ignored and that it raises further questions about the validity of a pure ticagrelor mortality benefit.

- PLATO allowed immediately pre-study clopidogrel making extrapolation of trial results to the label difficult. See "Pre-Study Clopidogrel Is Inconsistent with the Proposed Labeling" above.

- PLATO was easy to unblind by breaking open a clopidogrel/dummy clopidogrel tablet. (7.1.6.1.3) Furthermore, AZ was misleading in its initial NDA submission regarding the extent of unblinding in PLATO. The data sets initially submitted indicated that only 32 patients had been unblinded at the sites. Because I identified a patient not included in the 32 whose AE report stated that the patient had been unblinded, I queried AZ and learned that the 32 patients were ones unblinded through the IVRS system; unblinding was possible through other AZ systems. An updated dataset lists 452 patients as unblinded prior to database lock. Additionally, four groups within AZ and two contractors had treatment codes. I do not have confidence that the blind was maintained in PLATO.

  Maintaining the blind was not the only unblinding (or randomization list) issue in PLATO. I queried AZ regarding 26 patients who had been unblinded for SUSAR reporting but for whom AZ did not distribute SUSAR reports. For one of these patients AZ responded that they had not distributed a SUSAR because the patient had been "Unblinded to clopidogrel". When I queried AZ why this latter patient was unblinded to clopidogrel but was assigned to ticagrelor in all NDA data sets, AZ responded that "it has been determined that this subject was unblinded in GRand to ticagrelor (treatment A) and due to a transcription error the study treatment was entered into Sapphire as clopidogrel." We have no way of verifying whether this case represents a human transcription error or manipulation of the randomization list. I do note that for the ten patients randomized immediately before and after this one the randomization was 8:2 ticagrelor: clopidogrel and for the surrounding 20 patients 14:6. These ratios suggest that the more likely assignment is clopidogrel.

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COMMENT: If we don't have confidence in the treatment assignments we can't have confidence in the study results. This case illustrates why I and others in DCRP have been advocating that sponsors submit an encrypted randomization list prior to the start of any phase 3 trial and submit the encryption key with the NDA. Having a copy of an indisputably original randomization list would enable us to resolve this type of problem unequivocally.

- Recording and handling of dates and times, always problematic in clinical trials, was particularly problematic in PLATO and appears biased. The examples are as follows:

  - AZ frequently projected censoring dates way beyond actual follow-up, creating the impression of good follow-up (see General Analytical Issues, 1. Censoring above.)

  - AZ eliminated three ticagrelor primary endpoints based on misrecordings of dates or time (see General Analytical Issues, 3. Adjudication above.)

  - PLATO did not collect times for pre-study clopidogrel while randomization, initial study drug, and PCI times were recorded inaccurately, making analyses of timings of antiplatelet therapy and its relationships to early PCI and outcomes impossible (see Ticagrelor-ASA Interaction Is Not Significant for PLATO Long Term Mortality but Other Interactions Are, Comment.)

  - There appear to be unusual distributions of potential endpoint dates by treatment around the times of the AZ projected censoring dates. I show these distributions in Figure 1.

Figure 1: Counts of Site-Reported Endpoints (Excluding Adjudicated Deaths) Relative to the AZ Projected Censoring Dates by Treatment

Graphs by rx

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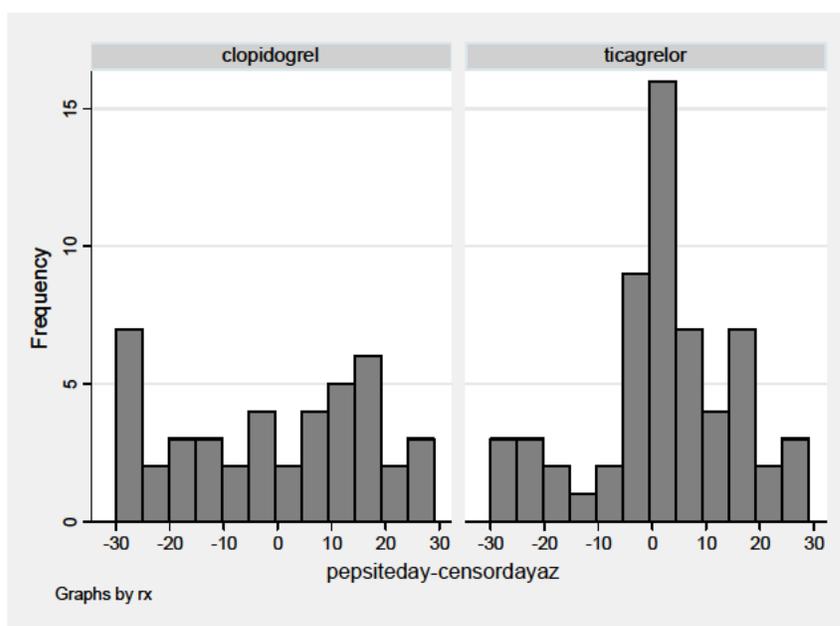
I exclude adjudicated deaths because the date of death is the AZ censoring date. The distribution for clopidogrel appears more uniform while that for ticagrelor appears to be skewed to the right, i.e., more events reported after the AZ censoring date.

Note the AZ's censoring day is not necessarily close to the last study drug day. Both AZ and I have examined events following study drug cessation. Both of our analyses suggest that, while events occurred slightly earlier following ticagrelor discontinuation compared to clopidogrel, within a week the rates of events had converged. However, there is a significant limitation for the estimates of event rates following withdrawal illustrated by this patient:

- A clopidogrel patient had last study drug on day 273. On day 277 he experienced ventricular tachycardia, on day 278 chest pain, and on day 283 he arrested. AZ did not send these events for adjudication.

COMMENT: I could detect this likely endpoint because the AEs were recorded. If sites were discouraged from even recording events after study drug discontinuation, then the analyses of withdrawal event rates are completely unreliable and the problem is undetectable.

Note also that this patient was a clopidogrel patient. I identified and evaluated problem cases without reference to the treatment assignment. I do find that the majority of extreme problem cases appear to favor ticagrelor (26 of 30).

o Individual patients also had suspicious time recordings: A ticagrelor patient was randomized at 11:09, received first study drug at 11:20, and then had an urgent angiography at "12:00". Relatives allegedly withdrew consent on day 1 because "patient no longer responsive after surgery" but the surgery is not described and the time of withdrawal is recorded as "12:00". Some additional information was collected, including a multiorgan failure SAE and a sudden death on day 18 that were "inactivated", although the death was adjudicated as unknown—CV by AZ's rules. AZ censored the patient on day 1 with no endpoints.

COMMENT: Besides the inconsistent times, this patient also illustrates the most frequent cause for missing data in recent clinical trials: withdrawal of consent. For this case, by the description, the patient has already suffered an event, i.e., "no longer responsive after surgery", before the relatives withdrew consent. There is no justification for censoring this patient with no endpoints.

In PLATO allegedly about 2.9% of patients withdrew consent, 47 more ticagrelor than clopidogrel patients. However, patients also discontinued treatment as "not willing" and these patients frequently had minimal subsequent follow-up as several examples in this review document. About 9.6% of patients discontinued as "not willing", 87 more ticagrelor

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patients than clopidogrel patients. The sum of the differences in these patient categories with "missing" data is 134, close to the difference in AZ's primary endpoint (147).

- Recording of bleeds was incomplete. If an investigator checked on the AE form that an event was a bleed and checked that "Bleed is related to a procedure and does not represent an adverse event", then he could not enter the severity of the bleed (minimal, minor, major, etc.) and he was not to complete the rest of the AE form. The AE form states boldly "**NB**: Per protocol bleeding associated with a procedure should not be reported as an AE if it is expected for the procedure." There is no guidance on the form about what is "expected" for the procedure. On the AE form there is also a "CABG related" checkbox in line with the "Bleed is related to a procedure ..." checkbox and the minimal, minor, major, etc. severity checkboxes. However, for CABG-related bleeds the investigator was to complete the rest of the AE form. In addition, the eCRF system automatically created a bleed event form for all CABG forms.

COMMENT: Recording of procedure-related, i.e., PCI-related bleeds, is likely to be incomplete in PLATO—and we have no idea of how incomplete. On the other hand, recording of CABG-related bleeds should be complete. I hypothesize that this very peculiar bleed recording approach may be related to expectations about the bleeding pattern with ticagrelor: Being a "better" platelet inhibitor, we would expect to see more PCI-related bleeds (as was seen with prasugrel.) But, with a supposedly faster offset, we would expect less CABG-related bleeding with ticagrelor compared to clopidogrel. The peculiar bleeding recording should minimize the greater expected PCI-related bleeds and maximize the expected fewer CABG-related bleeds with ticagrelor. The PLATO results, however, show more PCI-related with ticagrelor, as documented elsewhere in this review, but they do not confirm substantially lower CABG-related bleeds (see the primary safety review.)

- Follow-up was incomplete. (7.1.6.3 and 8.2) See also the discussion above under "Poor PLATO Follow-up Precludes Confidence in the Long Term Results."

- AZ failed to submit potential endpoint events for adjudication. Some examples are the following:

  - The first patient described under General Analytical Issues, 1. Censoring, above was a ticagrelor patient with multiple SAEs including an "unspecified neurologic problem" post-CABG that could be a stroke.

  - The two ticagrelor patients described in Data Collection and Reporting of Ticagrelor Events Was Flawed are examples of both unreported SUSARs and potential endpoints not submitted for adjudication.

  - A ticagrelor patient was hospitalized on day 22 with a coronary thrombosis. A troponin T was reported as >5x and an echo showed hypokinesis of the inferior wall with ejection fraction 55%. No other information on symptoms, physical findings, lab, treatment (of this event, prior concomitant medications are listed), or hospital course are provided.

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AZ unblinded the patient as a SUSAR but did not distribute the SUSAR because the investigator indicated the event was unrelated to study drug. AZ did not submit the event for adjudication.

COMMENT: I detected this case after requesting AZ to supply Medwatch forms for 26 ticagrelor cases reported as unblinded for expedited reporting but for whom AZ had not submitted Medwatch forms to the IND or the NDA. AZ initially submitted to the NDA only Medwatch forms for the 201 patients for whom Medwatch forms had previously been reported expeditely to the IND. There are about 2133 PLATO ticagrelor patients who suffered one or more SAEs. If the rate of unadjudicated endpoints is the same for the other unreported SAEs, then we would expect to identify (1/26)*(2133 – 201 – 26) = 73 additional primary endpoints in ticagrelor patients. The 95% upper confidence limit for this estimate is 373. The latter number dwarfs the difference between treatment arms in the AZ primary endpoint (147). This case also suggests that AZ's apparent reluctance to provide complete CRFs, including SAE forms and other clinical records, is based on a desire to conceal negative data regarding ticagrelor. See the further discussion of submission problems below.

The scanty information AZ alleges to have collected on this SAE as well as many others, e.g., the "unspecified neurologic problem", the "left anterior sylvian fissure abnormality", the "syncope ... seizure ... asystole", the thrombocytopenia with bilateral amputations (all described elsewhere in this review), is appalling. Literally this submission is the worst submission I have encountered for collecting—or at least submitting— information on SAEs. We can have little confidence that we understand the AE profile of ticagrelor and, as this example illustrates, its efficacy as well. We should also be highly concerned regarding whether AZ is executing adequately its primary responsibility of protecting the safety of participants in its clinical trials.

o A ticagrelor patient had a "suspicion of stroke" AE and ICH bleeding event "inactivated" almost one year after the event and not adjudicated. See the description of this case under Incomplete Submission below.

o A ticagrelor patient had an inferior wall MI AE on day 1 and a recurrent cardiac ischemia AE on day 2 inactivated because they were supposed to be recorded as cardiac ischemic events and not AEs. However, the site did not submit cardiac ischemic event forms for these events and AZ did not follow-up on them or submit them for adjudication.

o A ticagrelor patient had a scheduled visit on day 91 then suffered an NSTEMI on day 96. The last study drug day was day 97 and the patient withdrew consent on day 97. An NSTEMI SAE was "inactivated" and AZ did not submit the NSTEMI event for adjudication.

o A ticagrelor patient had ventricular fibrillation, hypotension, and arrest on day 9 that were not adjudicated.

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COMMENT: Non-adjudication of arrests was a problem in PLATO. An early arrhythmia, e.g., a reperfusion arrhythmia, may lead to an arrest that does not represent a cardiac ischemic event. Hence PLATO investigators were to submit for adjudication arrests that they judged to be cardiac ischemic events. How they judged arrests to be cardiac ischemic events is not defined.

   o A ticagrelor patient had the sudden onset of shortness of breath and chest pain on day 134 and was hospitalized for 6 days with ECG changes, with biomarkers done but not reported. AZ did not submit the event for adjudication but counts the patient as event free through day 301.

COMMENT: Not submitting suspicious events for adjudication is a pattern I have seen in other problematic submissions, e.g., the rosiglitazone RECORD study. It can enable a sponsor to manipulate the endpoints while proclaiming that a blue ribbon academic research organization adjudicated events fairly blinded to treatment assignment. Central adjudication facilitates having one control point so that one individual alone can potentially bias the results of the entire study. A related problem is incomplete adjudication packages, which I discuss next. The potential for biasing adjudications by one control point is, in my opinion, the major problem with central event adjudication for clinical trials today.

- Another problem with adjudication is completeness of adjudication packages. Unfortunately we have no good way of verifying that adjudication packages contained all data collected at the sites and that reasonable attempts were made to insure their completeness. Biomarkers for MI adjudication are particularly problematic because appropriate biomarker changes are required for adjudication of most MI events and omitting even one value (e.g., a return to normal) can change the adjudication. The following are some examples of problems with completeness of adjudication packages:

   o An adjudication form for a ticagrelor patient was not submitted for adjudication nor with the initial NDA submission. See the "suspicion of stroke" case under Incomplete NDA Submission below.

   o A ticagrelor patient on day 8 had chest pain, called an AMI by the site, and a stent thrombosis on angiography. No biomarkers or ECGs were provided and the event was adjudicated as severe recurrent ischemia, not an MI.

   o A ticagrelor patient was hospitalized on day 68 with ischemic chest pain, and ST changes and had an angiography showing three vessel disease and vein graft ostium obstruction. He had an AE of ventricular fibrillation. No biomarkers were reported and the adjudication was recurrent ischemia.

   o A ticagrelor patient day 3 had chest pain, new ST elevation, an urgent cath and then CABG. The event was adjudicated not an MI because, while troponins were elevated, CK-MB values (required by the adjudication rules) were not reported.

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- A ticagrelor patient arrested day 4 during closing of a CABG. No biomarkers were collected.

COMMENT: The current effort to create standardized definitions for cardiac events actually accentuates this problem. Because events not uncommonly occur remote from the investigator's control, the detailed biomarker, ECG, and imaging collections specified by the standard definitions are frequently not collected in practice or not obtainable. Incomplete biomarker reporting is frequently problematic even for events with the investigator in attendance. Adjudication remains an exercise in interpretation of missing data—and one that can be biased.

- The NDA submission has been incomplete and problematic. At the pre-NDA meeting on April 20, 2009, AZ agreed to the following:

  - "Your narratives appear to be based only on the data in the case report forms. We expect narratives to be based on all available information including narratives and hospital documents submitted by investigators. Please also submit case report forms as required by FDA regulations. Case report forms include all clinical information communicated from investigators to you or your contractors regardless of whether a document is labeled a "case report form"—e.g., a "serious adverse event worksheet" or a Medwatch form is a case report form. Endpoint adjudication packages should also be included with the case report forms. ... Case Report Forms (CRFs) would also be provided for deaths and SAEs. ... The sponsor assured the Division that all information in the clinical database was the same as that on the Medwatch."

  - "We expect study data in electronic format will include all data entered from the case report forms."

  - "Please provide a dataset documenting the audit trail for any values amended from the investigator's initial data entry."

All of these agreements have proved problematic. The one for which AZ clarified the minutes, likely correctly, in a letter dated July 22, 2009, was the requirement regarding for which patients to submit CRFs. AZ also clarified the discussion regarding providing information on unblinding:

  - "Case report forms (CRFs) will be submitted as required for each patient who died during a clinical study or who permanently discontinued study treatment because of an AE, whether believed to be drug related or not, including patients receiving reference drugs or placebo."

  - "The sponsor agreed to provide a by-subject listing whether patients were unblinded, the date of unblinding, reason for unblinding, whether included in the safety population (Y/N), and whether included in the efficacy population (Y/N). This additional PLATO variable will be provided for subjects randomized and unblinded at the investigator site prior to database lock."

In the NDA submission AZ appears to have ignored these agreements. The initial submission did not include all clinical documents, including Medwatch forms and endpoint adjudication packages, with the CRFs. It did include an audit trail and unblinding information that, while appearing and represented as complete, later proved to be substantially incomplete. The problems are the following:

- o Few Medwatch forms with sparse data. After a December 2009 teleconference at which the lack of Medwatch forms was discussed, AZ submitted in NDA Serial 007 dated December 18, 2009, only the Medwatch forms that were previously submitted to the IND as 7 or 15 day reports. AZ submitted them to provide assurance that "that all information in the clinical database was the same as that on the MEDWATCH form." The December 18, 2009, submission only includes Medwatch forms for 201 ticagrelor patients—compared to 2133 ticagrelor patients with SAEs and 690 ticagrelor patients classified discontinuing for an AE. (Likely 2 to 3 times as many patients actually discontinued for an AE because many patients experiencing an AE discontinued for withdrawal of consent or other reason.) While these initial Medwatch submissions did prove highly problematic, I later requested 26 additional Medwatch forms for 26 ticagrelor patients whom AZ had unblinded for expedited reporting but for whom AZ had not submitted expedited reports to the IND. Of these 26, one raised an issue regarding the randomization assignment and another provided data not available in the CRFs confirming a missed primary endpoint for a ticagrelor patient.

- o Incomplete case report forms. The submitted CRFs did not include the Medwatch forms, adjudication packages, and all clinical information as discussed at the pre-NDA meeting. AZ did submit in separate files adjudication packages for a different subset of patients. The submitted electronic CRFs (eCRFs) did include an audit trail section, and both the main subsections and audit trail appear complete to even a thorough review of them in isolation. However, besides the lack of detail information on SAEs, the adjudication packages and CRFs proved incomplete in other ways.

  Regarding adjudication packages AZ did not provide all adjudication forms but only those "applicable" as described in this example:

  - • A ticagrelor patient had an AE of a "according to MR there is a suspicion of stroke in the respiratory center" and a corresponding ICH bleeding event "inactivated" almost one year after the event and not adjudicated. When I queried AZ regarding this patient, they supplied an Investigator Assessment and Narrative Form that helped clarify the alleged reason for deleting this event—but the form had not been submitted previously with the CRFs and adjudication package for this patient. When I queried AZ further regarding the reason for omitting this CRF, AZ responded that "this form was provided when a hospital discharge summary was not available or did not completely summarize the information for

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The CRFs are even more problematic because of the various ways investigator entries could be "inactivated" or "soft deleted" or deleted by a "work order" to the vendor. One example is the following:

- The ticagrelor patient who was unblinded and not reported in the initial NDA submission as unblinded had the following SAE on day 3: "during planned pci the cardiologist wanted to know the treatment because the rca artery was thrombosed on a long distance the patient got 3 stents back to back --the patient was unblinded" (the latter statement being the reason why I caught the unblinding.) The patient discontinued study drug day 3 and had no visits after visit 2 (day 31). The patient was reported alive by phone call on day 325 with no other details. AZ counts this patient as endpoint free through day 301.

  The AE was apparently "inactivated" as an SAE and the inactivation was provided in the third version of the CRF audit trail submitted to the NDA. However, the inactivation was not recorded in the Audit section of the CRFs, generated on 24 Apr 2009, submitted in with the original NDA. After I queried AZ about this inactivation, they provided more complete CRFs, dated 12 May 2009, that did include the inactivation.

COMMENT: I do not understand why AZ did not submit the more complete CRFs, available long before NDA submission with the original NDA submission. I can see no justification for AZ selecting adjudication forms or CRFs to submit when we requested and they agreed to providing all clinical information. I fear that the only reason for not submitting complete data is to minimize problems and our ability to detect them.

o Incomplete audit trails. The initial audit trail file submitted was large (15 gigabytes) and appeared complete, in addition to assurance from AZ that it was. However, after reviewing many CRFs I encountered some in which AEs were "inactivated ... in error" and not included as deletions. I requested and AZ supplied an additional audit trail recording these inactivations. Many of these "inactivations" concealed critical data—do a search on "inactivat" in this review to see examples of the problems.

Furthermore, even having "inactivations" proved incomplete because entries could also be "soft deleted" by a "work order" to the vendor. While I requested and obtained descriptions of the "work orders", I have not had sufficient time—nor do I believe that it should be the FDA's responsibility—to sort out whether all "inactivations" and "soft deletions" and "work order" changes are appropriate.

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COMMENT: AZ used a commercial eCRF system for PLATO. While the system is allegedly Part 11 compliant, our difficulties with the PLATO eCRFs should be convincing that eCRFs as currently implemented are far from ideal. I and the other reviewers found the eCRFs difficult to review, particularly because they do not provide the clues regarding investigator uncertainties such as changes or marginal notes. At this time I am still not sure that we have complete copies of the original investigator entries as we requested at the pre-NDA meeting.

- o Incomplete unblinding data sets. Please see bullet 4 under PLATO Study Design, Conduct, and Submission Problems Destroy Confidence in the Validity of the Results for my discussion of the problems with the unblinding data sets.

COMMENT: This NDA submission is the worst in my experience regarding completeness of the submissions and the sponsor responding completely and accurately to requests. At this time after thousands of man-hours of review and 88 NDA submissions I believe that we still have incomplete CRFs, incomplete data sets and audit trails, and only a few hundred scanty safety reports. I do not have confidence from this submission that we sufficiently understand ticagrelor safety or efficacy.

A Ticagrelor-ASA Interaction Is Not Supported by Nonclinical Findings

The pharmacology and toxicology reviewer, Dr. Elizabeth Hausner, summarizes AZ's ticagrelor-ASA interaction hypothesis as follows: AZ proposes that ticagrelor plus a low dose of ASA is beneficial while increasing doses of ASA in combination with ticagrelor produce adverse effects. Ticagrelor, having nearly complete $P2Y_{12}$ blockade does not show the added antiaggregatory benefit from ASA that is seen with clopidogrel. The partial and variable $P2Y_{12}$ blockade seen with clopidogrel derives more benefit from ASA with less display of adverse effects. This hypothesis distinguishes between ASA-mediated effects in platelets versus in endothelial cells in the vessel wall; that is, in platelets, ASA's inhibition of COX-1 causes a decrease in thromboxane A2 formation, decreasing platelet aggregation. However, at higher doses, ASA also blocks the COX-2–mediated production of the vasodilator prostacyclin, causing an increase in vascular resistance.

She summarizes AZ's mechanistic studies as follows: AZ compared ticagrelor and prasugrel active metabolite alone and in combination with ASA. The *in vitro* platelet results indicated that the addition of either low dose (30 μM) or high dose (120 μM) ASA enhanced the platelet inhibitory effect when $P2Y_{12}$ inhibition was partial, but not when $P2Y_{12}$ inhibition was complete. Further, no additional platelet inhibition was seen under either partial or complete $P2Y_{12}$ inhibition when ASA was increased from 30 μM to 120 μM. This suggests that there is no difference in effect between the two drugs at the level of the platelet.

AZ conducted a study in anesthetized dogs in an attempt to show vascular effects secondary to inhibition of prostacyclin production. The study showed no difference

between ticagrelor + ASA compared to clopidogrel + ASA or ASA alone when absolute blood flow is examined. Published studies for other drugs, including aspirin, have confirmed the inhibition of vascular PGI_2 by demonstrating elimination of vasodilation in response to locally administered arachidonic acid. For vasoactive drugs, a challenge by arachidonic acid produces small but measurable difference in vasodilation or blood flow. For femoral arterial studies, femoral artery pressure is measured as a crosscheck for establishing that flow is due to vasodilation. AZ's dog study did not include a local vasoreactivity challenge, measurement of femoral artery pressure or concurrent controls. When the inherent variability of the test system is added to the lack of controls, challenges, and essential measurements, it becomes difficult to interpret the study with confidence.

Dr. Hausner concludes: "In summary, there is no clear explanation why aspirin's proposed inhibition of endothelial prostacyclin is able to outweigh ticagrelor's, but not clopidogrel's, beneficial effects of TXA2 inhibition, platelet inhibition, and interactions with phosphodiesterase isoforms."

COMMENT: My understanding of AZ's hypothesis is the same as Dr. Hausner's, i.e., that ASA adds to the lower platelet inhibition produced by clopidogrel but not to the greater platelet inhibition produced by ticagrelor and that at higher ASA dosages ASA's blocking of COX-2 mediated production of the vasodilator prostacyclin produces vasoconstriction only manifest in ticagrelor patients. The latter proposal is one of the two major weaknesses in AZ's hypothesis: I have not seen a clear explanation of why the reduced prostacyclin vasoconstriction should be relevant only to ticagrelor or that it is a clinically important mechanism in humans. The other major weakness is that the in vitro platelet aggregation assay results aren't consistent with the clinical bleeding rates in PLATO, for which higher ASA dosage is associated with more bleeding and likely more additive effect upon bleeding with ticagrelor than with clopidogrel. Finally, the only endpoints for which ticagrelor and higher dosage ASA produces worse results are the AZ primary and MACE endpoints. For mortality and short term endpoints there is no ticagrelor-ASA interaction. I see little support for AZ's ticagrelor-ASA interaction hypothesis.

A Ticagrelor-ASA Interaction Is Not Robust Statistically

The statistical reviewer, Dr. Jialu Zhang, focused on the relationship between concurrent use of aspirin during the PLATO trial and the regional treatment effect of ticagrelor compared to clopidogrel. She notes that a total of 13 different ASA definitions and 6 imputations were proposed and analyses were performed in a number of Cox proportional hazards models under these scenarios. She describes the "dataset was reproducible" (but I comment on this below.) Almost all ASA definitions under worst case scenario failed to suggest a significant treatment-ASA interaction. ASA doses calculated based on the first 30 days of ASA did not show much of treatment-ASA interaction when only looking at the first 30-day primary events. There appeared some degrees of consistency as shown using certain definitions and imputations.

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The justification for these prior observations is Table 2 from her review, which I have reproduced as my Table 20 below.

Table 20: Statistical Reviewer's Table 2 – Analysis Sets by Imputation Methods Showing Significant Ticagrelor-ASA Interactions in Green

	M1	M2	M3	M4	M5	M6
A1	green			green		green
A2	green	green		green		green
A3	green	green		green		
A4	green	green	green	green		
A5	green	green	green	green		
A6	green	green	green	green		
A7	green	green	green	green		
A8						
A9	green					
A10						
A11	green	green	green	green		
A12	green	green	green	green		
A13						

Dr. Zhang's review lists the details of various sets and imputations but the ones relevant to her comments are that A8 to A10 are the 30-day results and M5 and M6 are the worst case imputations of missing values. Additionally, A13 is the last daily dose taken prior to the event or censoring for events after 30 days.

COMMENT: I assert that A13 (the last daily dose) is the one most relevant to the AZ nonclinical mechanistic studies. Note that it shows no significant ticagrelor-ASA interactions regardless of the imputation method.

She observes that there appeared a consistently adverse trend for ticagrelor with high dose of ASA in US, while there did not in OUS. The treatment effect of ticagrelor was not so adverse compared to clopidogrel in US during the first 30 days (HR=1.06 in US). The divergence between US and OUS became more obvious in the later events (HR=1.53 in US and HR=0.77 in OUS).

She examined the potential treatment-ASA interaction in the TRITON study comparing prasugrel to clopidogrel. She did not find such an interaction between treatment effect and ASA.

She summarizes: "In summary, imputation methods and whether to include the first day loading dose seem to have the most impact on suggesting whether there is a significant treatment-ASA interaction. Various ASA definitions appear to demonstrate some

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degrees of consistency in analyses. These analyses are still limited by the fact that there were only a small number of high ASA dose subjects in OUS. It remains a concern whether ASA is truly the only factor that might affect the ticagrelor effect, as there appeared no such an interaction in TRITON study."

COMMENT: While I agree with the basics of her overall summary, I find other evidence that our confidence in a ticagrelor-ASA interaction should be minimal. In particular, her comment that the "dataset was reproducible" is not sufficient for concluding that AZ's analyses are reasonable. I have identified several problems with the AZ ASA classifications that I describe below. Finally, I am disappointed that Dr. Zhang did not comment on the most critical problem regarding statistical inferences from the ticagrelor-ASA analyses: ASA dosage is a wildly post-randomization factor. I present the implications of this fact below.

The Ticagrelor-ASA Interaction Is Significant for AZ's Primary Endpoint and MACE but a Spurious Correlation Can Not Be Ruled Out

AZ's proposed ticagrelor-ASA interaction suffers from many problems: the definition is not obvious; the determination is uncertain in many patients; the interaction is not consistent for various definitions and for different endpoints and timepoints; and the interpretation is flawed. I elaborate upon each of these problems below.

That the definition is not obvious should be obvious: What summary statistic of ASA dosage is correct: The mean? The median? The maximum? Over what time interval? The entire period? The last 10 days? The last dose? Should loading doses be included? How should "missing" data be handled? AZ had all of these variations to consider--and analyze the effects thereof--before choosing one. It should not be surprising that they can find one, or more, that are "significant". The definition of ASA dosage is completely *post hoc* and derived after the study was unblinded and analyzed.

Besides the definition not being obvious, there are problems with the AZ determinations of ASA dosage. I found that they had miscoded some drugs: carbasalate (a calcium salt of acetylsalicylate used in Europe), Anoprin (miscoded to chlorphenamine), and "inj loparin" (enoxaparin) miscoded to ASA. When I informed AZ and asked them to correct their analyses, their response was that the corrections "would not impact overall conclusions."

There is a converse problem with handling "missing" values. In PLATO sites recorded concomitant drugs, including ASA, if the patient received the drug. There was no specific place to record that a drug was not given. Hence, if a patient had no ASA records, the ASA data were not "missing" in the sense that a weight was not recorded—or an LDL cholesterol level was not measured. I examined the CRFs of patients without ASA records. Not infrequently there was a statement recorded justifying why ASA was not given. These patients also had higher baseline rates of histories of GI bleeding and peptic ulcer disease. Hence I assert that patients lacking all ASA records should be analyzed as ASA dosage 0, as recorded by the sites, rather than imputing median dosage

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for the country as AZ did for many analyses. AZ claims to have complied with "imputing" 0 for these patients in the analyses submitted in their complete response, the "M2" and "M4" columns in Table 20 above.

The problem that I consider most serious regarding AZ's ASA dosages is that I easily find discrepancies between AZ's dosages and the recorded ASA values, i.e., AZ's dosages differ from what they should be according to the AZ's English definitions. I show some discrepancy examples for MEDIAN55 because AZ "considers MEDIAN55 to be the most clinically relevant measure of ASA maintenance dose." MEDIAN55 is the median ASA dosage prior to the event or censoring day ignoring the loading dose. I show five examples of discrepancies in Table 21.

Table 21: Examples of Discrepant MEDIAN55 ASA Dosages

Case	ASA				Censoring day	MEDIAN55	FDA
	Start	Stop	Continuing	Dose			
1	1	2		325	96		100
	2		Yes	100	96		
2	-1		Yes	100	1		100
3	1	1		325	1	81	325
	2		Yes	81	1		
4	0	0		325	390		100
	1		Yes	100	390		
5		33		325	390	325	100
	33		Yes	100	390		

I have some speculations regarding the reasons for the discrepancies:

Case 1: MEDIAN55 may be missing either because, while the patient's last visit was on day 96, AZ's censoring day for this patient is day 391, or because AZ counted the continuing dose from day 2 as missing later.

Case 2: This patient had an endpoint on day 1. AZ may have considered the 100 mg dose to be the loading dose and so missing for MEDIAN55.

Case 3: This patient also had an endpoint on day 1. While I use the loading dose of 325 mg, by AZ's definition MEDIAN55 should be missing. The assigned MEDIAN55 dosage of 81 mg, not started until day 2, is inexplicable.

Case 4: Similar to Case 1, AZ may have counted the continuing dose of 100 mg as missing later.

Case 5: For this patient MEDIAN55 should either be missing (as for Cases 1 and 5) or 100 mg. How AZ assigned 325 mg I do not understand.

I detected these discrepancies by comparing the ASA dosage I pre-specified (modal dosage including loading dose) to MEDIAN55. Considering ASA dosages ≥ 300 mg, my classification differs from MEDIAN55 for 256 patients, or more than 25% of the high

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ASA dosage cases. I do not assert that my classification is the perfect classification—or that we even understand what an appropriate ASA dosage classification is. However, Table 21 documents that there are substantial problems with MEDIAN55, and I have found similar problems with all AZ ASA dosages that I have examined.

Despite the problems with defining and determining ASA dosages, I do find a statistically significant ticagrelor-ASA interaction using my ASA dosage classification and my corrected MACE version of the AZ primary endpoint. I show a full Cox regression model (comparable to the ones for the 30-day and mortality endpoints above) in Table 22.

Table 22: Cox Regression for MACE through Study End, Full Model

```
No. of subjects =          18624                 Number of obs   =      18624
No. of failures =           1863
Time at risk    =        5253862
                                                 LR chi2(16)     =     778.37
Log likelihood  =    -17664.203                  Prob > chi2     =     0.0000


------------------------------------------------------------------------------
        _t | Haz. Ratio  Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+------------------------------------------------------------------
1.ticagrelor |  1.042684   .1157789     0.38   0.707    .8387568    1.296193
       1.us |   .540626   .0836449    -3.98   0.000    .3992089    .7321391
           |
ticagrelor#|
        us |
       1 1 |  1.236825   .2525524     1.04   0.298    .8288922     1.84552
           |
     ageimp |  1.018041   .0029724     6.12   0.000    1.012232    1.023884
    crcl0imp |    .99116   .0009557    -9.21   0.000    .9892886    .9930349
    1.smoker |  1.195982   .0873617     2.45   0.014    1.036449    1.380072
           |
    smoker#|
 ticagrelor |
       1 1 |  .8431271   .0870926    -1.65   0.099     .688599    1.032333
           |
    ecgstemi |  1.191325   .0644826     3.23   0.001    1.071415    1.324656
 1.asafge300 |  3.977848   .5156869    10.65   0.000     3.08531    5.128587
           |
 asafge300#|
 ticagrelor |
       1 1 |  1.587366   .2595704     2.83   0.005     1.15209    2.187096
           |
    1.diabhx |  1.686799   .0883882     9.98   0.000    1.522161    1.869246
           |
    diabhx#|
  asafge300 |
       1 1 |   .464117   .0708044    -5.03   0.000    .3441681    .6258703
           |
   1.statin0 |  1.119811   .0895908     1.41   0.157     .957291    1.309921
           |
   statin0#|
 ticagrelor |
       1 1 |  .8130196   .0919862    -1.83   0.067    .6513207    1.014862
           |
 1.proclt24h |  .7382052   .0519167    -4.32   0.000    .6431519    .8473066
           |
 proclt24h#|
 ticagrelor |
       1 1 |  .9883125   .0944972    -0.12   0.902    .8194207    1.192015
------------------------------------------------------------------------------
```

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In this full Cox model of MACE through the end of study the ticagrelor-ASA interaction is significant; including the ticagrelor-ASA interaction in the model makes the ticagrelor-US interaction insignificant. I have the following additional observations about the full model:

- For a Cox regression of MACE including only the treatment factor treatment is statistically significant ($P = 0.027$, hazard ratio 0.9) but not highly significant. For the full model the adjusted hazard ratio is about 1.0 and insignificant.

- The strongest interaction is the diabetes-ASA interaction.

- The ticagrelor-statin interaction, despite being based on baseline statin use alone, is close to significant (and is by the $P < 0.10$ interaction standard.)

- The ticagrelor-early PCI interaction is not significant.

The significance of the ASA interactions in this full model of MACE using my ASA dosage determinations supports the use of my ASA dosage determinations in the other models, i.e., the 30-day and mortality models. However, the consistency or apparent informativeness of my ASA dosage determination does not obviate the fundamental flaw with any ASA dosage determination using wildly post-randomization observations: The correlations with ASA dosage may not express causal relationships but spurious correlations with unidentified factors related to outcomes as effects.

It is easy to demonstrate spurious correlations using post-randomization factors. I show a Cox regression incorporating various post-randomization factors in Table 23.

Table 23: Cox Regression for MACE through Study End, Full Model Incorporating Post-Randomization Factors in Addition to ASA Dosage

```
No. of subjects =        18624              Number of obs   =     18624
No. of failures =         1863
Time at risk    =      5253862
                                            LR chi2(16)     =    1209.36
Log likelihood  =   -17448.706              Prob > chi2     =     0.0000

------------------------------------------------------------------------------
        _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+------------------------------------------------------------------
1.ticagrelor | .9855874   .1366244   -0.10   0.917     .7511032   1.293274
      1.us | .6130564    .0938319   -3.20   0.001     .4541705    .8275264
           |
ticagrelor#|
        us |
       1 1 | 1.09434    .2220306    0.44   0.657     .7352784   1.628742
           |
    ageimp | 1.015524    .0028882    5.42   0.000     1.009879   1.021201
   crcl0imp | .9902789   .0009717   -9.96   0.000     .9883763    .9921852
 1.ecgstemi | 1.111608   .0642357    1.83   0.067     .9925767   1.244915
 1.asafge300 | 3.029988  .4364634    7.70   0.000     2.284689   4.018415
           |
  ecgstemi#|
  asafge300 |
       1 1 | 1.407894    .1980712    2.43   0.015     1.068606   1.854907
           |
   1.diabhx | 1.636005   .0853281    9.44   0.000     1.477029   1.812092
           |
    diabhx#|
  asafge300 |
       1 1 | .4869166    .0743313   -4.71   0.000     .3610045    .6567448
           |
  proclt24h | .4563044   .0278136  -12.87   0.000     .4049212    .5142081
      pcin | 1.962478    .0599051   22.09   0.000     1.848509   2.083473
      cabg | 2.046251    .1350299   10.85   0.000     1.797997   2.328781
           |
ticagrelor#|
  asafge300 |
       1 1 | 1.720082    .279163     3.34   0.001     1.251418   2.364265
           |
 1.statinon | .6981867   .0727239   -3.45   0.001     .5692585    .8563151
           |
  statinon#|
 ticagrelor |
       1 1 | .848839    .1237849    -1.12   0.261     .6378167   1.129678
------------------------------------------------------------------------------
```

COMMENT: So it's harmful to patients to perform multiple PCIs and CABGs? These latter two variables have hazard ratios near 2 and are the most significant factors in Table 23, i.e., extremely statistically significant. They are reliably recorded, simple to determine, and robust to all variations of definitions and determinations.

Obviously we recognize that numbers of PCIs and CABG are wildly post-randomization factors for which the relationship to outcome is more likely to be an effect than a cause. High statistical significance and robustness to definitional variations for post-randomization factors are no guarantee whatsoever that an association is causal rather than spurious. Higher ASA dosing is similar to PCI and CABG in that all three are interventions that practitioners may apply to patients who are not doing well. The high mortality rates with higher ASA dosage OUS suggest that OUS that was the case.

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We can glean the difficulties of evaluating ASA dosage by examining the factors related to ASA dosage. I do so with another multivariable analysis, in this case a logistic regression for ASA dosage ≥ 300 mg as shown in Table 24.

Table 24: Logistic Regression for FDA ASA Dosage ≥ 300 mg, Entire Study, MACE Censoring

```
Logistic regression                             Number of obs   =      18624
                                                LR chi2(14)     =    2592.79
                                                Prob > chi2     =     0.0000
Log likelihood = -3197.3365                     Pseudo R2       =     0.2885


------------------------------------------------------------------------------
    asafge300 | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
   ticagrelor |  1.027676    .0715645     0.39   0.695     .8965636    1.177963
           us |  35.51021    4.724144    26.83   0.000     27.35978    46.08864
       ageimp |  .9923567    .0032223    -2.36   0.018     .9860612    .9986925
         male |  1.334941    .1139856     3.38   0.001     1.129227    1.578131
        wtimp |  .9893928    .0021914    -4.81   0.000      .985107    .9936973
       diabhx |  1.014749    .0816033     0.18   0.856     .8667767    1.187982
       statin0 |  .9316948    .0772979    -0.85   0.394      .79187    1.096209
         pcin |  1.273757    .0800034     3.85   0.000     1.126221    1.440621
       1.cabg |  1.247915    .1873212     1.48   0.140     .9298516    1.674776
         1.us |  (omitted)
              |
      cabg#us |
          1 1 |  .7454939     .169232    -1.29   0.196     .4777667    1.163248
              |
    1.ecgstemi |  1.152237    .1189611     1.37   0.170     .9411537    1.410661
              |
   ecgstemi#us |
          1 1 |  .763823    .1294274    -1.59   0.112     .5479731    1.064697
              |
   1.proclt24h |  .928614    .1096968    -0.63   0.531     .7366872    1.170543
              |
  proclt24h#us |
          1 1 |  1.395669    .2260983     2.06   0.040     1.015986    1.917242
------------------------------------------------------------------------------
```

The overwhelmingly influential factor is US region. Because the US is also associated with both dramatically higher ASA dosages and poorer outcomes, separating the US effects from the higher ASA dosage effects is difficult. Multiple PCIs are associated with higher ASA dosage but the association does not appear to interact with region (not shown). The one other factor that interacts with region is early PCI. Because early PCI also interacts with ticagrelor to produce worse outcomes, these interactions may explain some of the observed ticagrelor-ASA interaction in the US.

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COMMENT: For MACE in the entire study, just as for 30-day outcomes and mortality, the strongest interaction is the diabetes-ASA interaction. The ticagrelor-ASA interaction is somewhat weaker and not supported by mortality and 30-day endpoints. The other interactions observed for mortality and 30-day endpoints are not supported by the MACE regressions, but I assert that MACE for the entire study is the least reliable of the endpoints based on the study conduct and submission problems that I identify above. I project that the diabetes-ASA interaction is the one most likely to be confirmed, followed in order by the ticagrelor-early PCI and ticagrelor-statin interactions, with the ticagrelor-ASA interaction being the least likely. I base my projections on the consistencies of the findings among all non-AZ endpoints and the short and long term results and the credibility of the nonclinical mechanisms.

Another problem with all of these analyses is that PLATO collected unreliably or not at all the critical factors that could explain these variations in outcomes. In particular, one US-OUS difference observed in other ACS trials has been that US practitioners tend to delay use of platelet inhibitors until the coronary anatomy is known while OUS practitioners tend to give platelet inhibitors early. We have some evidence that this difference was also true in PLATO based on the bleeding data. If ticagrelor has a problem with early activity, then the US patients on ticagrelor would be disadvantaged by delayed study drug. Some effect like partial agonist activity (before full allosteric inhibition is achieved) might explain both the US results and the poorer results for peripheral thromboembolic events. However, AZ failed to collect reliably timings of pre-study clopidogrel, study drug, and PCI such that we can not address this hypothesis of delayed activity with PLATO data.

Finally, the diabetes-ASA interaction shares the same serious flaw as the proposed ticagrelor-ASA interaction: both are based on the wildly post-randomization ASA dosages. I would not act clinically based on the diabetes-ASA interaction in PLATO; confirmation in other studies is needed, ideally with randomized ASA dosing. The same need for confirmation with another study applies to the ticagrelor-ASA interaction—and to the ticagrelor-US interaction and to approval.

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/s/

THOMAS A MARCINIAK
05/15/2011

Division of Cardiovascular and Renal Products

CLINICAL SAFETY REVIEW

Application Type	N
Submission Number	22401
Letter Date	1/20/11
Stamp Date	1/20/11
PDUFA Goal Date	7/20/11
Reviewer Name	Melanie Blank, MD
Review Completion Date	05/06/11
Established Name	Ticagrelor
(Proposed) Trade Name	Brilinta
Therapeutic Class	P2Y12 Platelet Inhibitor
Applicant	Astra Zeneca
Priority Designation	S
Formulation	Tablet
Dosing Regimen	90 mg BID
Indication	Acute Coronary Syndrome

Introduction:

There has been no new safety data submitted to NDA 22433 for ticagrelor during the second review cycle. Nevertheless, I took the opportunity to do a few analyses of the safety data that I felt might contribute to the understanding of the effect of aspirin on ticagrelor. In an attempt to understand the effects of ticagrelor from both a safety and efficacy perspective, I also analyzed the effect that ticagrelor has on other thromboembolic conditions besides myocardial infarction. I also performed a couple of analysis on the potential that AEs may have contributed to discontinuation of study drug that the sponsor attributed to other reasons such as "subject did not want to continue" or "other".

This review is comprised of a short regulatory background, my assessment of the aspirin hypothesis, my assessment of thromboembolic events, my assessment of reasons for discontinuation of study drug and an updated version of my safety summary from the first review cycle.

Regulatory Background:

The sponsor submitted an original NDA for Brilinta (ticagrelor) for treatment of ACS on November 16, 2009. The application was designated for standard review with a PDUFA goal date of September 16, 2010 and later extended to December 16, 2010. An Advisory Committee meeting was held on July 28, 2010. The committee was nearly unanimous in agreeing that ticagrelor's benefits outweighed the risks and that the finding of a trend toward harm in the U.S. population was not a finding that should dissuade the Agency from issuing an approval decision. The Agency issued a Complete Response letter on December 16, 2010 in which a request was made to the sponsor to substantiate their hypothesis that the negative trend in the U.S. could be explained by the increased use of high dose aspirin in the U.S. The sponsor resubmitted their NDA on January 20, 2011 and the Agency acknowledged in a letter dated February 3, 2011 that it was a complete, Class 2 resubmission with a July 20, 2011 PDUFA goal date.

Summary of Pivotal trial

The PLATO trial was extremely successful in demonstrating that ticagrelor is superior to clopidogrel in preventing MACE (MI, Angioplasty and Coronary Death) and cardiac death (as a secondary endpoint) in patients with acute coronary syndrome. PLATO was a double- blind, active-controlled, parallel arm, multinational trial with two treatment arms: ticagrelor 90 mg BID and clopidogrel 75 mg QD. 18,624 randomized patients were enrolled. There were 18,421 patients in the safety set (received ≥ 1 dose of treatment). There were 9235 patients in the ticagrelor safety set and 9186 patients in the clopidogrel safety

set. The mortality benefit was especially important because no other antiplatelet drug has been demonstrated to save lives.

The main problem that is delaying approval is a regional treatment effect. In the U.S. and North America there was no benefit demonstrated for ticagrelor. In fact, the results went the other way, with a nearly statistically significant increase in MACE in the ticagrelor arm compared to the clopidogrel arm.

Aspirin Hypothesis

Astra Zeneca provided a compelling argument to explain the difference in the performance of ticagrelor between the U.S. and outside of U.S. Their argument was that the dose of aspirin can explain the regional differences in ticagrelor/ clopidogrel treatment. In the U.S. there were many patients on high-dose aspirin. In the rest of the world there were also patients treated with high-dose aspirin, albeit a much smaller percentage. The sponsor's statistical analysis showed that in patients on high-dose aspirin there was no difference in outcome between the ticagrelor and clopidogrel arms. This finding the sponsor claimed could account for most of the anomalous U.S. / North America findings.

Astra Zeneca submitted several documents to the NDA in an attempt to support their hypothesis. All of the statistical analyses used a median aspirin dose that included aspirin dose from day 2 on. FDA agreed that this was acceptable. The statistical findings were dependent on what imputation method was used for missing data and whether the first day loading dose was included in the calculation of the median aspirin dose. If the first dose was used, the aspirin hypothesis was not supported. The aspirin hypothesis was also not supported by the "worst case scenario" model where missing aspirin data was imputed as high-dose (325mg) if the patient was on ticagrelor and did not have an event, and imputed to low-dose (81mg) if the patient was on ticagrelor and had an event. In this analysis missing aspirin dose was imputed to high-dose (325mg) if the patient was on clopidogrel and had an event, and imputed to low-dose (81mg) if the patient was on clopidogrel and did not have an event. Failure in the "worst case scenario" imputation model is common as this is the most stringent sensitivity analysis. It was very concerning that there was no statistically significant effect on outcomes for OUS patients who were on high dose aspirin within 10 days or 30 days of having an event or censor date. Numerically, the trend was for worse outcomes in patients who were OUS and on a median dose of > 300 mg/day of aspirin but the lack of statistical significance makes it hard to feel comfortable that there is a high aspirin effect operating OUS. Without confidence that there is a high aspirin effect OUS there can be no confidence that high dose aspirin is driving the outcomes in the US. Furthermore, it is difficult to accept a post hoc analysis of a factor that is not a pre-randomization factor and was not prespecified. Please refer to the statistical review written by Dr. Jailu Zhang, Ph.D. for more details and an in-depth analysis.

Melanie J. Blank, MD   NDA: 22433   Sponsor: Astra Zeneca   Drug: ticagrelor   3

Astra Zeneca compiled their preclinical studies in an attempt to support the biological plausibility of the negative effect that high-dose aspirin on ticagrelor performance. The invitro studies focused on differential effects on platelet aggregation between high-dose and low-dose aspirin in the presence of clopidogrel or ticagrelor. These in vitro studies showed 3 things: 1) aspirin augments the clopidogrel-induced inhibition of platelet aggregation induced by arachidonic acid and collagen 2) aspirin does not augment the ticagrelor-induced inhibition of induced platelet aggregation, and 3) high-dose aspirin does not augment the improvement in clopidogrel-inhibition of platelet aggregation any more than low-dose aspirin.

Astra Zeneca also submitted dog studies to support the biological plausibility of the high-dose aspirin effect. AZ used a mechanical injury model of arterial thrombosis in the anesthetized dog to study ticagrelor ±ASA and clopidogrel ±ASA on vascular resistance. One leg was injured in each animal mimicking arterial thrombosis. Vascular resistance was measured in the contralateral leg. The results of the studies were that the best "equivalent" of high-dose aspirin caused increased vascular resistance to the same extent in the leg contralateral to the injury in animals irrespective of whether they were dosed with clopidogrel, ticagrelor or neither drug. There was no difference between the treatment groups suggesting that while high-dose aspirin has deleterious effects on vascular resistance, there is no difference between ticagrelor and clopidogrel in this regard. There is evidence that increases in vascular resistance in response to aspirin is a dose-related effect. There is no evidence that ticagrelor or clopidogrel have any interaction with the aspirin induced increase in peripheral vascular resistance. While there is no evidence from dogs that the aspirin effect on vascular resistance can explain the difference in performance of ticagrelor when patients are also on high dose aspirin, no firm conclusions can be made in terms of the peripheral vascular effects of aspirin in humans. According to the Pharmacology/Toxicology Review by Dr. Elizabeth Hausner, D.V.M., the caveat for interpreting the dog studies is that the relative concentrations of aspirin and salicylates are vastly different between the dog and the human. This difference makes it difficult to feel entirely comfortable about translating the dog results to what occurs in the human. See Table 1, taken from Dr. Hausner's review. Please see Dr. Hausner's review for more details and an in-depth analysis.

Table 1: Difference in Aspirin and Salicylate levels after a Single Dose of Aspirin

Dog plasma values after a single dose of aspirin, 50 mg/kg	Human plasma[1] values after a single dose of aspirin, 320 mg
$AUC_{0-\tau}$ ASA = 3.50 μmol/L= 0.63μg/ml	$AUC_{0-\tau}$ ASA = 3 μg/ml
$AUC_{0-\tau}$ SA = 547 μmol/L = 75.5 μg/ml	$AUC_{0-\tau}$ SA = 19 μg/ml

My approach to the question of whether there was biological plausibility for a difference in the relative performance of ticagrelor and clopidogrel depending on aspirin dose was to look at the safety data set to see if there was a difference in

the relative occurrence rate of important AEs that varied depending on aspirin dose. My approach was to look at the relative risk for both dyspnea and major bleeding between ticagrelor and clopidogrel by using different cut points to define high-dose aspirin. If high-dose aspirin could lower the relative risk of dyspnea and major bleeding, this would lend support for the hypothesis that high-dose aspirin alters the relative efficacy of the two drugs.

I performed an analysis in which I looked at the relative risk (RR) of dyspnea depending on median aspirin dose (not counting day 1), the results of which are in Table 2. The risk of dyspnea increases in both treatment groups with increasing aspirin dose and the relative risk of dyspnea also increased if patients were on ticagrelor. What this means is that the higher dose of aspirin does not interfere with the dyspnea associated with ticagrelor. In fact, the high dose aspirin augments the incidence of dyspnea in patients. This example detracts from the theory that aspirin interferes with the effects of ticagrelor.

I also performed an analysis in which I looked at the RR of major bleeds depending on median aspirin dose, the results of which are in Table 3. I used the median dose of ASA before a major bleed or if there was no major bleed, for the entire study. In order to calculate median aspirin dose, I did the following: if the patient had a major bleed, I calculated the median aspirin dose between day 2 and the day of major bleed, if the patient did not have a major bleed, I calculated the aspirin dose by day 2 to study end. The relative risk of major bleeds increased with aspirin doses > 300 mg/dL. Interestingly, the overall percentage of major bleeding decreased for both groups when the aspirin dose was > 300 mg/dL. This result was unexpected and could be dismissed because of the small numbers of patients with aspirin dose > 300 mg. Nevertheless, there is a rise in RR for major bleeds (% major bleeds in ticagrelor arm / % major bleeds in clopidogrel arm) to 1.08 when patients received >300 mg ASA. In conclusion, this bleeding analysis speaks against a differential effect of high dose aspirin on ticagrelor at the level of the platelet.

Both of these analyses speak against the theory that high dose aspirin interferes with the actions of ticagrelor.

Table 2: Relative Risk of Dyspnea by ASA cutoff dose

Median dose aspirin	>90 mg/day	> 125 mg/day	>150 mg/day	> 200 mg/day	> 300 mg/day
clopidogrel					
N in category	5821	988	697	503	416
n with dyspnea	495	98	74	56	48
% with dyspnea	8.5	9.9	10.6	11.1	11.5
ticagrelor					
N in category	5815	930	672	471	383
n with dyspnea	800	155	125	97	85
% with dyspnea	13.8	16.7	18.6	20.6	22.2
RR	1.62	1.69	1,75	1.86	1.93

Table 3: Relative Risk of MAJOR bleed by sponsor's definition by ASA cutoff dose

median dose ASA	<=90 mg/day	>90mg/day	>100mg/day	>125mg/day	>150mg/day	>200mg/day	>250 mg/day	>300 mg/d
clopidogrel								
N in category	3369	5817	1116	1073	782	550	521	420
n with bleed	372	557	196	189	160	106	89	54
% with bleed	11.04	9.58	17.56	17.61	20.46	19.27	17.08	12.86
ticagrelor								
N in category	3430	5805	1065	1024	757	511	481	388
n with bleed	379	582	194	186	142	81	69	54
% with bleed	11.05	10.03	18.22	18.16	18.76	15.85	14.35	13.92
RR	1	1.05	1.04	1.03	0.92	0.82	0.84	1.08

There are three ways of looking at the aspirin analyses. One is that you can't explain away the statistical findings and therefore they must be true.

Another way is to dismiss the aspirin analyses because they might be chance or unreliable findings. The third way to look at the aspirin analyses is to suspect that aspirin dose may have been determined by clinical considerations and therefore was not a baseline characteristic. This would mean that aspirin dose could have been determined indirectly because of an effect of ticagrelor on the patients that received it.

Therefore, it is possible that medical care differences (for eg., early PCI) or other differences between Americans and people from the rest of the world may have accounted for the different outcomes and that aspirin dose has nothing to do with it or is determined by a change in risk after the initiation of study drug treatment. With the absence of clinical benefit for ticagrelor in the U.S. and the possibility that this absence is not caused by high dose aspirin but rather by other factors, it is difficult to justify an approval decision. Another study should be called for.

Additional Safety Analysis

As with all good things, it is important to be concerned that worldwide mortality results may have been "too good to be true". For this reason, I decided to recalculate all vascular events which were recorded by the onsite investigators as AEs. See Table 4. One might expect that ticagrelor should have a lower relative risk compared to clopidogrel in other vascular events such as TIA, CVA, peripheral vascular disease (PVD), and thromboembolic phenomena. Of note, the relative risk for CVA and hemorrhagic stroke are imbalanced. The risks of CVA and hemorrhagic stroke occurring in the ticagrelor-treated patients relative to the clopidogrel-treated patients were 1.24 and 1.63, respectively. While there was a similar observation in the prasugrel trials, it is disconcerting that drugs that claim to lower heart attack and death, increase risk for stroke and other thrombotic events.

There were too few of the following arterial events to make a fair comparison between the two treatment groups: retinal artery occlusions, amaurosis fugax, renal artery disease, dissecting aneurysm or artery, necrotic limb, and amputation. Nevertheless, the trends are not favorable for ticagrelor except with stent thrombosis where ticagrelor showed an advantage.

Venous events were closely matched between the treatment groups except for pulmonary embolism which had a considerably higher risk of occurring if the patient was being treated with ticagrelor.

Table 4: Vascular Events in PLATO

	Ticagrelor	Clopidogrel	RR
Hemorrhage intracranial or SDH	28	17	1.65
SDH	2	1	2
Intracranial hemorrhage	28	17	1.65
Arterial event	375	367	1.02
Retinal artery occlusion	1	1	1
Amaurosis fugax	7	3	2.33
Ischemic colitis	2	4	0.5
Renal artery disease	9	10	0.9
CVA	138	111	1.24
TIA	37	41	0.9
CVA/ TIA	178	152	1.17
Hemorrhagic stroke	26	16	1.63
Cerebrovascular +carotid disease	214	190	1.13
Stent thrombosis or stenosis	140	156	0.9
Stent thrombosis	45	58	0.78
Stent stenosis	96	97	0.99
Thromboembolic disease (arterial and venous)	84	68	1.24
PVD	155	132	1.17
Arterial occlusion or "stenosis"	29	28	1.04
Dissecting aneurysm or artery	3	4	0.75
Necrotic limb	2	1	2
Amputation	2	0	0
Venous event	72	65	1.11
Thrombophlebitis	65	66	0.98
DVT	49	43	1.14
PE	35	24	1.46

AEs were derived from AEVTLOG.JMP data set
Safe period only (Patient had to have had the event after at least one dose of medication)
One event per patient counted if more than one of the same event occurred
If TIA and Stroke in one patient, only counted stroke
If Stroke and Hemorrhage stroke in one patient, only counted hemorrhagic stroke
There was no patient in whom both stent thrombosis and stent stenosis occurred
PE=pulmonary embolism, TIA=transient ischemic attack, CVA= cerebrovascular attack, DVT=deep venous thrombosis, SDH= subdural hematoma

I then revisited discontinuations of study treatment for AEs to check the sponsor's analysis. Table 64 from the original ticagrelor NDA submission provides a breakdown of the reasons for discontinuation between the two groups.

Table 64   Summary by PT of the most common AEs (≥0.1% in either group) leading to discontinuation of study treatment, including bleeding events – safety analysis set

Characteristic	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Patients with at least 1 event	687 (7.4%)	500 (5.4%)
Dyspnoea	77 (0.8%)	10 (0.1%)
Epistaxis	38 (0.4%)	12 (0.1%)
Atrial fibrillation	27 (0.3%)	37 (0.4%)
Intracardiac thrombus	22 (0.2%)	17 (0.2%)
Gastrointestinal haemorrhage	19 (0.2%)	12 (0.1%)
Contusion	17 (0.2%)	7 (0.1%)
Nausea	15 (0.2%)	7 (0.1%)
Pulmonary embolism	15 (0.2%)	7 (0.1%)
Diarrhoea	14 (0.2%)	9 (0.1%)
Ecchymosis	13 (0.1%)	5 (0.1%)

There were more discontinuations of study treatment in the ticagrelor arm. As a way of trying to assess if there was "under calling" of discontinuations of study treatment for AEs I investigated the sponsor's list of discontinuations for other reasons aside from AEs. there is no concerning change in the relative risk of discontinuation of study drug because of AEs by treatment group.

Table 5 shows that there were many patients [656 (7.1%) and 570 (6.2%) that were treated with ticagrelor and clopidogrel, respectively] whose discontinuations of study drug may have been related to AEs that ended up to 30 days prior. Of those, there were several patients [60(0.65%) and 25 (0.27%) that were treated with ticagrelor and clopidogrel, respectively] whose discontinuations of study drug may have been related to dyspnea that ended up to 30 days prior. If 30 days seems implausible, the same analysis done for AEs and dyspnea AEs that ended up to 7 days prior to treatment discontinuation is shown in Table 6. Approximately 25% of the discontinuations of study treatment that were attributed by the sponsor to reasons other than AEs had AEs that ended up to 7 days prior to treatment. This suggests that there may have been some cases of discontinuing of study treatment for AEs were missed. However, on a reassuring note, if one assumes that patients who had AEs within 7 days of discontinuation of treatment discontinued because of those AEs there is no concerning change in the relative risk of discontinuation of study drug because of AEs by treatment group.

Table 5: Discontinuation of drug for reasons other than AE according to sponsor in patients who had AE within 30 days before discontinuing drug

		Ticagrelor 90 mg bd N=9235 n(%)	Clopidogrel 75mg qd N=9186 n(%)	RR
	Discontinued treatment (from sponsor)	2186 (23.7)	1999 (21.8)	1.09
A	Discontinued for an AE (from sponsor)	690 (7.5)	556(6.1)	1.23
B	Discontinued for dyspnea (from sponsor)	77 (0.8)	10 (0.1)	7.66
	Did not continue for reasons other than AE (from sponsor)	1496 (16.2)	1443 (15.7)	1.03
	not willing to continue	946(10.2)	859(9.4)	1.1
	reason unknown	4(0.0)	1(0.0)	3.98
	severe noncompliance	41(0.4)	47(0.5)	0.87
	didn't meet inclusion criteria	22 (0.2)	16(0.2)	0.14
	other	479(5.2)	518(5.6)	0.92
	lost to follow-up	4 (2)	2 (0.0)	1.99
C	with adverse event within 30 d	656 (7.1)	570 (6.2)	1.14
	without adverse event within 30 d	840 (9.1)	873 (9.5)	0.96
D	with adverse event (not including*) within 30 days	578 (6.3)	477 (5.2)	1.21
	without adverse event (not including*) within 30 days	918 (9.9)	966 (10.5)	0.95
E	with dyspnea within 30 days	60 (0.65)	25 (0.27)	2.39
	Total Discontinue for AE when counting A + C	1346 (14.6)	1126 (12.3)	1.2
	Total Discontinue for AE when counting A +D	1268 (13.7)	1033 (11.2)	1.22
	Total Discontinue for dyspnea when counting B + E	137 (1.5)	35 (0.38)	3.89

*Patient had atrial fibrillation, atrial flutter, liver failure, renal failure, pulmonary embolism, malignant tumor (all requiring treatments that might contraindicate ticagrelor or clopidogrel or whose only AE was relatively unimportant and not a plausible reason for D/C drug

Table 6: Discontinuation of drug for reasons other than AE according to sponsor in patients who had AE within 7 days before discontinuing drug

		Ticagrelor 90 mg bd N=9235 n(%)	Clopidogrel 75mg qd N=9186 n(%)	RR
	Discontinued treatment (from sponsor)	2186 (23.7)	1999 (21.8)	1.08
A	**Discontinued for an AE (from sponsor)**	690 (7.5)	556 (6.1)	1.23
B	**Discontinued for dyspnea (from sponsor)**	77 (0.8)	10 (0.1)	7.66
	Did not continue for reasons other than AE (from sponsor)	1496 (16.2)	1443 (15.7)	1.03
	not willing to continue	946 (10.2)	859 (9.4)	1.1
	lost to follow-up	4 (0.0)	1 (0.0)	3.98
	noncompliance	41 (0.4)	47 (0.5)	0.87
	didn't meet inclusion criteria	22 (0.2)	16 (0.2)	1.37
	other	479 (5.2)	518 (5.6)	0.92
	lost to follow-up	4 (2)	2 (0.0)	1.99
C	**with adverse event within 7 d**	365 (4.0)	329 (3.58)	1.1
	without adverse event within 7 d	1131 (12.2)	1064 (11.6)	1.06
D	**with adverse event (not including*) within 7 days**	315 (3.41)	272 (2.96)	1.15
	without adverse event (not including*) withing 7 days	1181(12.8)	1171 (12.7)	1
E	**with dyspnea within 7 days**	30 (0.32)	12 (0.13)	2.49
	Total Discontinue for AE when counting A + C	1055 (11.4)	885 (9.6)	1.19
	Total Discontinue for AE when counting A +D	1005 (10.9)	828 (9.0)	1.21
	Total Discontinue for dyspnea when counting B + E	107 (1.2)	22 (0.24)	4.84

*Patient had atrial fibrillation, atrial flutter, liver failure, renal failure, pulmonary embolism, malignant tumor (all requiring treatments that might contraindicate ticagrelor or clopidogrel or whose only AE was relatively unimportant and not a plausible reason for D/C drug

<u>Safety Summary</u>

There are several safety issues that should to be considered before making an executive decision on whether or not to approve ticagrelor; particularly in the light of the finding that ticagrelor did not benefit the U.S. population in PLATO.

There were 9235 patients that received at least one dose of ticagrelor and 9186 patients that received at least one dose of clopidogrel-in PLATO. These patients comprised the "safety set", according to the sponsor, and their data were used for most of my safety review. When I analyzed adverse events I included only those patients who had at least one dose of drug before having an adverse event.

One of the most significant findings from PLATO was the all-cause mortality benefit seen for ticagrelor. There were statistically significant fewer overall deaths in the ticagrelor group compared to the clopidogrel. In total there were 399 (4.28%) adjudicated deaths within the efficacy period in the ticagrelor treatment arm compared to 506 (5.45%) in the clopidogrel treatment arm (RR=0.78). Vascular deaths accounted for most deaths (~ 95% of deaths in both treatment groups). The term "vascular death" includes cardiovascular deaths, cerebrovascular deaths, bleeding deaths and any other death for which there was no clearly documented nonvascular cause. Bleeding deaths were not as common as other causes of death (0.2% of patients died of bleeds). Causes of death were similar between treatment groups. The most common cause of death was myocardial infarction occurring in about 1% of randomized patients. Sudden death, heart failure, other vascular events and stroke were among the more common causes of death. The U.S. population was an outlier when it came to death prevalence. In the U.S., there were more deaths in the ticagrelor treatment group compared to the clopidogrel treatment group [35 (3.8%) vs. 29 (3.2%), respectively].

The most important safety issue for ticagrelor was bleeding. There were more patients that met the criteria for PLATO major bleeds than would have met the criteria for TIMI major bleeds, largely because one of the criteria for a PLATO major bleed was transfusion of 2 or more units of packed red blood cells or whole blood, whereas transfusion is not a criterion for having a TIMI major bleed. Ticagrelor-treated patients had numerically more major bleeds than clopidogrel-treated patients [1031 (11.2%) vs. 997 (10.9%), respectively] and this difference was not statistically significant. The frequency of major + minor bleeding (any bleed requiring intervention or treatment) was greater in the ticagrelor treatment group compared to the clopidogrel treatment group [1339 (14.5%) vs. 1215 (13.2%), respectively (log-rank = 0.0083)] .The reason for this increase in major +minor bleeds in the ticagrelor treatment group was primarily the increased frequency of spontaneous (non-procedural/ non-CABG) bleeds in ticagrelor-treated patients. The HR for all spontaneous bleeds (% all spontaneous bleeds

on ticagrelor/ % all spontaneous bleeds on clopidogrel) was 1.62 (1.51, 1.74). Spontaneous major bleeds, accounted for [235/961(24.5%) vs. 180/929 (19.4%)] of the major bleeds, for ticagrelor and clopidogrel, respectively. The greatest difference between treatment groups in major bleeds was in the category of nonprocedural major bleeds [HR 1.31 (1.08, 1.60)].

Most bleeds (major + minor) in PLATO were CABG-related [737/1339 (55.0%) vs. 783/1215 (64.4%) for ticagrelor and clopidogrel, respectively]. Most major bleeds in PLATO were CABG-related as well [619/961 (64.4%) vs. 654/929 (70.4%) for ticagrelor and clopidogrel, respectively]. Interestingly, despite a numerically lower CABG-related frequency of overall bleeding in most PLATO-defined categories of bleeding for ticagrelor-treated patients, the frequency of bleeding was slightly worse in the ticagrelor arm within the first several days of stopping drug. Nevertheless, whether you look at all-cause mortality at any time following CABG or at any time up to 2 weeks following CABG, ticagrelor had lower all-cause mortality than clopidogrel no matter what the time interval was between stopping drug and CABG.

Dyspnea was also an important safety issue for ticagrelor. Dyspnea occurred frequently in patients treated with ticagrelor in all clinical phase 2 studies and in PLATO (14.6% of ticagrelor-treated patients vs. 8.7% of clopidogrel-treated patients). Dyspnea SAEs occurred in less than 0.9% of ticagrelor-treated patients and in less than 0.6% of clopidogrel-treated patients. Dyspnea in ticagrelor-treated patients resulted in more discontinuations than dyspnea in clopidogrel-treated patients (0.9% vs. 0.1%, respectively). More impressively, nearly 10% of ticagrelor-treated patients that had dyspnea discontinued treatment for other AEs compared to <6% of clopidogrel-treated patients. An additional concerning observation is that the onset of dyspnea was considerably earlier in the ticagrelor-treated patients compared to the clopidogrel-treated patients, lasted usually >20 days (up to approximately 400 days) and at any length of episode, there were numerically more patients in the ticagrelor treatment group than in the clopidogrel treatment group. A pulmonary function substudy was conducted to see if there were any effects of ticagrelor on pulmonary function tests. The substudy did not reveal any differences between treatment groups but it was designed, conducted and analyzed in such a way that might have obscured differences if they existed.

On the reassuring side, dyspnea is a symptom that resolved in 2/3 of the patients during the study. While two ticagrelor-treated patients with dyspnea AEs died, it is hard to assign the cause of these deaths to ticagrelor because of other comorbidities and confounding circumstances. The subgroup of patients with history of COPD and asthma while having an absolute greater incidence of dyspnea events did not have a difference in relative risk for developing dyspnea compared to all study patients irrespective of treatment. Most reassuringly, patients with dyspnea know they have it and can discontinue ticagrelor if they are troubled by it. Also, despite its exploratory nature, a retrospective analysis of

PLATO outcomes data showed that patients with dyspnea at any time during the trial had favorable clinical outcomes.

Arrhythmias were a concern for ticagrelor because of an increased frequency of arrhythmia related deaths in phase 2 data. In PLATO, the data for ticagrelor is numerically unfavorable for atrial arrhythmias and ventricular pauses but it is favorable for sudden death and ventricular arrhythmias. A limitation of the PLATO study is that patients with an increased risk of bradycardic events (e.g., no pacemaker and known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker) were excluded from the study.

There was a Holter monitor substudy in PLATO that confirmed the increased frequency of ventricular pauses.

Renal effects were a concern because of observations of increased serum creatinine levels during treatment with ticagrelor in the phase 1 and 2 studies. In PLATO, there was an increased frequency of patients that had extreme decreases in eGFR (>30% - 100%) in the ticagrelor group as compared to the clopidogrel group. It is possible that ticagrelor, because of its negative effects on adenosine uptake, could alter renal hemodynamics by decreasing vascular tone in the afferent arteriole thereby lowering the glomerular filtration pressure.

While there were no discernable differences between treatment groups for renal AEs, discontinuations for renal AEs or deaths from renal AEs, patients on ticagrelor with baseline eGFRs of < 30 cc/min had numerically more major bleeds than clopoidogrel-treated patients [23 (19%) vs. 16 (11.3%), respectively], and renal failure [12 (13.6%) vs. 5 (5.4%), respectively]. Because of the small numbers of patients in this subgroup, these observations could be chance findings.

However, when patients have poor baseline renal function they rely on hemodynamic changes within the kidney to maintain their GFR. It is possible that ticagrelor is more likely than clopidogrel to lead to the decompensation of renal function in patients who are completely reliant on hemodynamic factors to maintain their GFR. ACS Patients with poor baseline renal function are at higher risk for renal AEs and death. While there are too few data in this subgroup of patients to make firm conclusions, it is possible that ticagrelor might also contribute to the risk of progression to worsening renal failure in these already high risk patients.

A troubling observation in PLATO was the increased frequency and earlier time to overall stroke and intracranial hemorrhagic bleeding events (mostly from strokes) in the ticagrelor-treated patients. Hemorrrhagic bleeds carry a very high mortality. There were 11 patients in the ticagrelor treatment group that died of intracranial hemorrhagic events (almost 1/2 of the patients with intracranial

bleeds) while 1/14 patients in the clopidogrel-treatment group died of intracranial bleeding.

An exploration of patients who had histories of carotid, vertebrobasilar and cerebrovascular disease were considerably more likely to have strokes or TIAs while on ticagrelor (5.1 times the risk) and the relative risk of having a stroke or TIA for patients with preexistent disease was 2 times higher for ticagrelor-treated patients than for clopidogrel-treated patients.

Aside from stroke, there were some other thrombotic events were more common in the ticagrelor-treated patients, such as amaurosis fugax, deep venous thrombosis and pulmonary embolism. These are disturbing findings in a drug that is a more potent antiplatelet drug. On the reassuring side, there were fewer stent thrombosis events in the ticagrelor arm.

Only ~ 400 patients with "history of baseline hepatic disorder" were enrolled. While there were no differences in IPA and no significant difference in plasma binding protein, in PLATO, there was an increase in deaths (3.1% vs. 0.9%), SAEs (20.4% vs. 16.6%) and AEs (84.2% vs. 81.1%) for the ticagrelor-treated patients with a baseline of hepatic disorder compared to similar clopidogrel-treated patients. These patients were more likely to have major bleeds if on ticagrelor (11.2%) vs. 8.7% if on clopidogrel. Clinical outcomes data (MACE), however, were favorable in this subgroup.

Other important safety explorations were uric acid level increases, hepatic events, hormonally mediated events and neoplastic events. An interesting observation was the increased frequency of gynecomastia in the ticagrelor-treated patients. None of these explorations developed into major safety concerns.

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/s/

MELANIE J BLANK
05/06/2011
CLINICAL SAFETY REVIEW

Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Office Director Decisional Memo
NDA/BLA #	22-433
Applicant Name	Astra-Zeneca
Date of Submission	November 13, 2010
PDUFA Goal Date	December 16, 2010
Proprietary Name / Established (USAN) Name	Brilinta™/ticagrelor
Dosage Forms / Strength	90 mg Tablets
Proposed Indication(s)	1. Reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction who are to be: -managed medically -managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG 2. Brilinta as compared to clopidogrel has been shown to decrease the rate of combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes. 3. Brilinta as compared to clopidogrel has also been shown seperately to reduce the rate of: -CV death -MI
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Robert Fiorentino, MD, MPH (Efficacy); Melanie Blank, MD (Safety)
Statistical Review	Jialu Zhang, PhD
Pharmacology Toxicology Review	Elizabeth Hausner, DVM
CMC Review/OBP Review	Chhagan Tele, PhD (Drug Substance); Thomas Wong, PhD (Drug Product)
Clinical Pharmacology Review	Islam Younis, PhD; Kevin Krudys, PhD (Pharmacometrics); Michael Pacanowsky, PhD (Pharmacogenomics)
DDMAC	Emily Baker; Zarna Patel
DSI	Lauren Iacono-Connors, PhD
CDTL Review	Thomas Marciniak, MD
OSE/DMEPA	L. Shenee Toombs, PharmD
OSE/DRISK	Latonia Ford, MBA, BSN, RN
Other – Div Dir Review	Norman Stockbridge, MD, PhD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

I. Introduction

There has been extensive discussion and review of this NDA and the principal controlled trial intended to support approval; PLATO, a comparison of ticagrelor and clopidogrel in patients with acute coronary syndrome (ACS). My review at this time will focus almost entirely on clinical issues, specifically approvability based on PLATO. There are no outstanding chemistry, toxicology, or clinical pharmacologic issues. Like all platelet inhibitors, ticagrelor causes bleeding, which can be serious; major bleeds were somewhat more common on ticagrelor, including intracranial hemorrhage, but differences were small, not a basis for non-approval. The main issue, discussed extensively by Dr. Fiorentino, the primary medical reviewer, Dr. Marciniak, the CDTL, Dr. Zhang, biostatistics reviewer, and the Division Director, Dr. Stockbridge, is whether PLATO provided substantial evidence that ticagrelor is effective, and would be effective in a U.S. population.

Ticagrelor is the fourth oral ADP receptor antagonist (P2Y12 receptor) and the first whose binding and effect is reversible, unlike the effect of clopidogrel, prasugrel, or ticlopidine, a potentially valuable property if the patient needs surgery (ADP receptor antagonists cause bleeding), although in practice it reduces the needed delay by only 1.5 days or so because of its greater antiplatelet effect. The reversibility leads to a need for b.i.d. dosing, in contrast to dosing for clopidogrel and prasugrel. It provides greater inhibition of ADP stimulated platelet aggregation than clopidogrel (over 80% compared on average of about 40% for clopidogrel). It does not require metabolic conversion to an active metabolite, as do clopidogrel and prasugrel, a problem for clopidogrel as this conversion does not occur as much in CYP450 2C19 PM's and can be blocked by 2C19 inhibitors, such as omeprazole.

The PLATO study was a comparative study with clopidogrel intended to show greater effectiveness of ticagrelor on the endpoint of major adverse cardiovascular events (MACE).

II. Overall Study Results - PLATO

PLALTO was a large double-blind randomized multi-regional trial comparing the effects of clopidogrel (300 mg loading plus 75 mg daily thereafter) with ticagrelor (90 mg bid) in a broad population of people with acute coronary syndrome [including STEMI, NSTEMI, and unstable angina (UA); final determinations of diagnosis were made during the study, so this was not quite a baseline characteristic and it was not used for stratification] on the rate of Major Adverse Cardiovascular Events (MACE). Plans for patient management (invasive, medical) were known at the time of randomization but were not used for stratification. Unlike others studies (TRITON study of prasugrel included only patients with planned invasive management). PLATO included the full spectrum of patients with ACS, a feature that is primarily a virtue, I believe, but is also a potential problem.

PLATO randomized 18,624 patients within 24 hours of the index event 1:1 to ticagrelor (loading dose of 180 mg, with additional 90 mg if PCI was > 24 hours post-randomization, followed by 90 mg bid) or clopidogrel (loading dose of 300 mg with additional 300 at PCI at investigator's discretion). A double-dummy design disguised all this. The first dose of medication was to be taken immediately after randomization (before PCI). Investigators were allowed to give patients a 300 mg or larger dose of open label clopidogrel and patients could have been on clopidogrel prior to the study. Allowing this appeared to reflect the standard of care, with rapid introduction of a thienopyridine in ACS (at least if CABG is not planned), and would also appear to remove the putative advantage in a trial setting of the more rapid anti-platelet effect of ticagrelor, an advantage probably more reflective of the delay of treatment initiation in the trial setting than a real-life advantage.

Aspirin was a required concomitant treatment unless contraindicated, with dose chosen by the investigator, although 75-100 was recommended after a larger loading dose and 325 post-stenting was allowed.

It is apparent that there are many potential subgroups of interest. To name a few:
- Initial diagnoses (STEMI, NSTEMI, UA)
- Pre-randomiztion clopidogrel or not
- Early vs late PCI
- Region
- Aspirin dose

Study endpoints were assessed by an Independent Central Adjudication Committee and their assessments were the planned study endpoints. Investigators also provided assessments of endpoints and Dr. Marciniak has carried out analyses of these, which were numerically different and sometimes led to different conclusions. Absent some formal reason to prefer the investigator assessment, however, I do not believe we should reject the planned adjudicated study endpoint. This view could change if we undertook a formal, blinded assessment of the analyses.

The overall results of PLATO were strongly positive. Not surprisingly, given the 18,000 patient sample size, baseline characteristics were extremely similar (Fiorentino review of June 25, 2010, Table 5, p 36), as were features of medical history (Fiorentino, Table 6, p 37). The population had similar histories of angina (45%), past AMI (205%), CAD (27.5% - odd given the reported 45% angina), PCI (13%), CABG (6%), hypertension (65-66%), diabetes (25%), and used similar concomitant medications, including 30-36% ACEIs, organic nitrates, statins, and beta-blockers; and 14% PPIs.

PLATO results are shown in the following table:

	Ticagrelor n = 9333	Clopidogrel n = 9291	HR	P-value
Primary CCVD, NFMI, NF Stroke	864 (9.3%)	1014 (10.9%)	0.84 (0.27, 0.92)	0.0003
NFMI (not silent)	504 (5.4%)	593 (6.4%)	0.84 (0.75, 0.95)	0.0045
CV Death	353 (3.8%)	442 (4.8%)	0.79 (0.69, 0.91)	0.0013
NF Stroke	125 (1.3%)	106 (1.1%)	1.17 (0.91, 1.52)	0.22

[primary endpoint includes only first event]

The K-M curve is shown below
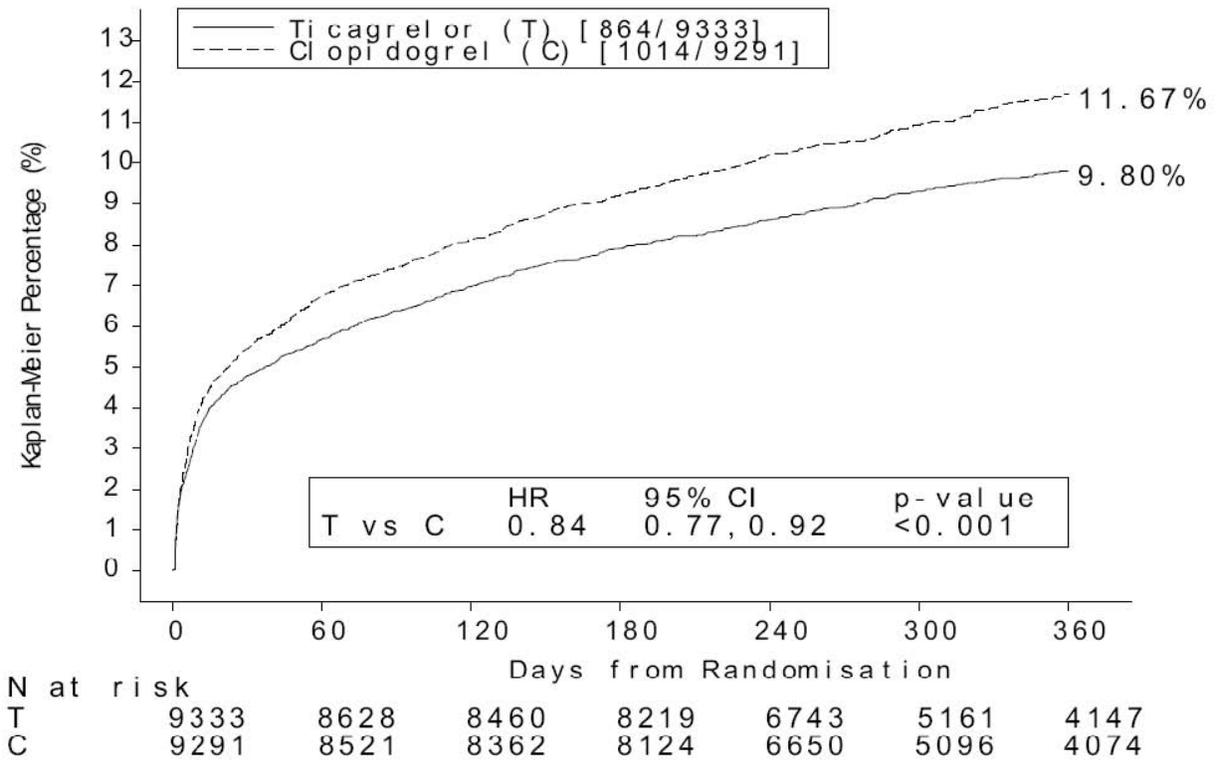
As shown in the K-M curve above for the primary endpoint, the curves continue to diverge for the duration of the study. It has become common practice to compare early and later results. The 0-30 and 31-360 day curves show only a modest early advantage (hardly any for a few days) and a growing benefit over time.
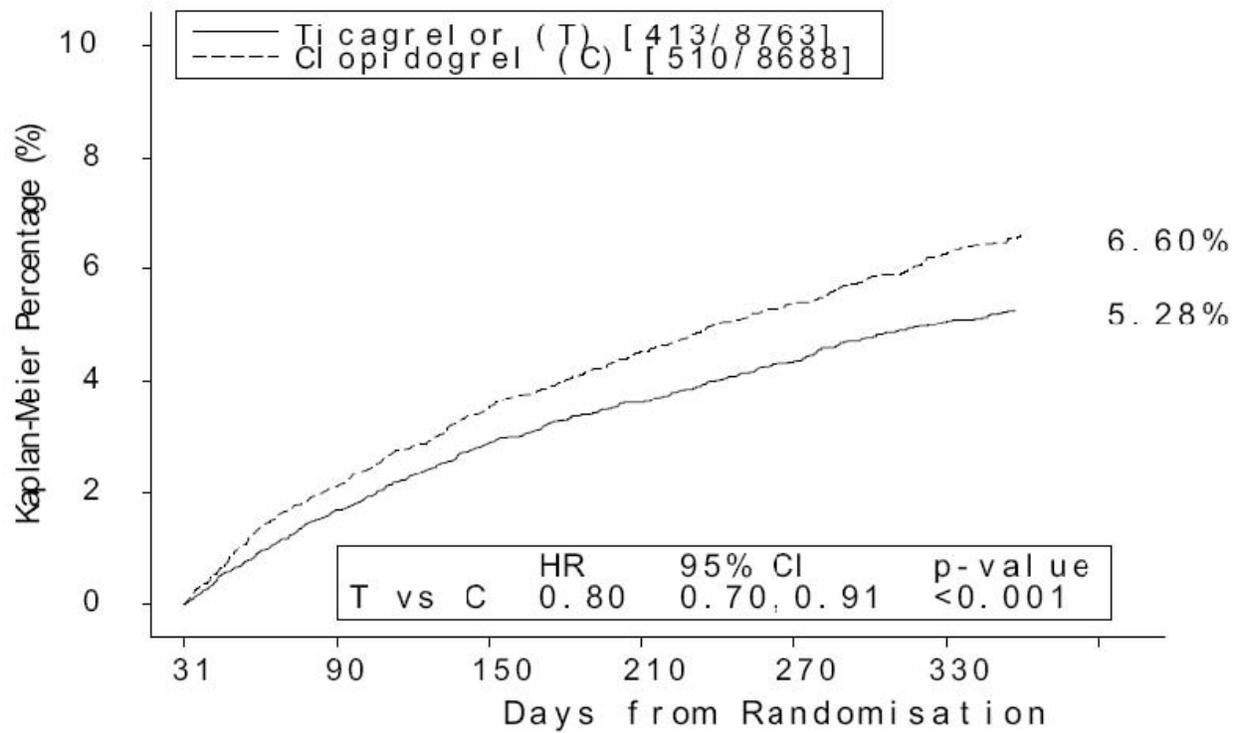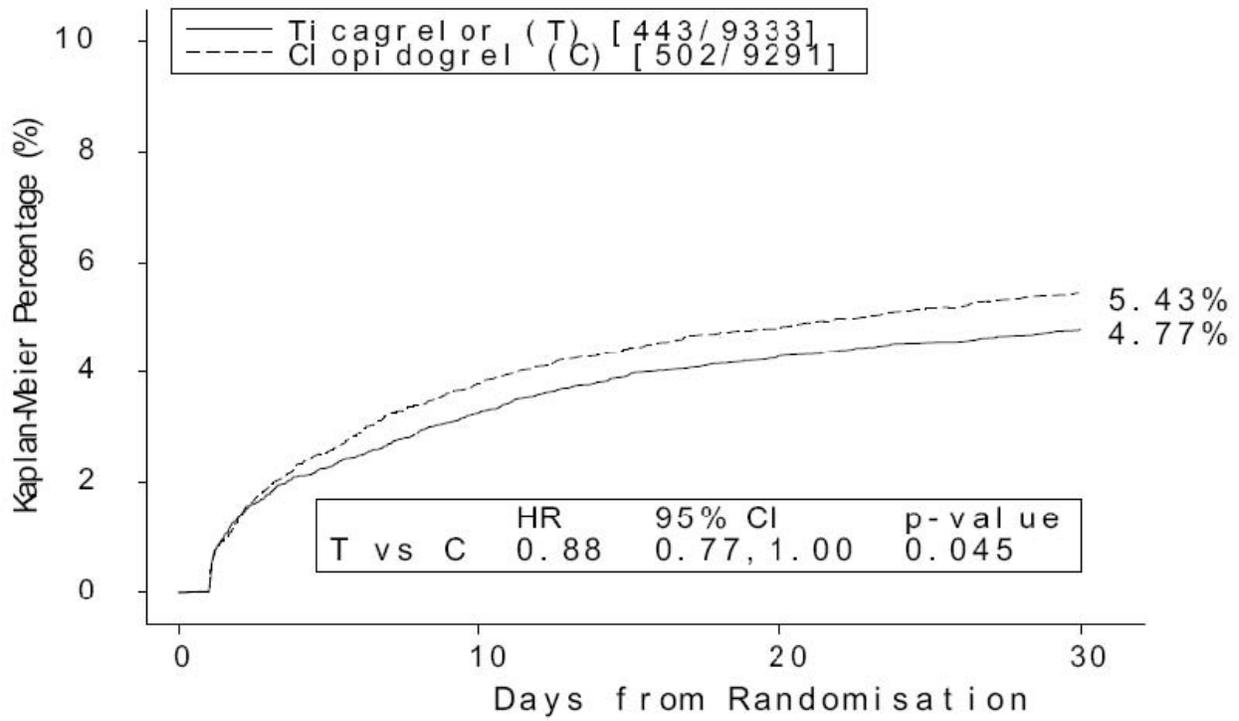
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Landmark Analysis

	Ticagrelor		Clopidogrel			
Primary Endpoint	n	events	n	events	HR	P-value
1-30 days	9333	443 (4.7%)	4291	502 (5.4%)	0.88 (0.77, 1.00)	0.045
31-360 days	8763	413 (4.7%)	8688	510 (5.9%)	0.80 (0.70, 0.91)	0.0008

A huge number of baseline (mostly) subsets were examined for the primary endpoint, including demographic, region, concomitant illness, planned invasive or medical treatment, final diagnosis (not quite baseline), CV history, concomitant drug use. The following figure shows hazard ratios and KM rates for MACE for many subgroups.

Figure 7. Hazard Ration and Rates of Primary Endpoint by Subgroup (forest plot)

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
Overall Treatment Effect					
Primary Endpoint		18624	9.8	11.7	0.84 (0.77, 0.92)
Age Group					
<65 Years		10643	7.2	8.5	0.85 (0.74, 0.97)
>=65 Years		7979	13.2	16.0	0.83 (0.74, 0.94)
<75 Years		15744	8.6	10.4	0.82 (0.74, 0.91)
>=75 Years		2878	16.8	18.3	0.94 (0.78, 1.12)
Sex					
Male		13336	9.2	11.1	0.85 (0.76, 0.95)
Female		5288	11.2	13.2	0.83 (0.71, 0.97)
Race					
Caucasian		17077	9.5	11.2	0.85 (0.77, 0.94)
Black		229	13.0	19.6	0.63 (0.32, 1.23)
Oriental		1096	12.5	14.8	0.87 (0.62, 1.21)
Other		221	14.4	21.4	0.63 (0.33, 1.21)
BMI Group					
<30 kg/m2		13354	10.1	11.9	0.86 (0.77, 0.95)
>=30 kg/m2		5178	8.9	10.8	0.83 (0.69, 0.99)
Median Weight (gender)					
males <82kg / females <71kg		9001	11.4	12.5	0.93 (0.82, 1.05)
males >=82kg / females >=71kg		9567	8.2	10.8	0.76 (0.67, 0.87)

0.5   1.0   2.0
← Ticagrelor (Ti.) better   Clopidogrel (Cl.) better →

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
Region					
Asia/Australia		1714	11.4	14.8	0.80 (0.61, 1.04)
Cent/Sth America		1237	15.2	17.9	0.86 (0.65, 1.13)
Euro./Mid E./Afr.		13859	8.8	11.0	0.80 (0.72, 0.90)
North America		1814	11.9	9.6	1.25 (0.93, 1.67)
Diabetes Mellitus					
No		13962	8.4	10.2	0.83 (0.74, 0.92)
Yes		4662	14.1	16.2	0.88 (0.76, 1.03)
Planned Treatment Approach					
Invasive		13408	8.9	10.6	0.84 (0.75, 0.94)
Medically managed		5216	12.0	14.3	0.85 (0.73, 1.00)
CYP3A Inhibitor (rand.)					
No		16717	9.7	11.6	0.84 (0.77, 0.93)
Yes		1907	10.4	12.1	0.85 (0.65, 1.12)
Glycoprotein IIb/IIIa (Index)					
No		13562	9.7	11.9	0.82 (0.74, 0.92)
Yes		5062	10.0	11.1	0.90 (0.76, 1.07)
ACE Inhibitor use (rand.)					
No		8102	9.4	10.6	0.90 (0.78, 1.03)
Yes		10522	10.1	12.5	0.81 (0.72, 0.91)
Final Diagnosis					
Unstable angina		3112	8.6	9.1	0.96 (0.75, 1.22)
NSTEMI		7955	11.4	13.9	0.83 (0.73, 0.94)
STEMI		7026	8.5	10.1	0.84 (0.72, 0.98)
Other		489	9.1	14.7	0.58 (0.34, 1.00)

0.5   1.0   2.0
← Ticagrelor (Ti.) better   Clopidogrel (Cl.) better →

Hazard Ratio (95% CI) — **Total Patients** — **KM % at Month 12 (Ti. / Cl.)** — **HR (95% CI)**

Characteristic	Total Patients	KM % at Month 12 Ti.	Cl.	HR (95% CI)
Hx of PCI				
No	16132	9.1	11.2	0.82 (0.74, 0.90)
Yes	2492	14.1	14.6	0.98 (0.79, 1.22)
Hx of CABG				
No	17518	9.2	11.0	0.84 (0.77, 0.93)
Yes	1106	19.5	21.7	0.88 (0.67, 1.15)
Index Event to Study Med				
< 12 hours	9556	8.2	10.4	0.79 (0.69, 0.90)
>= 12 hours	8854	11.4	12.9	0.90 (0.79, 1.01)
NSTEMI TIMI Risk Score				
0-2	730	4.2	4.1	1.11 (0.53, 2.31)
3-4	5488	8.2	10.9	0.77 (0.64, 0.92)
5-7	4849	14.4	15.6	0.92 (0.79, 1.07)
STEMI TIMI Risk Score				
0-2	3889	4.7	6.2	0.76 (0.58, 1.01)
3-6	2884	12.6	13.7	0.91 (0.74, 1.12)
>6	253	19.6	30.1	0.62 (0.37, 1.06)
Weight Group				
<60 kg	1312	13.1	17.3	0.75 (0.56, 0.99)
>=60 kg	17256	9.5	11.2	0.86 (0.78, 0.94)
<80 kg	9055	11.4	12.8	0.90 (0.79, 1.01)
>=80 kg	9513	8.3	10.5	0.79 (0.69, 0.90)

Scale: 0.5 — 1.0 — 2.0
← Ticagrelor (Ti.) better   Clopidogrel (Cl.) better →

Characteristic	Total Patients	KM % at Month 12 Ti.	Cl.	HR (95% CI)
Waist Circ.				
<100 cm	9627	9.6	11.1	0.88 (0.77, 1.00)
>=100 cm	7978	9.7	12.1	0.79 (0.69, 0.91)
Unknown	1019	12.6	13.4	0.95 (0.66, 1.35)
Lipid-Lowering use (rand.)				
No	3768	11.0	11.2	1.02 (0.83, 1.24)
Yes	14856	9.5	11.8	0.80 (0.73, 0.89)
Beta Blocker use (rand.)				
No	4564	9.0	11.6	0.79 (0.65, 0.95)
Yes	14060	10.1	11.7	0.86 (0.78, 0.96)
First Troponin I				
Positive	15089	10.3	12.3	0.85 (0.77, 0.94)
Negative	2968	7.0	7.0	1.00 (0.75, 1.32)
Antiplatelet Therapy				
None	12147	8.2	10.0	0.82 (0.73, 0.93)
Clopidogrel	289	18.7	17.1	1.26 (0.70, 2.28)
ASA	5024	11.8	14.0	0.84 (0.71, 0.98)
Clopidogrel+ASA	1108	15.0	18.0	0.88 (0.65, 1.19)
Other	56	24.4	13.9	1.93 (0.55, 6.85)

Scale: 0.5 — 1.0 — 2.0
← Ticagrelor (Ti.) better   Clopidogrel (Cl.) better →

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
ASA at Rand.					
No		927	11.6	13.8	0.87 (0.60, 1.27)
Yes		17697	9.7	11.6	0.84 (0.77, 0.93)
Clopidogrel loading dose					
300 to 375 mg		7449	9.2	12.0	0.77 (0.65, 0.91)
600 to 675 mg		3104	7.2	9.1	0.79 (0.61, 1.03)
Other		2036	10.1	11.6	0.84 (0.63, 1.13)
Continuing on clopidogrel		1004	17.6	17.9	1.09 (0.80, 1.48)
No clopidogrel >75mg		5031	9.9	10.9	0.77 (0.41, 1.44)
Previous MI					
No		14800	8.6	10.2	0.85 (0.76, 0.94)
Yes		3824	14.6	17.4	0.84 (0.71, 0.99)

0.5   1.0   2.0

← Ticagrelor (Ti.) better   Clopidogrel (Cl.) better →

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
Heparin use					
No		6696	10.4	12.6	0.84 (0.73, 0.98)
Yes		11928	9.5	11.1	0.85 (0.75, 0.95)
Angiotensin II (rand.)					
No		16981	9.6	11.6	0.83 (0.76, 0.92)
Yes		1643	11.8	12.8	0.96 (0.72, 1.28)
Ca-Channel Blocker (rand.)					
No		15888	9.6	11.3	0.86 (0.78, 0.95)
Yes		2736	10.8	13.8	0.76 (0.61, 0.95)
Hx of TIA/Non-Haem. Stroke					
No		17462	9.2	11.1	0.84 (0.76, 0.93)
Yes		1152	19.0	20.8	0.87 (0.66, 1.13)
PPI use (rand.)					
No		12249	9.2	11.0	0.83 (0.74, 0.93)
Yes		6375	11.0	12.9	0.86 (0.75, 1.00)

0.5   1.0   2.0

← Ticagrelor (Ti.) better   Clopidogrel (Cl.) better →

The forest plots show great consistency, with one major exception, a distinctly poorer result in North America (mainly US, some Canada), and a few other differences (smaller effect in patients with a diagnosis of unstable angina, patients with history of PCI).

III. Subset Analyses - MACE

Although we are appropriately wary of subset analyses, it is usual to look at components of a primary endpoint, different baseline diagnoses (UA, STEMI, NSTEMI), regional differences and many others, as the forest plots almost invariably shows in publications and the growing number of forest plots in labeling demonstrates.

A. Index ACS event

The effect of ticagrelor seemed greater in the STEMI/NSTEMI patients than in the UA patients.

	N	Ticagrelor Events (%)	Clopidogrel Events (%)	HR
STEMI	7026	281/3496 (8.5%)	337/3530 (10.1%)	0.84 (0.72, 0.88)
NSTEMI	7955	432/4005 (11.5%)	510/3950 (13.9%)	0.83 (0.73, 0.94)
UA	3112	124/1549 (8.0%)	132/1563 (9.1%)	0.96 (0.75, 1.22)

B. Planned Invasive Management

N	Ticagrelor	Clopidogrel	HR
Invasive 13,408	569/6732 (9.0%)	668/6676 (10.1%)	0.84 (0.75, 0.94)
Medical 5216	295/2601 (12.1%)	346/2615 (14.3%)	0.85 (0.73, 1.00)

It appeared that much of the late advantage of ticagrelor was in the medically managed patients.

Figure 8. KM Curve: Planned Invasive vs. Medical Management
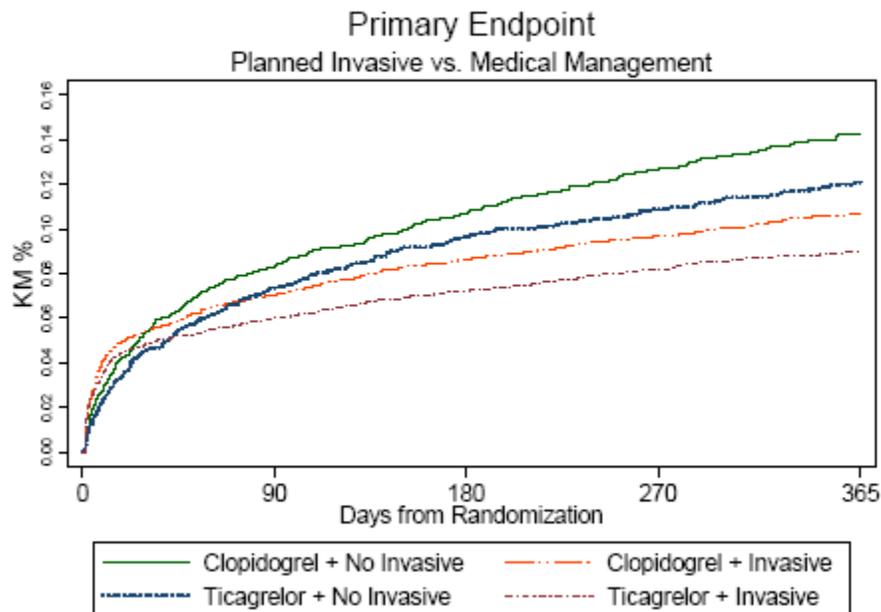
Results were similar in patients who actually had PCI within 24 hours of randomization.

Figure 9. Kaplan-Meier plot of primary clinical endpoint events for patients intended to have invasive management who received PCI within 24 hours
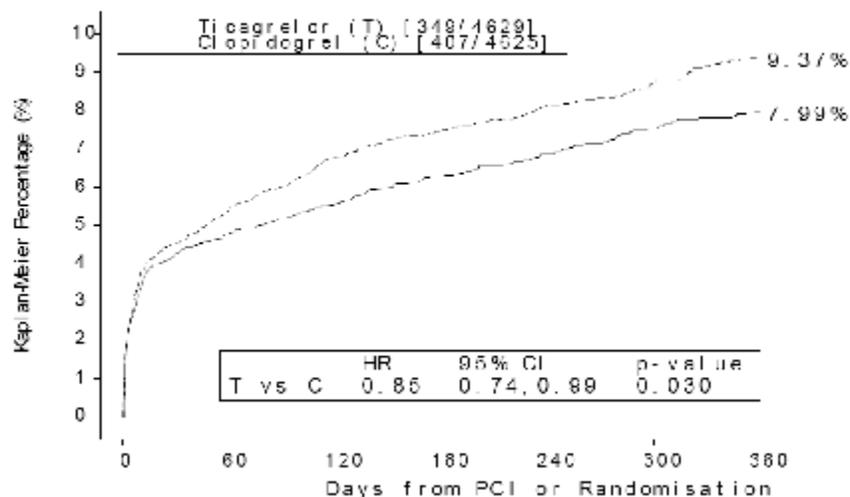
C. Clopidogrel Use at Randomization

Early open-label clopidogrel might be expected to reduce an advantage of "rapid-acting" ticagrelor and it may indeed have done so, at least a little, but the results are not consistent.

	Ticagrelor Patients with event		Clopidogrel Patients with event		HR
Open Label before randomization	Yes 3422	330 (9.6%)	3401	370 (10.9%)	0.89 (0.76, 1.03)
	No 5911	534 (9.0%)	5890	644 (10.9%)	0.82 (0.73, 0.92)
Open Label before randomization	Yes 4441	410 (9.2%)	4410	493 (11.2%)	0.82 (0.72, 0.94)
	No 4892	454 (9.3%)	4881	521 (10.7%)	0.87 (0.76, 0.98)
Open Label before randomization	Yes 3748	330 (8.8%)	3701	408 (11.0%)	0.80 (0.69, 0.92)
	No 5585	534 (9.6%)	5590	606 (10.8%)	0.88 (0.78, 0.99)

D. Regional Differences

As has been apparent from the beginning of the review, the principal problem with PLATO is the regional difference, i.e.,
a distinctly poorer result in NA/US, an obvious concern for a drug intended for use in the US population,1
Regional results were:

Figure 20. Forrest Plot: Region

Source: Sponsor, CSR Fig. 16, page 159

11
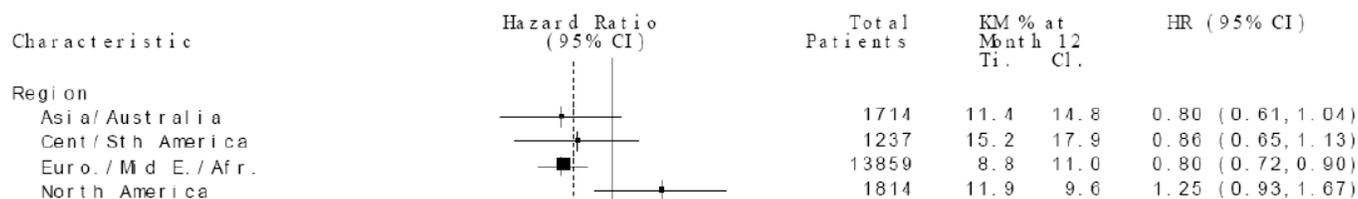
Country by country results are shown in a funnel plot

Figure 24. Funnel plot by Country
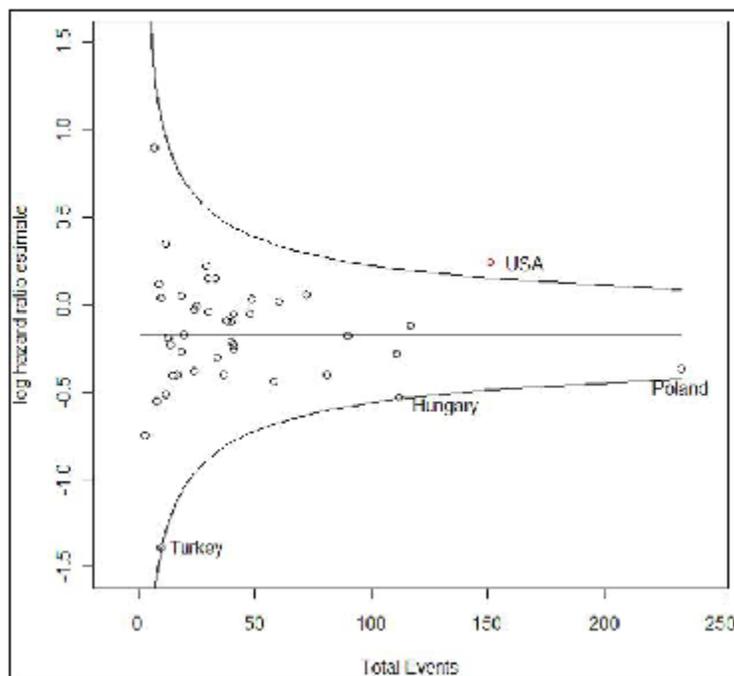
Source: Jialu Zhang, FDA Biostatistician

	Ticagrelor	Clopidogrel	HR	P
Overall n = 18,624	864/9333 (9.8%)	1014/9291 (11.7%)	0.84 (0.77, 0.93)	< 0.001
Non-US n = 17,211	780/8626 (9.6%)	947/8585 (11.8%)	0.81 (0.74, 0.90)	< 0.0001
US n =1413	84/707 (12.6%)	67/706 (10.1%)	1.27 (0.92, 1.75)	0.146

HRs in other regions ranged from 0.76 (E Europe) to 0.86 (Latin America). The fact that US results actually leaned adversely (as opposed to being merely neutral) has been extensively noted but given the small US sample, this adverse "lean" is based on an excess of just 17 events, and should probably not be over-interpreted. What is clear is that there is unequivocal heterogeneity of the results, with an overall region-treatment heterogeneity (p = 0.045) and a US/non-US heterogeneity of about p = 0.001, not overwhelming, but quite strong. It is also noteworthy that the "weaker" result was present for both NFMI and CV death, somewhat surprising if the difference were random. Again, of course, the numbers of events are small.

	Region	n	Events	n	Events	HR	P	P-interaction
Primary	US	707	84 (11.9%)	706	67 (9.5%)	1.27	0.15	0.009
	OUS	8626	780 (9.0%)	8585	947 (11.0%)	0.81	< 0.0001	
CV death	US	707	24 (3.4%)	706	19 (2.7%)	1.26	0.45	0.12
	OUS	8626	329 (3.8%)	8585	423 (4.9%)	0.77	0.0005	
NFMI	US	707	64 (9.1%)	706	47 (6.7%)	1.38	0.10	0.007
	OUS	8626	440 (5.1%)	8585	546 (6.4%)	0.80	0.0004	

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The OUS/US difference has been the subject of intense scrutiny. There have been found to be many baseline differences between the US and OUS populations (greater weight in US; different distribution of index events, with 67/5 NSTEMI in US vs 40.7% OUS and 15.7% STEMI in US vs 39.5% OUS; more prior PCI in US (29.4% vs 12.1%) and more prior CABG (16.7% vs 5.1%)). There were also drug treatment differences, including those in the following table:

Measure	US n = 1413	OUS n = 17,211
> 12 hr from index event to first dose	63%	46%
Intended invasive	94%	70%
Early PCI (< 24 hr)	61%	49%
DES	46%	19%
Bare Metal Stent	23%	46%
GP IIb/IIIa use	50%	25%
Beta blocker day 1	87%	75%
ASA dose (median) median	325	100
Mean	217	99
Median ASA > 300	44%	1.4%

There are thus clear differences between the US and OUS populations, but both populations had representation of patients with all variables, so that as single variables these differences do not explain the results, except for aspirin dose (more about that below).

USA

Non US

Hazard ratio

Hazard ratio

USA

non US

Hazard ratio

Hazard ratio
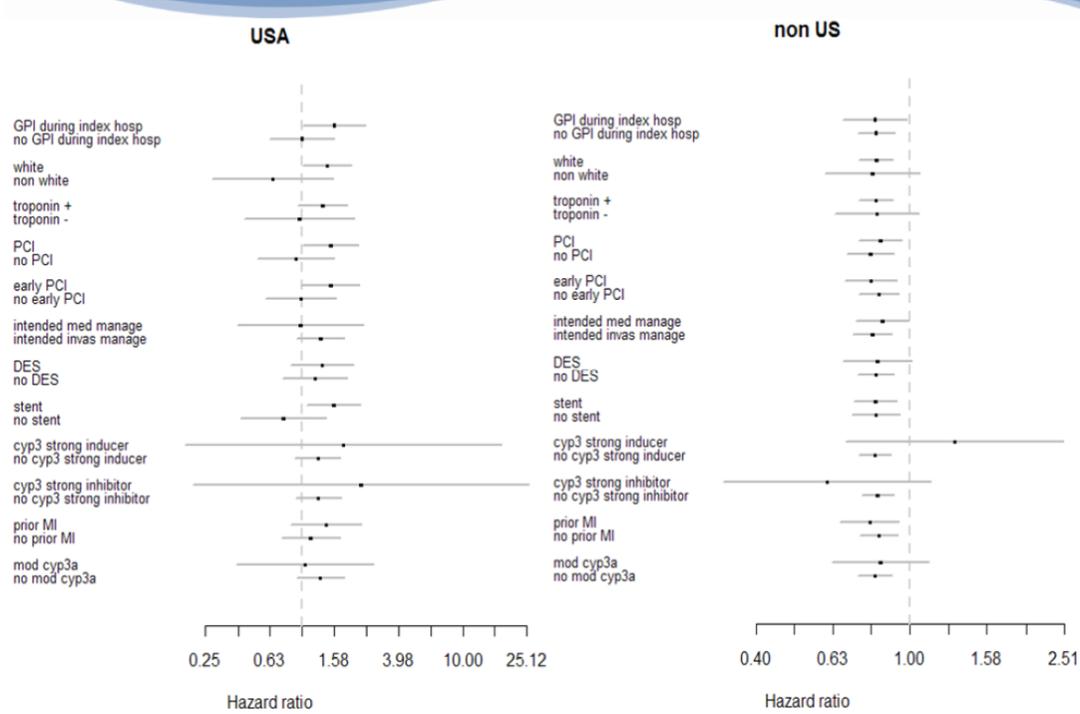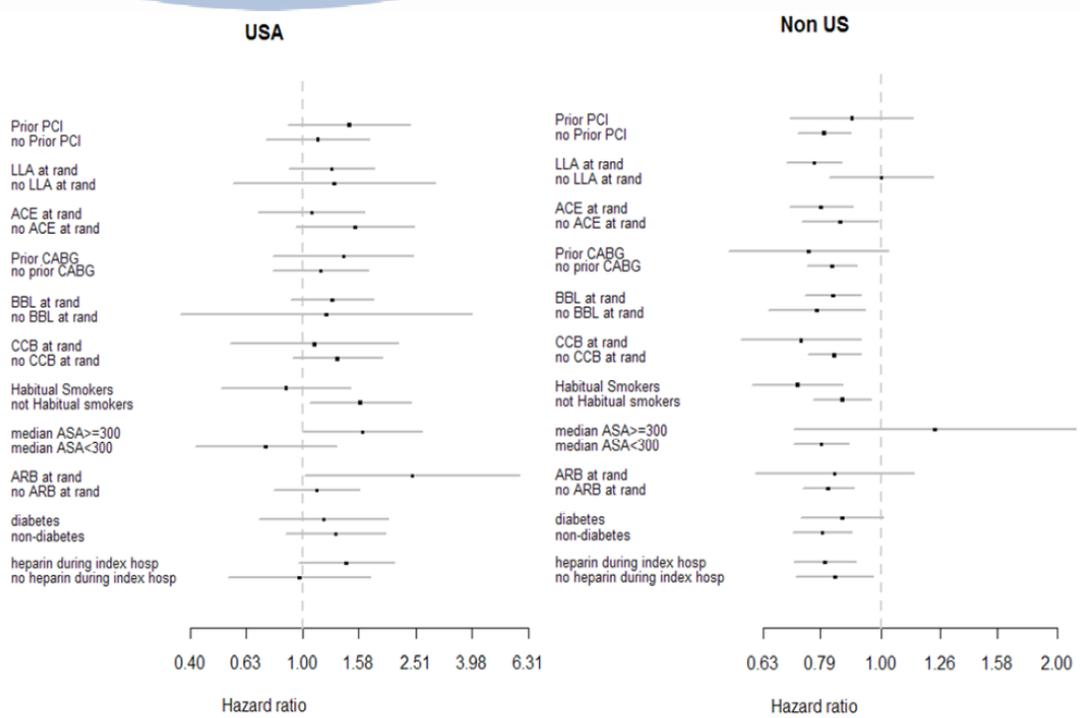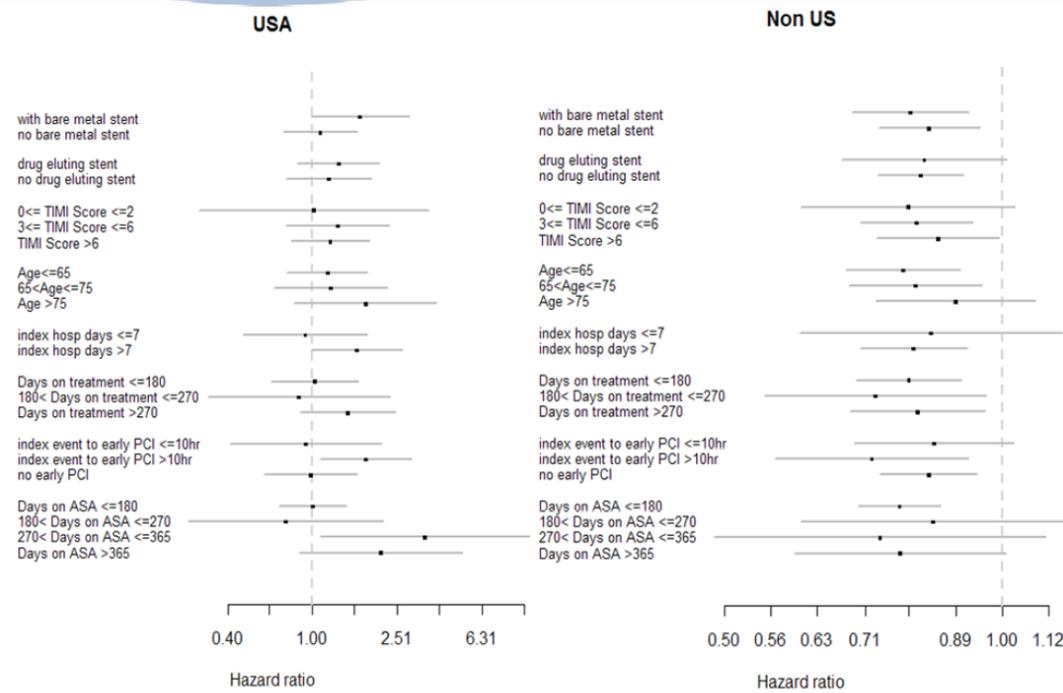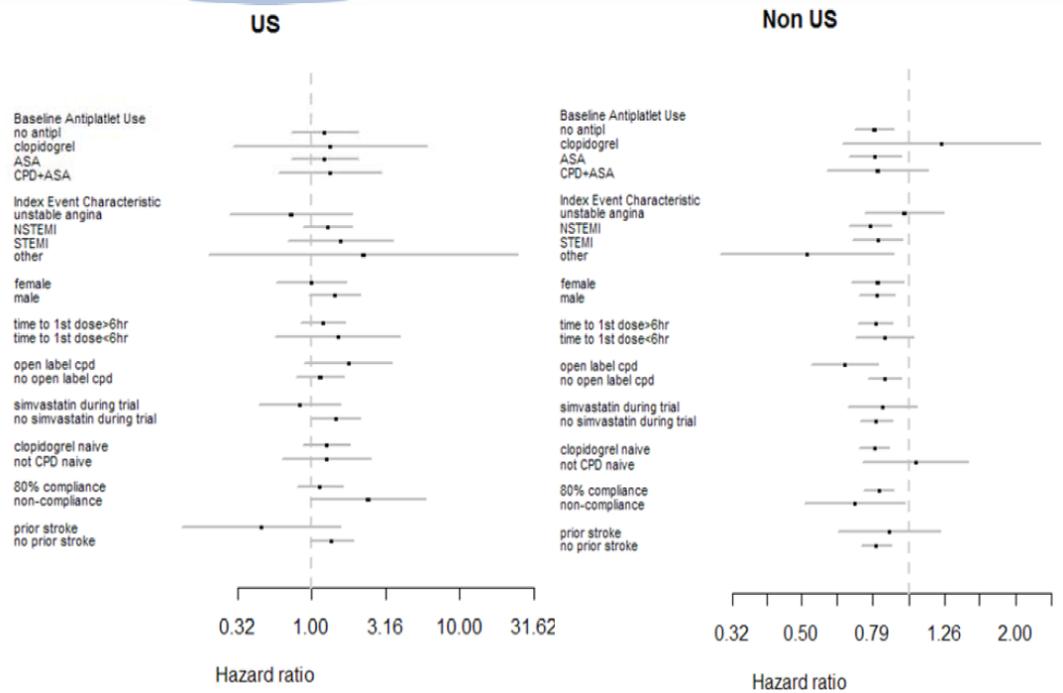
For all other variables, results are region-consistent; favorable OUS and adverse or neutral in US. In addition to looking at single variables, Dr. Zhang performed multivariate analyses using these covariates; these did not explain the US/OUS difference. Another display of this is a figure relating many variables to the extent to which they explain the regional interaction. Only aspirin dose seems to do so.

PLATO: No Factor Potentially Accounts for the Regional Interaction with the Exception of ASA Maintenance Dose During Therapy

CC-84
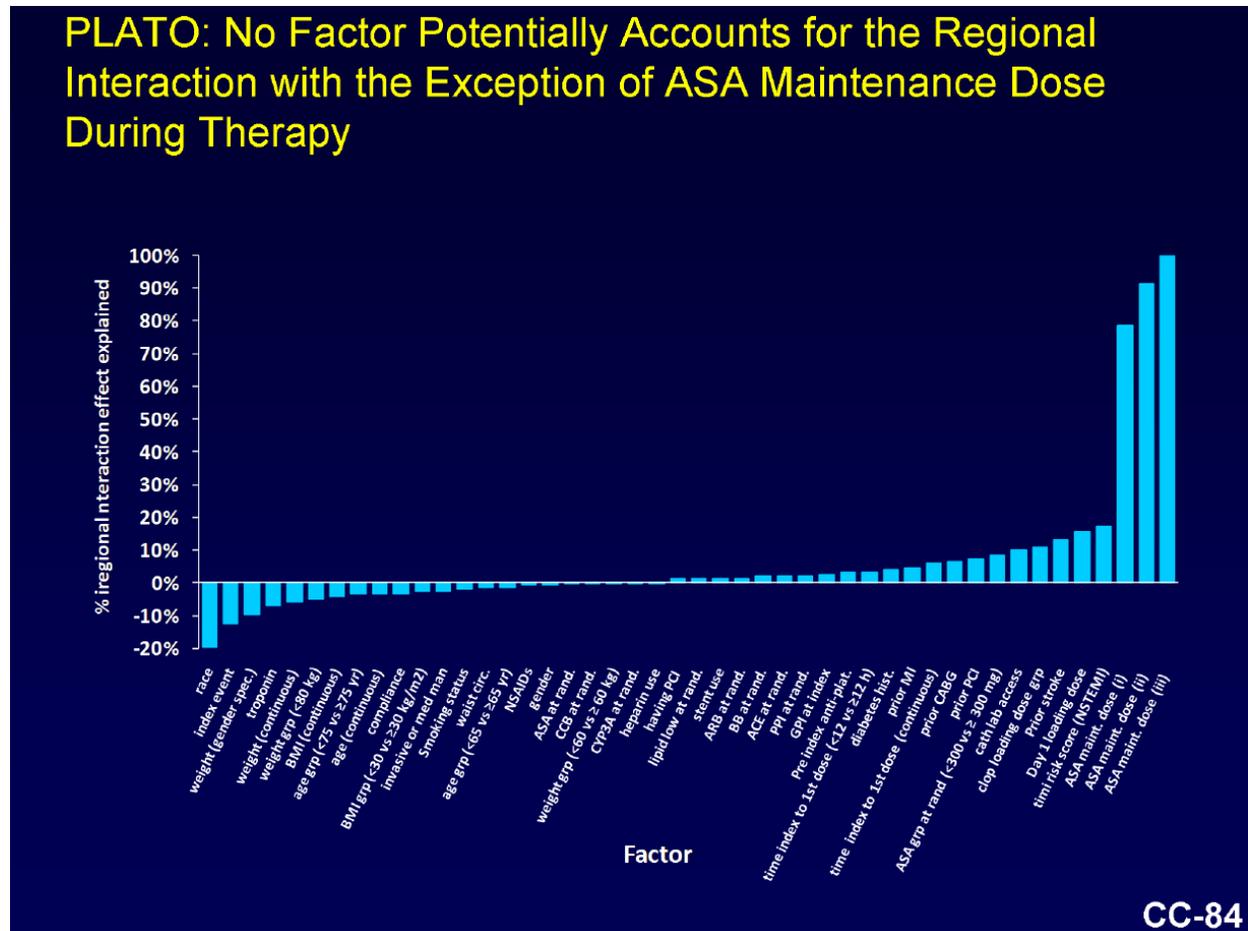
E. Effect of aspirin dose

The sponsor made a significant effort to establish the aspirin maintenance dose in the US and OUS (this was not easy because ASA dose was not recorded continuously. Their conclusion was that the aspirin dose, based on their preferred estimates of dose, explained essentially all of the regional disparity.

PLATO: Similar Pattern of Treatment Effects in Relation to ASA Maintenance Dose in US and Non-US
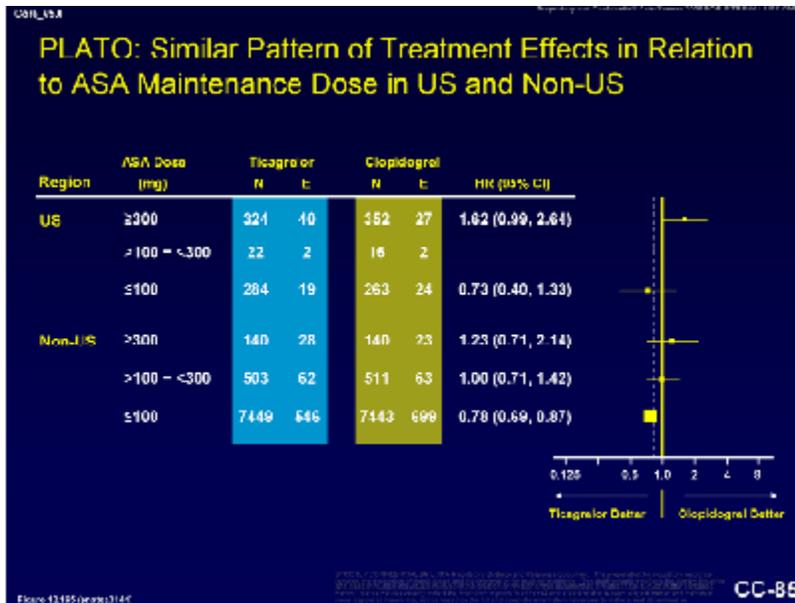
In particular, US results in the ≤ 100 mg ASA group are virtually identical to the OUS results, and results at ASA ≥ 300 mg are uniformly adverse, favoring clopidogrel both in the US and OUS. The nominal P value for the difference between the higher and lower dose results is p = 0.00006.

	ASA ≤ 100		ASA ≥ 300	
	US	OUS	US	OUS
Primary C	9.1% (24/263)	9.4% (699/7443)	7.7% (27/352)	16% (23/140)
T	6.7% (19/284)	7.3% (546/7449)	12% (40/324)	20% (28/140)
CV Death C	2.7% (7/263)	4.1% (302/7443)	1.7% (6/352)	7.1% (10/140)
T	2.1% (6/284)	2.8% (209/7449)	3.7% (12/324)	7.9% (11/140)
NFMI C	6.8% (18/263)	5.5% (413/7443)	5.7% (20/352)	10% (14/140)
T	4.6% (13/284)	4.5% (335/7449)	9.6% (31/324)	14% (19/140)

These results are very impressive on face, showing great similarity for all endpoints between US and OUS results once patients are divided into high and low aspirin dose, but there remains uncertainty as to just how ASA dose was defined. If this question can be explored fully and validated, a statistically powerful explanation for the regional heterogeneity would exist, with a very extreme statistical significance. Apart from the above issue of how aspirin dose was determined, this conclusion is limited by the lack of a clear mechanistic explanation of why ASA ≥ 300 interferes with the effect of ticagrelor [It does not, in Oasis 7, seem to enhance a low dose (75 mg) of clopidogrel, another possible explanation of the results above.]

IV. Concerns about the Aspirin Conclusion

Drs. Fiorentino, Zhang, and Stockbridge have noted the impressive aspirin dose effect but do not at this time urge approval of ticagrelor. One concern is that aspirin dose is not a baseline characteristic and could have been influenced by patient status. That is undoubtedly true, but it would matter only if the choice was differentially chosen for the two drugs, e.g. that patients doing badly on ticagrelor tended to be

moved to 300 mg aspirin but similar patients on clopidogrel were not. It is difficult to imagine how this could occur. There was in Europe evidence that higher risk patients (with higher event rates) were given higher doses of aspirin, but this was true for both treatment groups and cannot explain the findings.

It was clear that different attitudes toward dose prevailed in US and OUS. Aspirin dose was roughly evenly split in US between < 100 and > 300 mg. In contrast, in OUS patients, barely 2% received a dose of > 300 mg, a marked difference in practice. Nonetheless, as noted the higher dose appeared to obliterate any advantage of ticagrelor in the OUS patients.

Dr. Zhang has examined US/OUS results with ASA dose defined in various ways by the sponsor in a June 8, 2010 submission and although most methods show very similar results (low dose ASA favorable in US and OUS), not all do or do so due to the same extent. It is plainly critical that the ASA dose relationship be very robust, not dependent on small numbers of classification decisions.

It seems clear that we must understand exactly how ASA dose was determined for these analyses, and how much the analyses changed with various decisions. I believe, as will be explained further, that if the sponsor can show the ASA dose explanation is robust to differences in methods of determining what dose patients took, ticagrelor should be approved to provide patients with the first P2Y12 antagonist that has had a clear survival effect.

V. Action to Be Taken

There is long-standing and well-established concern, expressed by Yusuf, Peto, and many others, with over-concentration on subset effects in outcome studies. All commenters on these data are aware of this, but are concerned by the particular nature of the US/OUS difference – the drug, after all, is intended for a US population. The Cardio-Renal Advisory Committee, after extensive discussion, concluded that the US/OUS difference was most likely due to chance and recommended approval, 7 to 1. I have considerable sympathy with that conclusion, but as noted earlier, although numbers are small, all components of the MACE endpoint show the US/OUS difference, which I find concerning. In considering the aspirin "explanation," there have been two major concerns. One is whether the estimates of use of doses (number of patients < 100 mg and > 300 mg) are accurate (do we really know what dose a patient took at a given time or over a given period). The second is whether the decision about the dose to attribute to patients is credible and unbiased; i.e., there are many ways to assign the dose in the face of different doses being given to patients early and late, occasional brief changes, etc. Given a range of ways to calculate this (characterized in Dr. Zhang's review as "original definition," "MEDIAN 55," "Median 10, 20, 24, 25, etc," how much do results depend on the specific way dose is calculated? My read of Dr. Zhang's results is that all of the methods (except one with an odd measure of total aspirin dose) show consistently that higher doses in US and OUS lead to an HR (vs clopidogrel) of > 1, but this needs further close analysis and our CR letter will ask the applicant for a detailed presentation of all methods used (and with databases we can use to examine all conclusions), including some approaches different from their's.

In dealing with subgroups that were not pre-specified, we exercise great caution, but we have at times included results in labeling (LIFE study notes that the advantage of losartan over atenolol was not seen in Black patients; Val-HEFT gave a claim for CHF only for valsartan added to placebo, not added to an ACEI; MERIT trial of slow-release metoprolol with markedly inferior overall effect and no mortality effect in US). In another case, benefits of ARB's on preserving kidney function in the RENAAL and IDNT studies were minimal to absent in the US and were driven by the "Asian region." This did not affect approval.

In the present case, although there are various population and treatment differences, as decribed above, none of them provide any explanation of the different outcome results in the US and OUS except for ASA

dose. Once one begins to consider subsets (US vs OUS), even ones of interest, it seems hard to justify ignoring the ASA subset when it provides a statistically overwhelming explanation of the US/OUS difference (if we believe the dose assignments).

The CR expresses concern about the US/OUS difference and reluctance to dismiss the finding, but it also clearly conveys the idea that the ASA dose explanation, if stringently defined and tested and consistent, could be a basis for a favorable conclusion on resubmission. We will clearly have an opportunity to probe these data further.

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/s/

MICHAEL V MONTELEONE
12/16/2010

ROBERT TEMPLE
12/16/2010

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 22433 Ticagrelor (Brilinta) for reduction of cardiovascular events in patients with ACS.

Sponsor: Astra Zeneca

Review date: 26 September 2010

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22433
HFD-110/Monteleone/Marciniak

This memo conveys the Division's recommendation to issue a "Complete Response" letter for this application.

This application has been the subject of reviews of CMC (Tele and Wong; 23 July 2010, 12 August 2010), biopharmaceutics (Duan 23 July 2010), pharmacology/toxicology (Hausner; 23 June 2010, 10 August 2010), clinical pharmacology (Younis, Krudys, Pacanowski; 27 June 2010, 29 August 2010), clinical effectiveness (Fiorentino; 25 June 2010, 25 August 2010), clinical safety (Blank; 28 June 2010, 20 July 2010, 25 August 2010) and statistics (Zhang; 29 June 2010, 31 August 2010). There is also a CDTL memo (Marciniak; 17 September 2010).

Ticagrelor has ⬚ (b) (4). There are no residual CMC issues. Different dissolution specifications are recommended; unusually, the recommended specifications are less onerous than the sponsor proposed.

There are no remaining pharmacology or toxicology issues. One degradant generated a structural alert as a possible genotoxicant; this was assessed in an Ames assay and found acceptable.

Of note, ticagrelor is a reversible inhibitor at the P2Y12 receptor, which mediates ADP-dependent platelet inhibition. Unlike irreversible inhibitors, clopidogrel and prasugrel, inhibition takes places through binding at the adenosine receptor, and this effect is not specific for the adenosine receptor of the platelet; there are similar IC50s for the human platelet ADP receptor and for the human adenosine A3 receptor. Off-target effects on adenosine receptors elsewhere are thought to underlie ticagrelor's effects of dyspnea and ventricular pauses. Ticagrelor also has a similar IC50 for PDE5, but no human adverse events have been attributed to this effect.

Ticagrelor and its main (CYP 3A) metabolite are equipotent platelet inhibitors. Absolute bioavailability is about 36%; about 99% of ticagrelor circulates protein-bound. Moderate CYP3A inducers and inhibitors produce about 2-fold effects on exposure; ketoconazole increases exposure about 7-fold. Moderate hepatic impairment and severe renal impairment have lesser effects.

Ticagrelor increases exposure somewhat to digoxin (Pgp inhibition) and statins (CYP 3A inhibition). Statin doses were limited in both groups in PLATO; as Dr. Marciniak notes, the resulting differential exposure to statins may have contributed to beneficial effects observed on ticagrelor.

The onset of platelet inhibition is clearly faster with ticagrelor; by 1 hour ticagrelor 90 mg achieves a higher platelet inhibition than is ever achieved with clopidogrel 600 mg. The offset of platelet inhibition is somewhat faster with ticagrelor 90 mg than it is with

clopidogrel 75 mg; however, ticagrelor achieves higher peak inhibition (IPA in response to 20 μM ADP), so it is not until about 36 hours that the mean response to ticagrelor falls below the mean response to clopidogrel, and it is not until about 48 hours that the response to ticagrelor falls below 30% (thought clinically relevant). Thus, the reversible nature of ticagrelor's blockade remains largely unrealized; its recovery is slower than one would like if one were interested in managing a hemorrhage or urgent surgery. On the other hand, the risk associated with missing a dose of ticagrelor is probably no worse than it is with clopidogrel.

There are no identified genetic factors affecting response—pharmacodynamic or outcomes—to ticagrelor.

The proposed indication is supported by PLATO, a multi-national, event-driven study in which 18624 subjects with either ST-elevation or non-ST-elevation acute coronary syndromes, whether intended for medical or invasive management, were randomized to clopidogrel 75 mg (bolus initiated prior to PCI) or to ticagrelor 90 mg bid and followed for 12 months for time to first event of cardiovascular death, myocardial infarction or stroke. Aspirin was given 75-325 mg per investigator preference.

In my view, there are no major issues with study design or conduct. Dr. Marciniak raises concern about possible unblinding by opening capsules and with the number of study personnel in possession of the randomization list; I have not much concern about this, as referral for adjudication appears to be unbiased. Dr. Marciniak raises concerns about adequacy of follow-up, but missed events would have had to have been very skewed from the overall study to have impacted the outcome.

The main results are shown below:

	Clop	Ticag	HR	P
CV death, MI, stroke	11.7%	9.8%	0.84	0.0003
CV death	5.1%	4.0%	0.79	
MI	6.9%	5.8%	0.84	
Stroke	1.3%	1.5%	1.2	

For subjects presenting with STEMI, the benefit of ticagrelor does not appear during the first month, while for NSTEMI, it appears in the first week (CDTL memo, page 25). This is quite different from the results of TRITON in which a similarly more aggressive platelet inhibitor was compared to clopidogrel, and the benefits appeared within the first day. The difference between the studies may reflect more common early use of clopidogrel in PLATO.

There is a claim made for reduction of stent thrombosis. While not reachable through the planned hierarchical analysis, I would have considered it a valid claim, robust whether one looks at definite only, definite plus probable, or definite through possible stent thromboses. One need only believe clopidogrel not worse than placebo. We reached a similar conclusion with prasugrel.

While I remain concerned about pooling these subgroups of ACS (very different from what was done in TRITON), treatment effects were similar in subjects for whom the planned treatment strategy was medical or invasive, and for those for whom the final diagnosis was STEMI or NSTEMI.

```
Planned Treatment Approach
    Invasive
    Medically managed

Final Diagnosis
    Unstable angina
    NSTEMI
    STEMI
    Other

Region
    Asia/Australia
    Cent/Sth America
    Euro./Mid E./Afr.
    North America
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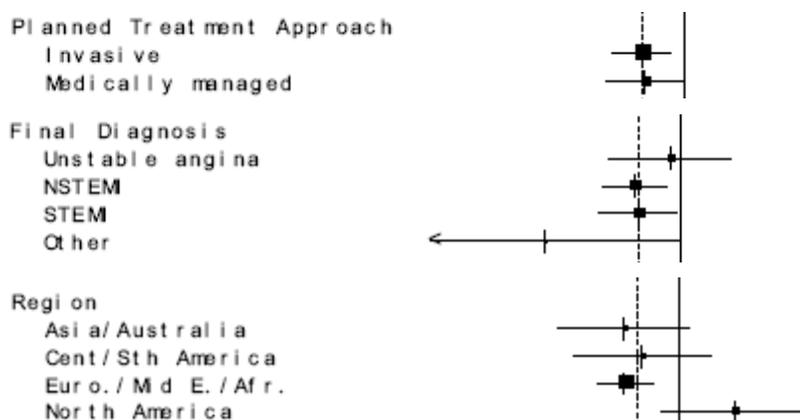
I questioned whether there were reasons to consider independently the various ACS presentations and treatment strategies, and the following table is from Dr. Fiorentino's first review:

Table 22. Primary Endpoint: Planned Treatment Approach at Randomization *vs.* Index ACS event

HR (95%CI) events / N	STEMI	NSTEMI	UA
Medical Mgmt	0.73 (0.46, 1.16) 75/451	0.85 (0.70, 1.02) 416/2910	0.97 (0.69, 1.37) 132/1726
Invasive Mgmt	0.86 (0.72, 1.01) 543/6575	0.82 (0.70, 0.97) 526/5045	0.95 (0.67, 1.35) 124/1386

The only one of these that would have been even nominally statistically significant would have been for invasive management of NSTEMI. Except for the problem that the final diagnosis was not known at randomization, one could argue that no correction was needed for these six independent "studies", but even so, the corresponding p-value might not have been considered sufficient for approval with a single study.

Despite the Advisory Committee's rejection of the idea, I still believe they are sufficiently distinct entities with different responses to treatment, so that they ought to be considered separately. The "pooled" effect is merely an accident of the proportion of subjects who happened to be enrolled.

The development program for prasugrel always considered STEMI distinct from UA/NSTEMI and medical management distinct from invasive management. Thus, currently, labeling for prasugrel only indicates it for use with invasive management (because that is what TRITON was) and never shows the pooled ACS data, even though that was an end point in TRITON. If we think that all ACS is much the same, then perhaps we should revise the prasugrel label accordingly, and halt the ongoing study of prasugrel in medically managed subjects (which was thought sufficiently different by its designers that it utilizes a different dose than did TRITON).

As shown above, effects were heterogeneous with respect to region with the US results being the main driver of the North American anomaly. Substantial efforts have been made by the sponsor and the review team to investigate the cause of the discrepancy in results in the US vs. the rest of the world.

As shown in the table below (Table 1 in the statistical review of 31 August), in the US, ticagrelor fared worse with respect to each of the components of the primary end point.

	Characteristic	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Hazard ratio (95% CI)
Non-US	Composite of CV Death/MI (excl. silent MI)/Stroke	780	947	0.82 (0.74,0.90)
	CV death	329	423	0.77 (0.67, 0.89)
	MI (excl. silent MI)	440	546	0.80 (0.70, 0.90)
	Stroke	118	102	1.15 (0.88, 1.50)
US	Composite of CV Death/MI (excl. silent MI)/Stroke	84	67	1.27 (0.92,1.75)
	CV death	24	19	1.26 (0.69, 2.30)
	MI (excl. silent MI)	64	47	1.38 (0.94, 2.01)
	Stroke	7	4	1.73 (0.51, 5.92)

In the US the point estimate of the hazard ratio was about 1.27. The point estimates for the hazard ratios in placebo-controlled studies of clopidogrel are in the ballpark of 1/1.27, so, by the most generous of non-inferiority calculations, based solely on point estimates, the US results are entirely consistent with there being no effect whatsoever of ticagrelor in the US.

No single or combination of baseline covariates was found to explain the US-foreign differences in outcome. However, post-randomization dose of aspirin does appear to account for regional differences, at least in the statistical sense.

The sponsor proposes, but has not confirmed, a possible means by which aspirin could exert differential effects on clopidogrel and ticagrelor: Aspirin has thromboxane-dependent beneficial effects and prostacyclin-dependent adverse (thrombogenic and vasoconstrictive) effects. At low levels of P2Y12 inhibition, the former effects of aspirin predominate, but high levels of P2Y12 inhibition however obtained (in this case, with the more aggressive dosing of ticagrelor) somehow interfere with the thromboxane pathway. Thus, aspirin is not differentially affecting the ticagrelor group because of ticagrelor so much as it is differentially affecting that group because of its greater platelet inhibition.

Although Dr. Marciniak interprets the study differently, results of CURRENT-OASIS 7 (which has not been reviewed) do provide some support for this hypothesis. In this study, 25086 subjects with ACS and planned invasive management were randomized to clopidogrel high dose (600 mg x 1, 150 mg/day for 5 days, then 75 mg) or low dose (300 mg x 1, then 75 mg daily) and to aspirin high dose (300 mg daily) or low dose (300 mg x 1, then 75-100 mg) with 30-day follow-up for CV death, MI, and stroke. With 1079 MACE events, the study was unsuccessful in showing benefit to a higher dose of clopidogrel, ruling out as much as a 17% benefit. With 568 "major" bleeds (at least 2 unit transfusion), the study showed high-dose clopidogrel 24% worse (UCI 46% worse). Aspirin dose also made no difference on MACE or bleeding, ruling out as much as a 14% difference on MACE or 17% on bleeding. On standard clopidogrel, the HR for MACE high-dose/low-dose aspirin was 1.1 (p=0.3), scant evidence of harm on high-dose aspirin. Since the aspirin dose was different only for the first few days, one might expect any difference in outcomes at early times, but that is not evident in published KM curves.

Dr. Zhang reports the p-value for the US-OUS comparison in PLATO to be <0.01 (the pre-specified 4-region comparison has a somewhat higher p-value). She notes that the chance of the US result being ≥1.27 when the overall HR is 0.84 also has p-value <0.01. The sponsor's analysis of the effect of aspirin has a p-value in the same ballpark—0.003—but Dr. Zhang gives several reasons to question this: (1) It is based on a post-randomization factor. While it may be possible to discuss multiplicity correction for a finite set of baseline factors, it is much more difficult to adjust once one enters the

universe of post-randomization factors. (2) The reported aspirin model is very sensitive to the disposition of a relatively small number of OUS subjects on high-dose aspirin, and generally on who is included in the analyses—subjects with missing data on aspirin dose, those discontinuing aspirin after a single dose, or those never receiving aspirin.

Emphasizing various aspects of these concerns, none of Drs. Zhang, Hung, Fiorentino, and Marciniak are sufficiently convinced of the aspirin hypothesis to base approval upon it. I interpret the call for a confirmatory US study by _____ (b) (4) and by the Advisory Committee to be evidence of similar concern. And I interpret the discussion at the Regulatory Briefing to be further evidence of concern.

Like some on the review team, _____ (b) (4) (acting as consultant to the sponsor), the Advisory Committee, and others, I believe that the effectiveness in the US requires further study. Fewer agree with me that said study needs to be conducted prior to approval.

Dr. Blank tallies the major safety considerations thusly:

	Ticagrelor N=9235 patients with events	Clopidogrel N=9186 patients with events	RR	Increase or decrease in events/1000 patients treated
Death (All-cause)	408 (4.4%)	505(5.5%)	0.8	-10
Major Bleed	961 (10.4%)	929 (10.1%)	1.03	3
Major Fatal/Life-threatening	491 (5.3%)	480 (5.2%)	1.02	1
Fatal Bleed	21 (0.2%)	23 (0.3%)	0.91	0
TIMI defined Major Bleed	657 (7.1%)	638 (6.9%)	1.02	2
Non-procedural Major Bleed	235 (2.5%)	180 (2.0%)	1.3	6
Intracranial Bleed	27(0.3%)	14 (0.2)	1.9	1
Deaths from Intracranial Bleed	11 (0.1)	2 (0.0)	5.47	1
CABG	**N= 770**	**N=814**		
CABG-related bleed Major Bleed	619 (80.4%)	654 (80.3%)	1	0
CABG-related fatal Bleed	6 (0.8%)	6 (0.7%)	0	0

Given the net benefit in all-cause mortality, Dr. Blank sees the incremental harm in non-fatal hemorrhage to be not an impediment to approval, and I agree.

Dyspnea was more common on ticagrelor (14.6% vs. 8.7% as an adverse event, 0.9% vs. 0.6% as a serious adverse event, and 0.9% vs. 0.1% as cause for discontinuation). Generally, subjects persisted despite dyspnea, and in many it resolved on treatment.

PLATO excluded subjects with structural heart disease, so perhaps is not entirely reassuring with regard to possible clinical implications of ventricular pauses, but reductions in overall and sudden death certainly are reassuring.

There is a minor, reversible increase in uric acid levels in subjects on ticagrelor, thought to be the effect at another off-target adenosine receptor.

I note that Dr. Marciniak proposes approval of ticagrelor in patients with ACS, but not patients with STEMI undergoing early PCI. He appears to reach this recommendation upon a highly selective analysis—STEMI vs. NSTEMI, site-reported events rather than adjudicated events, exclusion of subjects with prior thienopyridine exposure, events in

the first 30 days rather than the whole period of follow-up, MACE rather than primary end points, and PCI within 12 hours—far too many steps for me to find this argument persuasive.

Dr. Marciniak raised issues about the sponsor's Advisory Committee presentations. Dr. Harrington appears to have been mistaken about whether randomization was stratified by intended management strategy, but since that information was provided to the IVRS, one can understand how he might have thought that information was used. I do not believe that anyone misrepresented the facts, nor can I imagine any possible rationale for so doing, nor for having this error call into question the reliability of other information presented to the Committee or in the sponsor's regulatory submission.

At the AC meeting, the sponsor made a statement regarding the extent of follow-up. By a certain definition, the Agency agrees. Dr. Marciniak notes that other definitions of follow-up lead to other numbers, and calls that discrepancy a "misrepresentation" by the sponsor, too. It is not misrepresentation; it is semantics.

I assert that we cannot merely relegate the anomalous US results to mention in labeling. I note that we routinely give credence to findings in subgroups and other descriptions of study results that are not founded on a prospectively set and alpha-conserving analytic plan.

Examples of this behavior are:

- On the basis of unplanned analyses of the LIFE study, we wrote "COZAAR is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients."

- In response to Val-HeFT, we wrote "Diovan is indicated for the treatment of heart failure (NYHA class II-IV). In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefits when it is used with an adequate dose of an ACE inhibitor." However, (a) hospitalizations for heart failure was not one of the study's two primary end points, and (b) there was no planned analysis by dose of ACE inhibitor.

- In the label for eplerenone, we called out two subgroups: "Patients with diabetes without clinical evidence of CHF and patients greater than 75 years did not appear to benefit from the use of INSPRA."

- From results of the TRITON study, we divined "In patients ≥ 75 years of age, Effient is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (diabetes or prior MI), where its effect appears to be greater and its use may be considered." Note that this recommendation is based on the analysis of a subgroup (high risk) of a subgroup (elderly).

In addition to subgroups, we never describe the results of a composite end point the way a statistician would. We often grant the claim to a subset of the components (as would, undoubtedly be true if ticagrelor were approved on the basis of PLATO.

I probably did not support all of the recommendations I cited above, but I do believe that making such recommendations is appropriate. We are (usually) pretty confident that something is true from the study's primary analysis, and then we interpret the rest, applying our best judgment. We do this because we are familiar with the data, thought carefully about it, and cannot expect the practicing physician to replicate our efforts. This is part of our regulatory obligation.

So what is different about the regional anomaly in PLATO? It cannot merely be that all of these other analyses I cite (among many others) are all so plausible (although some are), while this one is implausible. And it is not that the others were so much more statistically robust in terms of a nominal p-value. I think the big difference is that none of the other unplanned interpretations caused one to question whether the product should be approved, while this one is very hard to approve (in the US) if you accord the anomaly any credibility, because it applies to the entire at-risk population for whom the approval applies.

There has been some discussion regarding approval under Subpart H. By scope, Subpart H would apply:

> *Sec. 314.500 Scope.*
>
> *This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).*

ACS is a "serious and life-threatening illness", and there are findings of superiority over at least one "available therapy" (although the case for superiority to another "available therapy—prasugrel—would be speculative).

Where it gets difficult to apply Subpart H is with the next section:

> *Sec. 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.*
>
> *FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.*

By the section title and text of the section, it does not apply to findings of "survival or irreversible morbidity", but that is exactly what we have here.

In addition, I question whether, with ticagrelor labeled for morbidity and mortality, one could conduct a subsequent confirmatory study, and I am not sure what the point would be if the study were largely complete (so completion was likely) before approval.

I favor issuing a Complete Response until evidence is developed that ticagrelor provides benefit likely to be realized in US practice. Ideally, that would be an outcome study in the US, but it could be independent support for the aspirin hypothesis as an outcome study anywhere and in ACS or some closely related condition. It might also be possible to support the hypothesis that higher degrees of P2Y12 inhibition adversely affect the response to high dose aspirin using measures short of outcomes.

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/s/

NORMAN L STOCKBRIDGE
10/07/2010

Cross-Discipline Team Leader Review Memo

Date	September 16, 2010
From	Thomas A. Marciniak, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-433
Supp #	000
Proprietary / Established (USAN) names	Brilinta™ / ticagrelor
Dosage forms / strength	film-coated tablet / 90 mg
Proposed Indication(s)	reduce the rate of thrombotic events in patients with acute coronary syndromes (ACS)
Recommended:	approval for reducing the rates of cardiovascular death and myocardial infarction in ACS patients excluding STEMI patients undergoing early PCI

1. Introduction to Review

Ticagrelor (Brilinta™) is a novel $P2Y_{12}$ platelet receptor inhibitor submitted for approval for the indication of reducing the rate of thrombotic events in patients with acute coronary syndromes (ACS, including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI)). Two other drugs (clopidogrel, prasugrel) are approved for similar indications and a third (ticlopidine) is approved for related indications. All three approved drugs have both common and individual limitations: The common limitations are that they are all members of the thienopyridine structural class administered as pro-drugs requiring metabolic activation for effect and binding irreversibly to the $P2Y_{12}$ receptor. Ticagrelor does not require metabolic activation and binds reversibly. The individual limitations are that ticlopidine is rarely used because of a higher rate of neutropenia, clopidogrel may be less effective in some patients because of reduced activation due to genetic or drug-interaction factors, and prasugrel is associated with higher rates of bleeding and a question of cancer promotion. A novel drug without these limitations would be a therapeutic advance.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

This is the first NDA submission for ticagrelor. The sponsor Astra-Zeneca discussed the development program with the Division at a guidance meeting and at an end-of-phase 2 meeting but did submit the protocol for the pivotal study for a special protocol assessment. Ticagrelor has not been approved elsewhere in the world.

3. CMC/Microbiology/Device

The CMC reviewers, Drs. Chhagan Tele and Thomas Wong, recommend approval of the application from a CMC perspective. They note that adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). The DS and DP are manufactured and packaged in accordance with the procedures and

proposed specifications to assure their quality throughout shelf life. The did note some initial deficiencies regarding specifications for ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4) ⬛⬛⬛⬛⬛⬛⬛ (b) (4) and qualification of impurities that the sponsor resolved in later submissions.

4. Nonclinical Pharmacology/Toxicology

4.1. General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The nonclinical pharmacology and toxicology reviewer, Dr. Elizabeth Hausner, considers this NDA to be approvable from the non-clinical perspective for the purpose of preventing platelet aggregation. She notes that the toxicities that were identified in the non-clinical stages have been shown to be not clinically significant or satisfactory safety margins have been demonstrated. She accepts that that the sponsor qualified one impurity, ⬛⬛⬛ (b) (4) which has a structural alert for genotoxicity. She does recommend that a receptor binding profile be done for one of the two main metabolites, AR-C133913XX ⬛⬛⬛⬛ (b) (4)

The other most clinically relevant observations from Dr. Hausner's review are the following:

- The non-clinical studies have shown *in vitro, ex vivo* and *in vivo* that ticagrelor inhibits $P2Y_{12}$-mediated platelet effects in a reversible manner. Studies using washed human platelets showed inhibition of ADP-induced platelet aggregation with an IC_{50} of 13 nM. *Ex vivo* studies using platelet rich human plasma showed that AZD6140 inhibits ADP-induced platelet aggregation with an IC_{50} of 398 nM. Assessment of the human adenosine A3 receptor transfected into human embryonic kidney cells (HEK) showed an IC_{50} of 0.3µM, suggesting that there may be effects for both the $P2Y_{12}$ and A3 receptors at equivalent plasma concentrations.

- Ticagrelor also shows affinity for the phosphodiesterase 5 (PDE5) enzyme with an IC_{50} for inhibition of 0.482µM. The steady state plasma C_{max} in humans is 687ng/ml (1.3µM) for 100 mg, BID, making it possible that the PDE5 effect will be clinically significant.

- Pulmonary function changes of increased respiratory rate (up to 20% of pre-dose baseline, p<0.01), peak inspiratory flow(up to 35% of pre-dose baseline, n.s.) and expiration time (decreased by up to 20% from pre-dose baseline, p<0.01) were identified in the safety pharmacology studies in rats.

- Liver effects in rats occurred at doses ≥80 mg/kg and included indications of altered function or damage evidenced by decreased triglycerides (67%, p<0.001), increased AST (20%, p<0.001) or ALP (31%, p<0.001) when compared to the control groups. Centrilobular hypertrophy was inconsistently reported (mice ≥250 mg/kg/day; rats ≥180 mg/kg).

- Immune system effects such as splenic lymphoid depletion, thymic atrophy and bone marrow atrophy were reported for rats given doses ≥300 mg/kg/day. Marmosets showed lymphocytolysis of the thymic cortex, follicular atrophy of lymph nodes, splenic lymphoid atrophy and bone marrow hemorrhage at doses ≥1000 mg/kg/day, which was also associated with unscheduled mortality. Some lymphoid atrophy was reported in marmosets for doses of ≥20 mg/kg/day.

- Other than the findings noted above and the carcinogenicity and reproductive toxicology findings noted below the pre-clinical findings across species were typically minor blood loss, consistent with the activity of a $P2Y_{12}$ inhibitor.

COMMENT: Of the above pre-clinical findings, the hepatoxicity and the immune system effects are the ones that have not been observed in humans.

4.2. Carcinogenicity

Dr. Hausner recommends the following labeling: Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29 fold the maximally recommended dose of 90 mg bid per day on the basis of AUC comparison).

COMMENT: The clinical safety review examines the evidence in PLATO regarding carcinogenicity in human sexual organs. The short summary is that in the relatively short (for carcinogenicity) follow-up in PLATO there was no evidence of carcinogenicity.

4.3. Reproductive toxicology

Dr. Hausner recommends the following labeling: Doses of ≥100 mg/kg/day (5.5 fold the maximum recommended human dose (MRHD) of 90mg bid for a 60 kg human on a mg/m2 basis) in rats were associated with supernumerary liver lobe, incomplete ossification of parietal bone and sternebrae, displaced articulation of pelvis, supernumerary ribs and misshapen or misaligned sternebrae. Doses of ≥ 63 mg/kg/day given to rabbits (6.8 fold the MRHD on a mg/m2 basis) were associated with delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae. Doses of ≥ 10 mg/kg (approximately half the MRHD on a body surface area basis) given to rats in late gestation and lactation caused developmental delays in pinna unfolding and eye opening. The pregnancy category should be C (no human studies and the animal studies indicate harm to the fetus).

4.4. Other notable issues

There are no other notable nonclinical pharmacology or toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

5.1. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The Office of Clinical Pharmacology (OCP) recommends approval of ticagrelor with a study post-approval aimed to reconcile the findings from the US region. They cannot resolve the differential effectiveness of ticagrelor in US and OUS sites on the basis of clinical pharmacology findings.

The most relevant pharmacokinetic (PK) findings are the following:

- Ticagrelor is rapidly absorbed with a T_{max} of about 1.5 hours. Absolute bioavailability is about 36% without a significant food effect.

- Ticagrelor and its active metabolite are extensively bound to human plasma proteins (>99.7%).

- Ticagrelor does have active metabolites, with one, AR-C124910XX, having systemic exposure about 30-40% of ticagrelor itself. The mean $t_{1/2}$ was approximately 7.2 hours for ticagrelor and 8.5 hours for AR-C124910XX.

- Ticagrelor is metabolized by CYP3A. See also Drug-drug interactions and Pathway of elimination below.

The most relevant pharmacodynamic (PD) findings are from the Onset/Offset study (D5130C00048). Regarding mean final inhibition of platelet inhibition (IPA) by light aggregometry, the onset of platelet inhibition was earlier with ticagrelor 180 mg than clopidogrel 600 mg loading (47% vs. 10% respectively at 0.5 hours.) The maximum mean IPA effect of ticagrelor was approximately 88% reached at around 2 hours while the mean IPA of clopidogrel did not reach near maximal until about 4 hours and remained below 50%. After repeated dosing the offset of ticagrelor was faster than that of clopidogrel. However, because ticagrelor started at a higher IPA, IPA remained higher for the first 36 hours after discontinuation with residual IPA at 3 days (20%) and some at 5 days (10%).

Treatment differences for ticagrelor versus clopidogrel tended to be greater, in favor of ticagrelor in patients with CYP2C19 loss-of-function alleles. Bleeding rates did not differ substantially across genotype groups. CYP2C19 genotype did not appear to account for the geographic differences in ticagrelor treatment outcomes. Single nucleotide polymorphisms examined did not show any pharmacogenomic interactions for pharmacodynamics, exposure, or dyspnea.

Per OCP the studies do not establish an exposure-response relationship to efficacy or ventricular pauses, while they do suggest a shallow exposure-response relationship for bleeding and dyspnea. Exposure-response differences do not appear to explain the US-OUS discrepancy in efficacy.

COMMENT: While the onset results suggest a substantial advantage for ticagrelor, the more critical results are from PLATO. The offset results do not seem entirely consistent with the PK and suggest only a modest advantage for ticagrelor vs. clopidogrel—but the more critical results for offset are also from PLATO. The PK and PD data do not explain the US vs. OUS discrepancy.

5.2. Drug-drug interactions

Ticagrelor is both metabolized by CYP3A and an inhibitor of CYP3A and P-glycoprotein (PgP). Ketoconazole (200 mg twice daily) increased ticagrelor C_{max} and AUC about 2.4-fold and 7.3-fold, respectively. It reduced the C_{max} and AUC of the active metabolite by 89% and 56% respectively. Diltiazem (240 mg daily) increased the ticagrelor C_{max} by 69% and AUC by 174% and decreased the active metabolite C_{max} by 38% without changing AUC. Rifampin (600 mg daily), a potent inducer of CYP3A and CYP2B6 and an inducer of CYP2C9, CYP2C19, and CYP2C8, decreased ticagrelor C_{max} and AUC of 73% and 86%, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46% respectively.

Co-administration of ticagrelor (180 mg bid for 7 days) with simvastatin (single 80 mg dose on day 5) increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases 2 to 3 fold. Co-administration of atorvastatin and ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by 36%. Concomitant administration of ticagrelor (single 400 mg dose) increased the digoxin (a PgP substrate) C_{max} by 75%, C_{min} by 30% and AUC by 28%.

Aspirin 75-300 mg daily did not alter the pharmacokinetic profiles or pharmacodynamic effect of ticagrelor and AR-C124910XX. To explain the US vs. OUS discrepancy the sponsor has proposed a complex PD interaction with aspirin: "Data suggest that when a high degree of P2Y$_{12}$ inhibition is achieved (ie, by ticagrelor, prasugrel, or high clopidogrel response), thromboxane (TXA2)-dependent pathways of platelet activation are potently and consistently inhibited even in the absence of ASA. This gives rise to a hypothesis that ASA, especially at high doses, would not further improve platelet inhibition, but the additional dose-dependent reduction in prostacyclin (PGI2) levels could leave unopposed the thrombogenic and vasoconstrictive effect of ASA therapy. When a lower degree of P2Y$_{12}$ inhibition exists (ie, low-to-medium clopidogrel response), TXA2 pathways are not potently inhibited."

COMMENT: We will incorporate these drug interactions into the labeling with the exception of the speculative aspirin interaction.

5.3. Pathway of elimination

The primary pathway of elimination is hepatic. However, about 32% of the radioactivity was recovered from the urine in the mass balance study.

5.4. Demographic interactions/special populations

Higher exposures to ticagrelor (approximately 60% for both Cmax and AUC) and AR C124910XX (approximately 50% for both C_{max} and AUC) were observed in elderly (≥65 years) subjects compared to younger (18-45 years) subjects. Higher exposures to ticagrelor (approximately 52% and 37% for C_{max} and AUC, respectively) and AR C124910XX (approximately 50% for both C_{max} and AUC) were observed in women compared to men. The exposure (C_{max} and AUC) to ticagrelor in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians.

Exposure to ticagrelor and AR-C124910XX were approximately 20% lower in patients with severe renal impairment compared to subjects with normal renal function. C_{max} and AUC for ticagrelor were 12% and 35% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively. Ticagrelor has not been studied in patients with severe hepatic impairment.

COMMENT: OCP is recommending a study in patients with moderate and severe hepatic impairment. However, the special population of most concern is the US population. See the Clinical/Statistical section below.

5.5. Thorough QT study or other QT assessment

The sponsor performed a thorough QT study and submitted it to the IND in 2008. The FDA QT team evaluated it and concluded that there is no apparent QTc prolonging effect of the drug on the QTc interval despite lack of assay sensitivity of the moxifloxacin control.

COMMENT: The results of the PLATO Holter substudy and the overall CV outcomes are also reassuring that ticagrelor is not pro-arrhythmic.

5.6. Other notable issues

There are no other notable clinical pharmacology or biopharmaceutics issues

6. Clinical Microbiology

Brilinta is an oral non-antimicrobial drug for which there are no clinical microbiology concerns.

7. Clinical/Statistical

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The sponsor based the proposed to-be-marketed dosing, 180 mg loading followed by 90 mg BID maintenance without adjustment, on the dosing in the PLATO study. The sponsor selected this dosing based on the results of the earlier DISPERSE and DISPERSE-2 studies and concerns about ventricular pauses with 180 mg BID in DISPERSE-2 and a potential need for dosage adjustment for CYP3A4 inhibitors with the higher dosing. The sponsor asserts that the concerns about PLATO did not confirm the concerns regarding ventricular pauses and that the efficacy and safety results in PLATO support the proposed dosing.

COMMENT: The PLATO results do support the proposed dosing as reasonable, at least based on the OUS results. The major issue regarding dosing is not the dosing of ticagrelor but the concomitant dosage of aspirin.

7.1.2. Studies essential for approval

The substantial evidence submitted to support the approval of ticagrelor comes from PLATO, a large, international, multi-center, randomized, double-blind, active-controlled trial. The primary reviews summarize well the details of protocol and study design. I discuss specific efficacy and safety findings in this review.

7.1.3. Other studies

7.1.3.1. Ticagrelor studies

PLATO provides the vast majority of the exposure in the ticagrelor development program. As mentioned above, the phase 2 studies DISPERSE and DISPERSE-2 provided data regarding other than the proposed marketed dosing as well as preliminary data on adverse effects. However, the sponsor did not size these studies to provide definitive answers regarding efficacy and safety. Please see the primary clinical efficacy review for summaries of them.

7.1.3.2. Other $P2Y_{12}$ inhibitor studies

Ticagrelor is not the first $P2Y_{12}$ inhibitor to be tested in acute coronary syndromes (ACS). We have reviewed several studies of clopidogrel vs. placebo and recently the large TRITON trial of prasugrel vs. clopidogrel. There have also been recent publications on ACS trials of cangrelor, another non-thienopyridine, ADP/ATP analog $P2Y_{12}$ inhibitor. I summarize below pertinent findings from the clopidogrel, prasugrel, and cangrelor trials for convenient comparisons and contrasts to PLATO.

7.1.3.2.1. Prasugrel vs. clopidogrel

The trial most relevant to PLATO is the TRITON trial of prasugrel vs. clopidogrel in ACS. It is most relevant because it is also a trial of an allegedly faster, better $P2Y_{12}$ inhibitor against the established drug clopidogrel. While it was also in ACS, its design does have some differences from the PLATO

design: (1) TRITON excluded patients with prior thienopyridine use. (2) In TRITON all patients underwent percutaneous coronary intervention (PCI). (3) In TRITON administration of study drug was delayed until after coronary angiography in all but the STEMI patients who presented within 12 hours of symptom onset. (4) While TRITON studied both STEMI and NSTEMI/UA patients, its primary analysis was in NSTEMI/UA patients.

TRITON, like PLATO, had a primary endpoint of MACE, i.e., time to first MI, stroke, or CV death. I show in Figure 1 the landmark analyses of this primary endpoint from Figure 8 of the CDTL review of NDA 22-307.

Figure 1: Landmark Analyses of Primary MACE Endpoint in TRITON
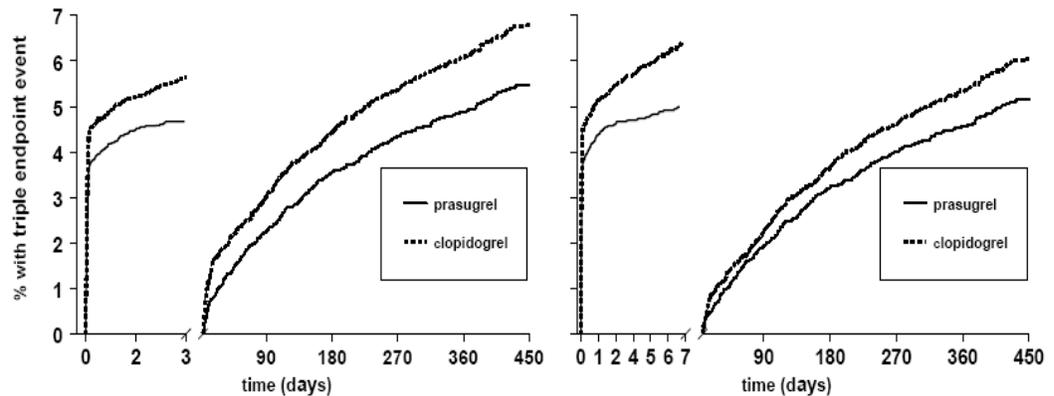
Note that the separation of the curves is almost immediate. The continuing separation of the curves late is far less impressive. In fact, it is apparent only in the sponsor's adjudicated endpoint—TRITON had a blinded adjudication by an academic organization similar to that done for PLATO—and not in site-reported events or all cause mortality. Because mortality is an important finding in PLATO, I show the all cause mortality results for TRITON in Figure 2.

Figure 2: All Cause Mortality in TRITON
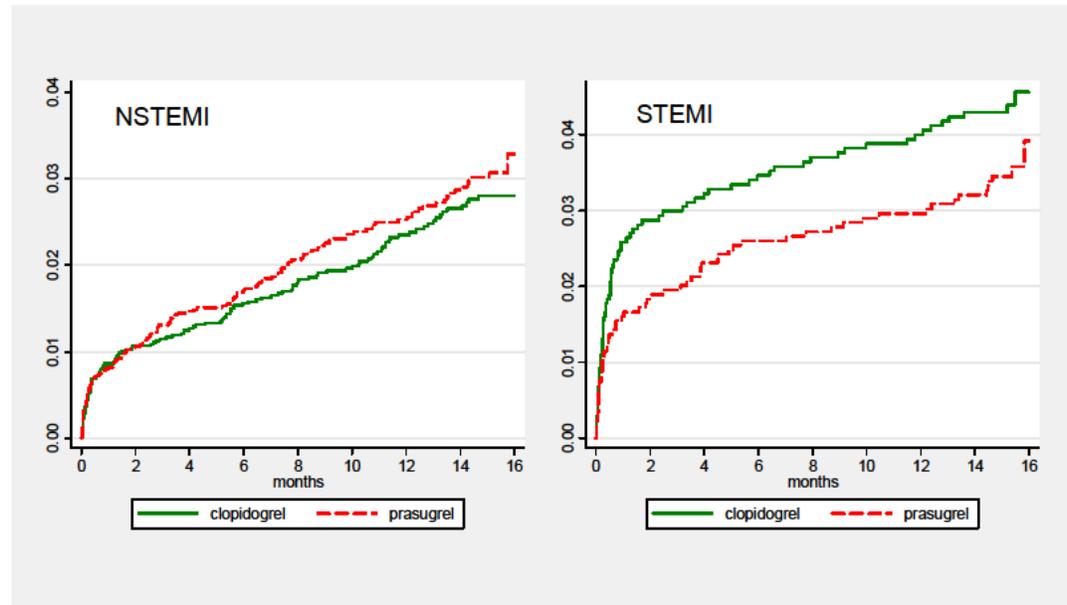
For mortality there is an immediate and impressive early benefit with prasugrel in STEMI while for NSTEMI the point estimates show a detriment for prasugrel. For both ACS types there is no later benefit with prasugrel. TRITON also shows the typically high initial event rates for STEMI with NSTEMI having the steeper slope after the initial month.

7.1.3.2.2.   Clopidogrel vs. placebo

Clopidogrel has had several major outcome trials as shown in Table 1.

Table 1: Clopidogrel Studies

Study	Population	Aspirin	Median age	n	Median months
CAPRIE	high CV risk	325 control	63	19,185	20
CREDO	PCI	325 then 81-325	61	2,116	12
CURE	ACS NSTEMI	75-325	65	12,562	9
CHARISMA	high CV risk	75-162	64	15,603	28
COMMIT	STEMI without PCI in China	325 then 162	63	45,582	0.5
CURRENT OASIS-7	ACS early PCI	300-325 vs. 75-100	mean 61.4	25,087	1

The most relevant clopidogrel trials to PLATO are CURE in NSTEMI and COMMIT in STEMI. OASIS-7 is relevant to aspirin dosage. I show in Figure 3 the MACE results for CURE from the publications. (Investigators 2001; Berger and Steinhubl 2002)

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Figure 3: MACE in CURE (NSTEMI)
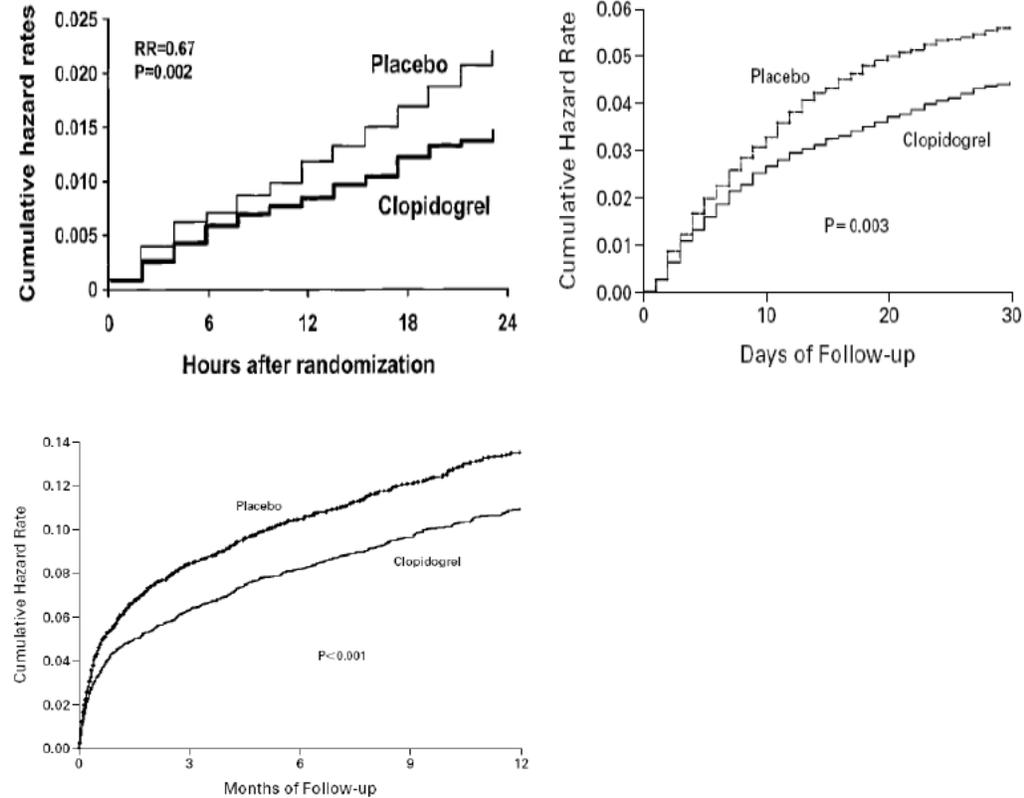
Clopidogrel showed a beneficial effect upon MACE within hours in CURE with rapid separation of the curves through 20 days. However, there is minimal separation of the curves after 20-30 days. COMMIT showed a similar pattern for mortality (its primary endpoint) as shown in Figure 4. (Group 2005)

Figure 4: Mortality in COMMIT (STEMI)
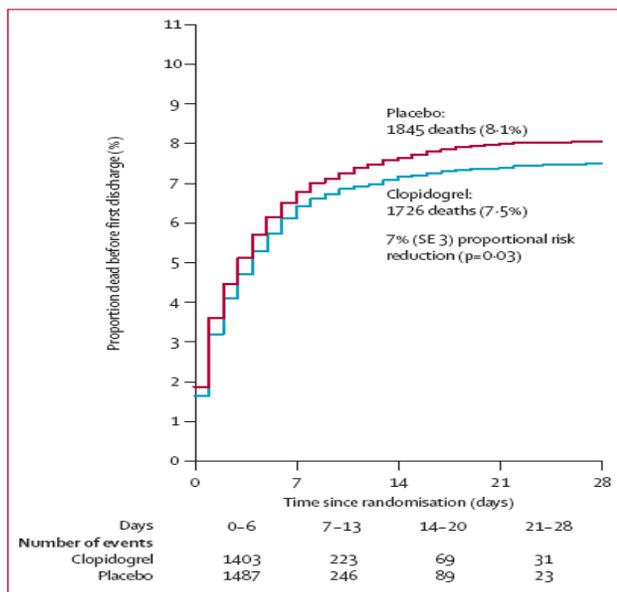
In COMMIT there was again a rapid benefit for clopidogrel vs. placebo but little effect after 20 days. COMMIT was a trial of medical management: 54% received thrombolytics while the 3% who got PCI were discontinued from the trial.

COMMENT: The thienopyridine P2Y$_{12}$ inhibitor trials in ACS show very similar patterns. There is an early benefit on MACE for inhibitor vs. placebo or better inhibitor vs. poorer inhibitor. There may be some benefit on MACE beyond 30 days but it is more difficult to show. A short term mortality benefit is demonstrable only with a huge trial; no other trials show a late improvement in mortality. We need to compare these patterns to the PLATO results.

CURRENT-OASIS 7 was a 2 by 2 factorial study of double dose clopidogrel (600 loading then 150 daily x 7 then 75 mg) vs. standard clopidogrel (300 loading then 75 mg daily) and high dose aspirin (300-325 mg) vs. low dose aspirin (300 loading, then 75-100 mg) in ACS patients with planned early invasive management. The primary endpoint was MACE at 30 days. Results from OASIS 7 were reported at the European Society of Cardiology meeting in 2009 and recently published. (Investigators 2010) While the intent was for invasive management, only about 70% of randomized patients underwent PCI. For the entire study the PEP was not significantly different between high and low dose clopidogrel and high and low dose aspirin. For the 2 by 2 factorial the PEP results are distributed in a non-intuitive fashion: For high dose aspirin the 30-day PEP rates are 4.6% and 3.8% for standard vs. double dose clopidogrel respectively while for low dose aspirin they are 4.2% and 4.5% respectively. There was also a 15% reduction in PEP for double dose clopidogrel vs. standard clopidogrel in the 70% subset of patients who underwent PCI.

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COMMENT: The CURRENT-OASIS 7 results do not support the concept that high dose aspirin is deleterious with higher platelet inhibition.

7.1.3.2.3.   Cangrelor vs. clopidogrel

Cangrelor, like ticagrelor, is another new, unapproved, ADP/ATP analog $P2Y_{12}$ inhibitor being tested for PCI and ACS. The structural similarities between it and ticagrelor and both drugs and ADP are obvious as shown in Figure 5.

Figure 5: Structures of Ticagrelor, Cangrelor, and ADP
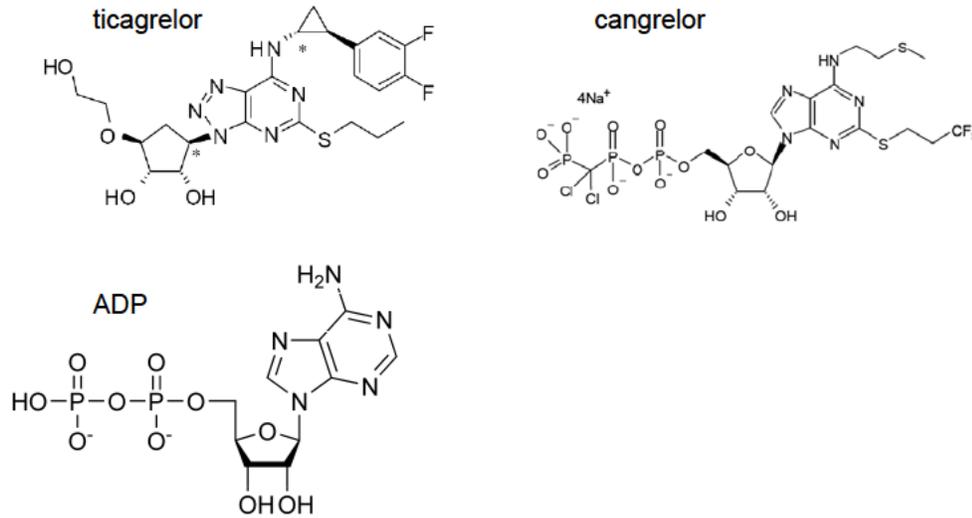
While there are structural similarities among the three molecular entities, there are sufficient differences such that the biologic behaviors differ. One example is that cangrelor is being developed as an IV drug and has a very short half-life while ticagrelor is being developed as an oral drug for twice daily use. Both, however, are supposedly good, fast, reversible $P2Y_{12}$ inhibitors by *in vitro* testing.

Cangrelor has been tested in two phase 3 trials: CHAMPION PCI and CHAMPION PLATFORM. (Bhatt, Lincoff et al. 2009; Harrington, Stone et al. 2009) [(b) (4)]

in

Note that neither trial won, i.e.,

COMMENT: I believe that the cangrelor trials have relevance because both ticagrelor and cangrelor are ADP/ATP analog, P2Y$_{12}$ inhibitors. As I discuss later for ticagrelor, both have early effects that are disappointing considering their in vitro platelet inhibition results.

7.1.4. Primary clinical and statistical reviewers' findings and conclusions

The primary clinical efficacy reviewer Dr. Robert Fiorentino recommends that ticagrelor not be approved. It is his view that the outcome in the US is unlikely to be an entirely random occurrence. There are uncertainties that he discusses in his review that cast some doubt that the best estimate of treatment effect for the US should be the same as the overall effect observed in the trial.

The primary statistical reviewer Dr. Jialu Zhang argues similarly: In her view, neither play of chance nor concurrent use of ASA provides a satisfactory explanation for the US vs. OUS disparity observed in this trial. Even though multiple factors have been screened for potential causes, the question remains unsolved. The disparity can still be caused by the difference in standard medical practice between US and OUS, which is hard to quantify and has not been quantified. She asserts that we ought to seek further data to either confirm or dismiss this disturbing finding. Without the data, she recommends that this drug not be approved.

COMMENT: Their basic findings regarding efficacy in the whole study as well as the US and OUS subgroups are not different than the sponsor's. Dr. Fiorentino performed a number of subgroup analyses that apparently convinced him that the US results are not random. Dr. Zhang focused primarily upon the US vs. OUS discrepancy and the ASA dosing. Despite analyzing together US and OUS ASA effects, which I argue later

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is inappropriate because of the heterogeneity in ASA use between US and OUS, she does provide sensitivity analyses convincing that the ASA effect is not robust. I share their concerns that the US results are unfavorable for ticagrelor and that we do not have an adequate explanation for the disparity between US and OUS. However, I am open to the possibility that we understand enough about PLATO results that we could approve ticagrelor—at least for the subgroups with clear benefits.

The problem all of us reviewers are having with PLATO is that PLATO tried to do too much, as I discuss below regarding notable efficacy issues. Depending upon which of the many questions PLATO answers incompletely a reviewer emphasizes, conclusions differ. I present my views in Section 7.1.6.

7.1.5. Pediatric use

ACS is not a pediatric disease so that pediatric studies of it are not possible and not needed.

7.1.6. Discussion of notable efficacy issues

7.1.6.1. PLATO study design issues

While the PLATO study design in general was appropriate, there were three significant flaws. The flaws were the following:

7.1.6.1.1. Multiple studies in one

As can be appreciated from my summary of other $P2Y_{12}$ inhibitor studies in Section 7.1.3.2, patients with STEMI and NSTEMI behave differently with platelet inhibitors. Percutaneous interventions also produce a need for immediate and effective platelet inhibition. Hence the studies of other $P2Y_{12}$ inhibitors have separated STEMI from NSTEMI and invasive from medical management.

The sponsor chose to include STEMI and NSTEMI patients and invasive and medical management in one trial. While *per se* this is not wrong, because of the evidence of heterogeneity of risks shown in other platelet inhibitor trials we need to examine the results in the appropriate subgroups as well as the trial as a whole. If there is evidence of heterogeneity of effect and we can not characterize well the heterogeneity, then the PLATO all-in-one approach and study interpretation are problematic.

The sponsor introduced a further complication for PLATO: The sponsor allowed the use of clopidogrel and other thienopyridines both as prior chronic therapy and as acute loading prior to randomization. The sponsor has defended this approach as being "real world". [(b) (4)]

We

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were aware of the inclusion of prior clopidogrel use in the PLATO protocol but we had assumed that it would be the infrequent exception rather than the rule. I show below how inaccurate our assumption was.

Finally, the "real world" dealt PLATO a final complication: The US and outside US (OUS) results are disparate. Clopidogrel appears better in the US while ticagrelor appears better OUS. We need to understand this heterogeneity —and be confident that the US results aren't really worse—if we are to approve ticagrelor in the US.

Hence PLATO ended up not being a large, simple, robust, two-armed, classic clinical trial but a complicated, heterogeneous, multi-celled comparison with small numbers in many critical cells (e.g., the US). I show the numbers of primary endpoint events for the critical comparisons in Table 3.

Table 3: Numbers of Primary Endpoints by Critical Comparison Groups

Arm	Prior/day 1 clopidogrel	region	NSTEMI*		STEMI	
			medical†	invasive	medical	invasive
clopidogrel	no	OUS	171	140	34	161
		US	2	28	1	10
	yes	OUS	109	160	23	149
		US	5	15	1	5
ticagrelor	no	OUS	140	117	24	150
		US	5	30	0	15
	yes	OUS	100	111	21	117
		US	5	25	0	4

 * STEMI by ST elevation or new LBBB on initial ECG, otherwise NSTEMI
 † medical/invasive by investigator intent recorded at randomization

Note that many of the comparison cell numbers are low, particularly for the US. The lowest are for planned medical management in the US, which are not the most important comparisons because of the bias favoring invasive management here. However, even the invasive management comparison cells in the US have few events.

COMMENT: The critical comparisons are more complicated than even Table 3 suggests because I have lumped prior clopidogrel use with clopidogrel loading on day 1. As I show later, patients having a new event while on chronic clopidogrel have a higher risk than those who do not. In Table 3 I have used the medical vs. invasive intent as recorded by the investigator at randomization as a binary stratification factor to keep the table simple. However, undergoing a PCI, rather than the intent to do one or to perform a CABG, is the determinant of criticalness of adequate platelet inhibition. In particular, having adequate platelet inhibition for an early PCI appears to be crucial. Hence I analyze the results not by invasive intent but by whether the patient had an early PCI (within 12 hours), by all other invasive management, and by medically managed.

7.1.6.1.2.   Inappropriate statin restriction and inadequate lipid measurements

Ticagrelor is a moderate inhibitor of cytochrome P450 CYP3A. Because several statins are metabolized by CYP3A and statins are commonly administered to ACS patients, the sponsor proposed at the end-of-phase 2 meeting in December 2005 that concomitant therapy with either simvastatin or lovastatin at doses higher than 40-mg should be avoided. We accepted this proposal as reasonable. The protocol states that "As simvastatin has recommended restrictions for concomitant therapy with inhibitors of CYP3A due to increased reporting of myopathy, concomitant study therapy with simvastatin or lovastatin (which is very similar pharmacokinetically to simvastatin) at doses higher than 40mg should be avoided." In hindsight this restriction on a class of drugs with a mortality benefit appears inappropriate. It was wrong to restrict statin dosage in the clopidogrel arm.

Simvastatin was the most frequently used statin in PLATO—about 54% of patients took it at some time. Atorvastatin usage was very similar. Rosuvastatin usage was a distant third at about 9%. Note that ticagrelor also affects atorvastatin pharmacokinetics, increasing its AUC by a mean of 36%. These changes in statin exposure may be relevant to the time course of the presumed ticagrelor benefit that I discuss below.

Because of the restriction of simvastatin dosage the protocol should have specified collecting the dosages of statins used in the trial. Unfortunately the protocol failed to do so. The protocol specified measuring lipids at baseline and "in at least 9000 randomized patients" at 1, 3, 6, 12 (end of treatment), and the follow-up visit or until "DSMB indicates that this testing is no longer required." The SETSLAB variable (for "Safety Lab Analysis Set") in the submitted data sets indicates that the 60% of patients randomized on or before January 31, 2008, as belonging to this set (11,192 randomized patients.) Per the sponsor's AC presentation 5,650 patients had LDL cholesterol measured at 12 months, about 50.5% of the safety lab set.

The protocol does not define what serum lipids were to be measured. Measured LDL values were rare in the data sets submitted. In them I count only 205 measured LDL values on or after the earliest study end date of October 8, 2008. Measurements of total cholesterol, HDL, and triglycerides (from which an LDL value can be estimated—if the patient is fasting) were more frequent but still not measured in the majority of patients: I count only 38% of the living patients who could have an estimated cholesterol at study end, and whether the lipid measurements were fasting was not captured.

COMMENT: Because of the missing data, the lipid values obtained are worthless for estimating whether a greater reduction in LDL in the ticagrelor arm could have contributed to the reported mortality benefit. Furthermore, we

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do not know the validity of any estimated LDL values because fasting status is not known. The contribution of ticagrelor increasing statin levels and lowering LDL-C to any benefit can not be evaluated from PLATO data.

7.1.6.1.3. Easy unblinding

PLATO was double-blinded but it was trivial to break the blind at the sites. The clopidogrel formulation used was a clopidogrel tablet cut into two and stuffed into a capsule. The dummy was identical in appearance. However, the sites could unblind any patient by breaking one of the patient's clopidogrel/ dummy capsules and examining its contents. The protocol submitted in August 2006 described this clopidogrel formulation but the reviewing FDA medical officer did not identify the formulation as problematic. The sponsor did not submit the protocol for a Special Protocol Assessment. In 2006 we might have complained about but accepted the clopidogrel formulation even if we had identified it as problematic. Because of bad experiences with open label trials since 2006, we should be more cautious about such formulations today.

The problem with unblinding of patients by examining the study drug was not limited to the sites. Per the protocol sites were to give all unused study drug to the sponsor's site monitors. Hence the sponsor's site monitors could unblind all patients.

The sponsor did employ another mechanism to avoid bias: The sponsor contracted with an academic center to perform blinded adjudications of CV and bleeding events. The sponsor named this adjudication group the Independent Central Adjudication Committee (ICAC). While the use of a blinded adjudication process is good, it does not guarantee that the adjudications are unbiased. Someone still has to decide what events to refer and what documents to include in the adjudication packages.

In addition to the easy unblinding of study drug there were other potential sources of unblinding: Besides the DSMB the sponsor reported in Serial 008 that four groups within its organization had treatment codes as well as two contractors, i.e., (b) (4) had access to a password protected list of the randomization code which was known to only named personnel. This was used for the identification of PK samples . . ." and a second contractor had treatment codes for the IVRS system.

COMMENT: Absolutely assuring the blind would appear to be difficult with so many parties having access to treatment codes. Because of the easy unblinding I consider PLATO to be more akin to an open label study than to a strictly blinded one. Note that both blinded adjudications and deaths can be biased through mechanisms that are difficult to detect. Blinded adjudications can be biased by constructing adjudication packages that are more or less complete depending upon the desired bias, e.g., omitting or including a critical troponin

value will frequently decide whether an event is adjudicated as an MI or not. Deaths can be eliminated by declaring a terminal patient "withdrawn consent" prior to the death and not following up on the ultimate death.

7.1.6.2. General study conduct

Most other aspects of the PLATO study conduct appear to be better (with one major exception discussed below.) The structure and processes of the trial, e.g., randomization by interactive voice or web response system, unblinded DSMB, blinded event adjudication committee, etc., are ones that we favor. The trial documentation submitted appears to be well-prepared and complete. The CRFs submitted are computer printouts from a data capture computer system. They are highly legible and appear complete but are difficult to read because of the computer formatting and are impossible to evaluate for investigator uncertainty and mistakes. However, we requested and the sponsor provided an audit trail of most changes to the CRF data base—a 16.5GB file. We could analyze this file with standard statistical packages; I found it helpful in understanding changes in CRF data. The sponsor also submitted adjudication packages that were predominantly in an easier to read document format. These adjudication packages included investigator notes, hospital discharge summaries, ECG tracings, etc., that were helpful in understanding the adjudications. However, these adjudication packages were computer dumps prepared for the NDA submission and hence we can not verify what the adjudication committee actually saw.

7.1.6.3. Incomplete follow-up

Another aspect of PLATO study conduct was not good: the follow-up rate. By the sponsor's statistics, about 5% of the patients died while about 82% had a final study visit ("completers" per the sponsor's terminology). Hence about 13% of the patients (100% - 5% - 82%) had incomplete follow-up for determining the primary endpoint of CV death, myocardial infarction (MI), or stroke by the sponsor's tallying.

For PLATO the maximum targeted follow-up was one year. Patients randomized less than one year prior to study termination were to have their final study visit at the time of a planned quarterly visit based on their quarter of randomization to insure a 6-month minimum follow-up. The sponsor's short summary of this rolling termination is the following: "In effect, patients were phased out uniformly over a 3-month period starting on 18 October 2008." A communication to the sites recommended a -10 day window. Hence I initially counted patients as having good CV follow-up if they had an adjudicated death or they had a CV event or study visit (with vital signs measured) on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria about 15% of patients had incomplete CV follow-up, with slightly but significantly more ticagrelor than clopidogrel patients having incomplete follow-up (15.9% vs. 14.7%). However, in PLATO patients did not always come in for a visit but may have had follow-up by another route

such as a hospital visit or an adverse event report.   Trying to account for all possible follow-up in PLATO is complex as shown by Figure 6, the program I used based on the sponsor's recommendations for determining follow-up.

Figure 6: Program for Determining CV Follow-up in PLATO

```
gen byte cvfutyp = cond(adjresl==1, 1, 2) if cvfudt!=.
  /* adjresl==1 death so 2 for all other adjudications */
gen int cvfudt = adjdtl /* adjudication date */
replace cvfutyp = 3 if cvfudt==. | (lstcldtn>cvfudt & lstcldtn!=.)
  /* last clinic visit with vital signs */
replace cvfudt =  lstcldtn if cvfudt==. | (lstcldtn> cvfudt &  lstcldtn!=.)
replace cvfutyp = 4 if cvfudt==. (cvvisdtl> cvfudt & cvvisdtl!=.)
  /* visit or phone contact with CV event checkboxes */
replace cvfudt =  cvvisdtl if cvfudt==. | (cvvisdtl>cvfudt & cvvisdtl!=.)
replace cvfutyp = 5 if cvfudt==. | (ciedtl> cvfudt & ciedtl!=.)
  /* cie = cardiac ischemic event */
replace cvfudt =  ciedtl if cvfudt==. | (ciedtl> cvfudt & ciedtl!=.)
replace cvfutyp = 6 if cvfudt==. | (hospdtl> cvfudt & hospdtl!=.) /*
hospitalization */
replace cvfudt =  hospdtl if cvfudt==. | (hospdtl> cvfudt & hospdtl!=.)
replace cvfutyp = 7 if cvfudt==. | (aedtl> cvfudt & aedtl!=.) /* adverse event */
replace cvfudt =  aedtl if cvfudt==. | (aedtl> cvfudt & aedtl!=.)
replace cvfutyp = 8 if termreas==1 | termreas==7 | termreas==8  /* bad-wd consent-
lost */
replace cvfudt =  termdt if termreas==1 | termreas==7 | termreas==8
```

Figure 6 is frightening. It should not be this difficult to determine what the last date of follow-up is in a one year study. referably patients come in for a last study visit unless they are dead, the simpler approach I initially used. By the complex determinations in Figure 6 incomplete CV follow-up is better but still concerning, about 8.6% in each arm. For the primary endpoint (counting any primary endpoint event as good follow-up) the incomplete PEP follow-up is slightly better, 7.8%. The distributions of days of missing CV follow-up were similar in both arms, with the overall distribution shown in Figure 7.

Figure 7: Distribution of Days of CV Follow-up Missing in PLATO
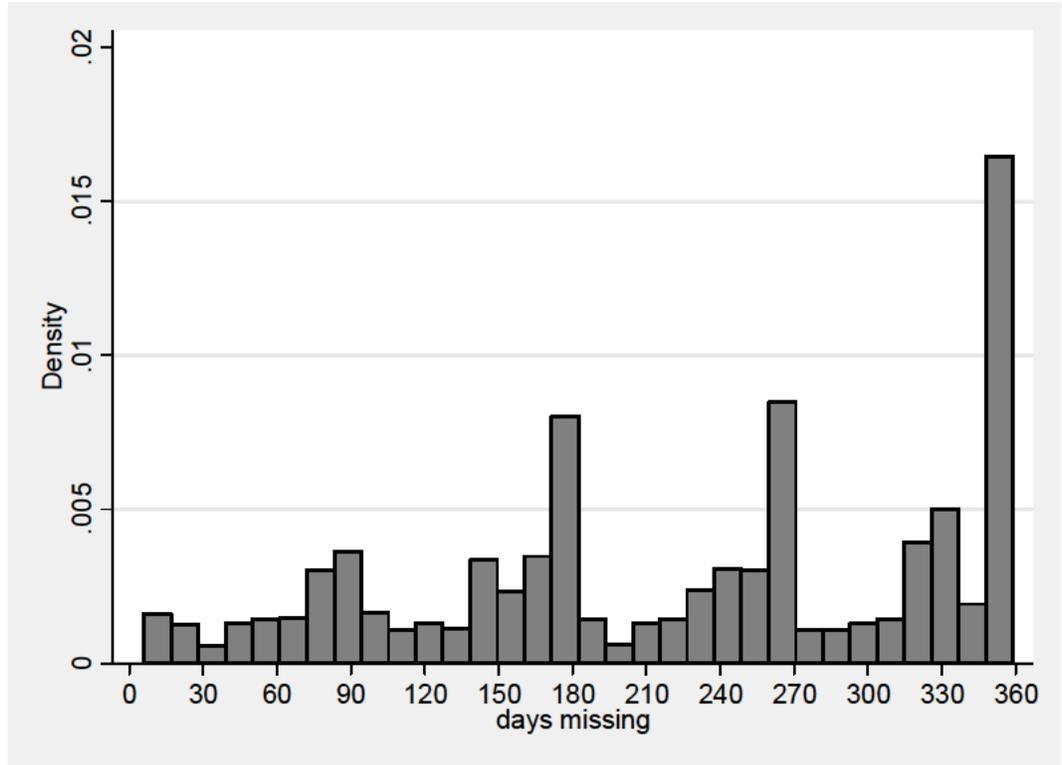
The peaks at 180, 270, and 360 days are due to patients withdrawing shortly after randomization, allowing for the rolling phase-out. The median days of CV follow-up missing were 241 days. Considering the rolling phase-out the median percentage of missing CV follow-up was 86%.

I analyzed vital status follow-up similarly, counting vital status follow-up as good if the patient died or had a last visit or contact on or after 8 October 2008 or 355 days on-study (whichever came first) and had not withdrawn consent for follow-up. (The sponsor did not use data from patients who had withdrawn consent after the date of withdrawal.) By these criteria 3.1% of ticagrelor and 2.6% of clopidogrel patients had incomplete vital status follow-up. The median days of vital status follow-up missing were 262 days (91% missing) for ticagrelor and 255 days (86% missing) for clopidogrel. By the sponsor's classification of premature termination 52 more patients in the ticagrelor group terminated early for a reason other than death; the difference in such early terminations was 50 patients in OUS vs. 2 in the US.

The sponsor does claim to have obtained vital status follow-up on many patients who had withdrawn consent. By the dates of last contact provided by the sponsor, 54 ticagrelor and 52 clopidogrel patients did not have vital status determined on or after the targeted study completion date—see my discussion in Section 8.

COMMENT: These rates of incomplete follow-up are concerning. They greatly exceed the differences between arms in rates for any of the endpoints. If the endpoint results were consistent, then we would be less concerned about the follow-up rates. However, the efficacy results are inconsistent by region and the time course of the effects are inconsistent with those from the thienopyridine ACS trials. The mortality benefit appears impressive at face value but, with these follow-up problems, are we certain that it is real? Consider in particular that the region for which we have the most confidence about lack of bias, i.e., the US, does not show the mortality benefit.

This problem with incomplete follow-up rates has been an issue for other recent CV outcome trials. While I am sympathetic to the difficulties of performing outcome trials in the modern era of increased patient awareness of medical treatments and mounting privacy concerns, if this trend continues we will not be able to interpret CV outcome trial results. This problem is the number one study conduct problem today threatening the integrity of CV outcome trials.

7.1.6.4. Censoring date issues

The PLATO efficacy analyses are time-to-first-event analyses. The sponsor, for its time-to-event analyses, used censoring dates for patients without the event of interest based on the last study visit date for the "completers" but projected based on either a future planned visit date plus 30 days for withdrawals or upon the last dispense date plus 90 days for patients who continued on study medication after a "last" visit.

COMMENT: While the use of these strange censoring rules does not change the statistics greatly, I can not see the validity of projecting follow-up particularly when we do not have a good idea why patients did not complete the study. I censored patients at the time of an event or the earlier of the time of the last study contact (for CV events) or the time of the last vital status follow-up (for all-cause mortality). My final comment is that, as usual, there is no good solution for incomplete follow-up, whether one censors at the last follow-up or tries a more esoteric approach. Incomplete follow-up significantly reduces our confidence in the validity of the results.

7.1.6.5. Sponsor's primary adjudicated results

I show the Kaplan-Meier (K-M) plot for the sponsor's first primary endpoint event (PEP - CV death, MI, or stroke - MACE) in Figure 8 and for death in Figure 9.

Figure 8: Time to Sponsor's PEP (MACE)
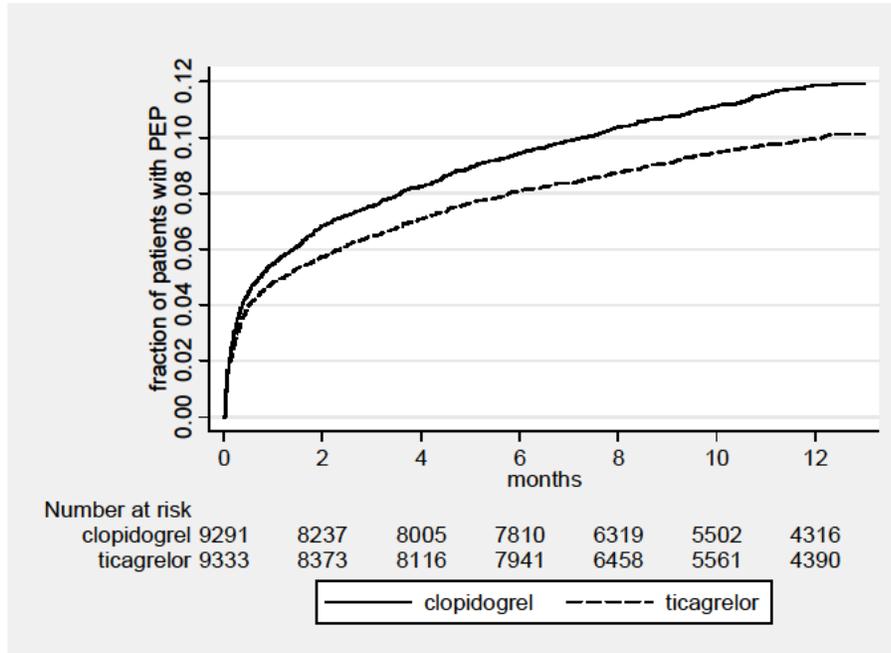
Figure 9: Time to Death from Any Cause
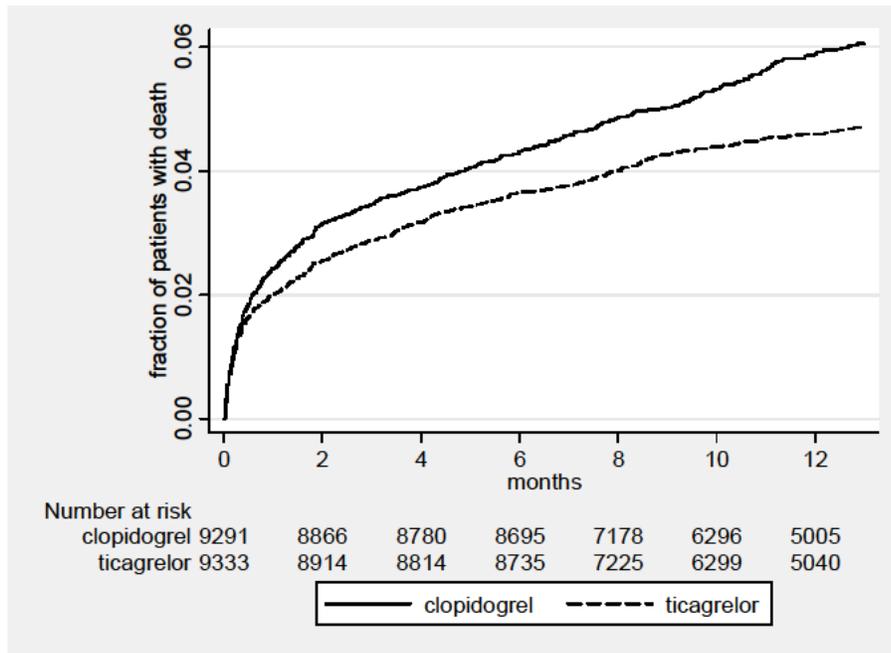
Both time-to-first event analyses are highly statistically significant by the log rank test.

COMMENT: One relevant question is that, given the incompleteness of follow-up, are the results real? The most relevant questions are regarding whether these results apply to all important comparison groups.

7.1.6.6. Site-reported MACE

As a check I counted CV death, MI, and stroke events (MACE) as reported by the sites without the ICAC adjudication. For these site-reported statistics I also implemented two variations from the sponsor's classification of CV deaths: (1) The sponsor counted bleeding deaths as CV deaths. While that is reasonable for the primary endpoint (PEP) to estimate a net benefit, for an endpoint to explore efficacy effects alone I believe that it is preferable to exclude bleeding events not related to a cardiovascular or cerebrovascular event. Hence I excluded gastrointestinal bleeds but included non-traumatic intracranial hemorrhages. (2) The sponsor counted all unknown deaths as CV deaths, again reasonable for a PEP for net benefit. I counted sudden unknown deaths as CV deaths but excluded completely unknown deaths. I show the K-M plot for this site-reported MACE in Figure 10.

Figure 10: Time to First Site-Reported MACE
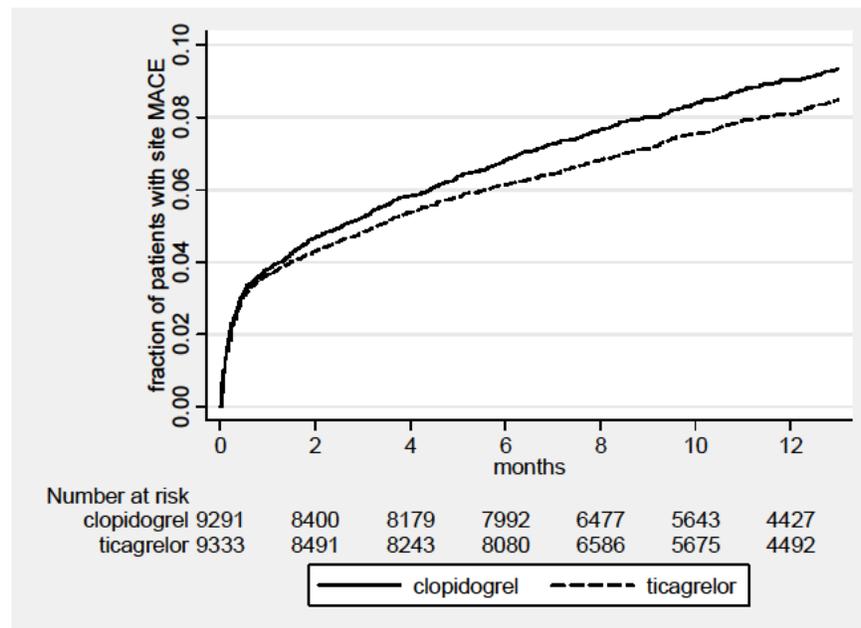
The possible benefit of ticagrelor is much less impressive for site-reported events and not statistically significant (p about 0.075 by log rank). For site-reported events there is only a slight benefit regarding MIs (relative risk (RR) about 0.94), a detriment regarding strokes (RR about 1.2), with the best benefit regarding CV deaths (RR 0.85). Note that the curves do not diverge early. In fact, there is little divergence for the first 30 days as shown in Figure 11.

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Figure 11: Time to First Site-Reported MACE – 30 Days
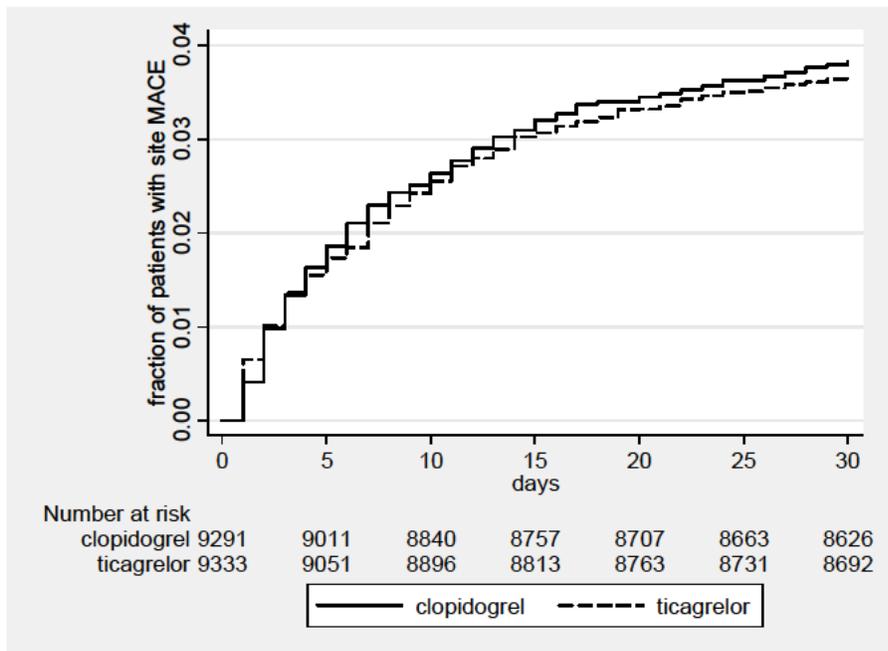
The time course in Figure 10 and Figure 11 is quite different from what we have seen with the thienopyridines in ACS. Typically there has been an almost immediate benefit that rapidly accrues during the early days. The benefit beyond 30 days is harder to establish. For ticagrelor there appears to be little early benefit regardless of type of ECG presentation by site-reported MACE as shown in Figure 12 and early benefit only for NSTEMI by the sponsor's MACE as shown in Figure 13.

Figure 12: Time to First Site-Reported MACE by ECG Presentation
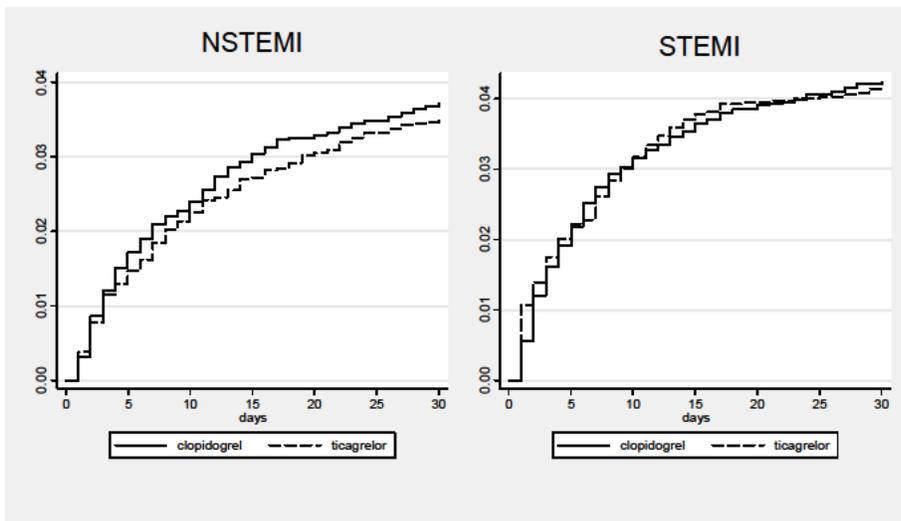
Figure 13: Time to Sponsor's PEP by ECG Presentation
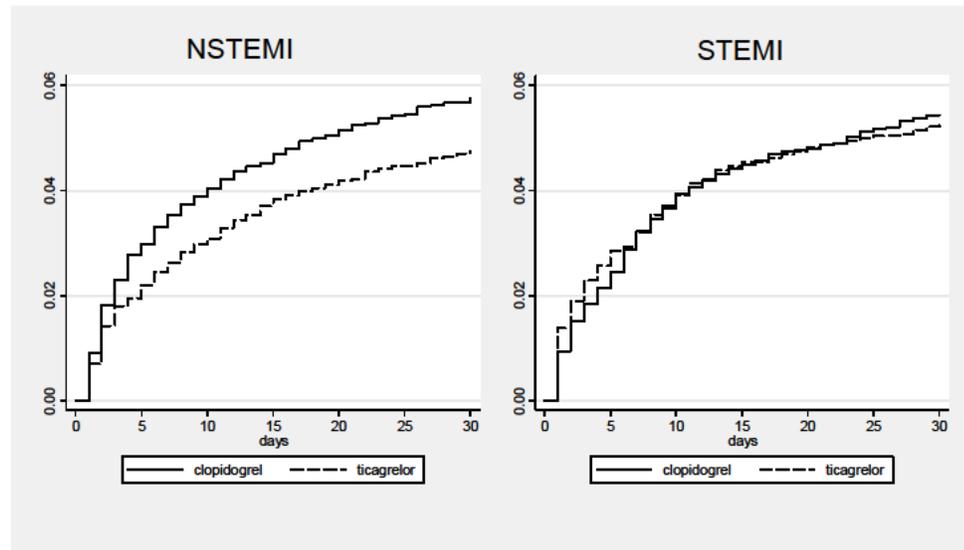
The short term effects for ticagrelor are the opposite of what we've seen with prasugrel compared to clopidogrel: For prasugrel there was an immediate and dramatic benefit in STEMI patients in the TRITON trial but, at least for site-reported events, little benefit for NSTEMI patients. Also the early MACE rates were higher for STEMI patients in TRITON but are similar in PLATO regardless of ECG presentation. There are three significant differences of TRITON compared to PLATO: (1) TRITON excluded patients with prior thienopyridine use; PLATO included them. (2) In TRITON all patients underwent percutaneous coronary intervention (PCI); in PLATO about 60% of patients had a PCI within the first 10 days after study drug administration. (3) In TRITON administration of study drug was delayed until after coronary angiography in all but the STEMI patients who presented within 12 hours of symptom onset; in PLATO the investigator was to give study drug immediately after randomization regardless of angiography having being done and prior to PCI. However, in PLATO the investigator could delay randomization until after angiography at his or her discretion.

7.1.6.7. Prior non-study thienopyridine

We might expect that patients who suffer an event while having recent thienopyridine use may be different than patients without recent thienopyridine use. The results shown in

Table 4 for the sponsor's primary MACE endpoint by non-study thienopyridine use appear to support this belief.

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Table 4: Sponsor's PEP by Non-Study Thienopyridine Use

Non-study thienopyridine	n		MACE ≤ 30d		MACE anytime	
	clopidogrel	ticagrelor	clopidogrel	ticagrelor	clopidogrel	ticagrelor
none	4,716	4,760	5.3%	4.4%	10.5%	9.0%
prior*	513	478	6.6%	9.0%	16.2%	18.2%
day 1†	4,062	4,095	5.4%	4.7%	10.7%	8.5%

* prior thienopyridine use within 5 days prior to randomization
† excluding patients with prior non-study thienopyridine

For Table 4 I counted prior thienopyridine use if it was started more than 5 days prior to randomization and was continued within 5 days prior to randomization, the typical time recommended for waiting to perform CABG after discontinuing clopidogrel. About 5.3 percent of patients had such use, while about 7.5 percent had any prior use. The vast majority was clopidogrel, with only 75 patients OUS receiving ticlopidine. I do note that some of these patients appear to have had interventions within the month prior to randomization for which clopidogrel was given.

Note that both the short term (30 day) and overall rates for the sponsor's primary MACE are substantially worse in both arms for the patients with prior thienopyridine use and particularly worse in the ticagrelor arm. Because the prior thienopyridine use patients are few and because they behave differently than the substantial majority without prior thienopyridine use, I exclude them from most of my subsequent analyses.

7.1.6.8. Relationship to very early invasive management

About 61% of PLATO patients had at least one PCI after study drug administration at some time during the study, virtually identical rates in both arms. I examined MACE rates in patients who did or did not have a subsequent PCI but did not find any discernible differences. However, about 51% of the patients had a PCI within 24 hours of randomization and only 10% had a first or subsequent PCI after the first 24 hours. About 89% of PCIs within the first 24 hours were within the first 5 hours, 92% were within the first 10 hours and 93% within the first 12 hours, with the last 8% starting at about 16 hours. For my advisory committee memo I selected 10 hours as a reasonable cutoff to differentiate patients who underwent an early— or very early—invasive strategy from a delayed one or medical management. For this final CDTL memo my colleagues persuaded me that 12 hours is a more usual cutoff—and the results vary minimally regardless of whether I use 10, 12, or 24 hours. I believe that looking at a very early invasive strategy is important for determining whether the claimed faster onset of ticagrelor than clopidogrel is advantageous—or whether it actually exists.

Because we might expect that the early thienopyridine and invasive management therapy should have the greatest effect upon the early endpoints, I analyzed primarily the endpoints within the first 30 days. To focus on the cardiac events I analyzed site-reported MIs or CV death and, as a less challengeable endpoint, all

cause mortality. I show the results within the first 30 days for site-reported MI and CV death by non-study thienopyridine use day 1 and invasive management in Table 5, for all-cause mortality in Table 6, and for the sponsor's primary MACE endpoint in Table 7.

Table 5: Percentages of Patients with Site-Reported MI or CV Death within 1st 30 Days by Non-Study Thienopyridine Use Day 1 and Invasive Management

Thienopyridine d1:	no		yes	
Invasiveness	clopidogrel	ticagrelor	clopidogrel	ticagrelor
`medical	4.7%	3.3%	3.8%	2.2%
PCI≥12h or CABG	4.4%	4.3%	3.2%	3.3%
PCI<12h	2.7%	3.0%	2.6%	2.7%

Table 6: Percentages of Patients Who Died within 1st 30 Days by Non-Study Thienopyridine Use Day 1 and Invasive Management

Thienopyridine d1:	no		yes	
Invasiveness	clopidogrel	ticagrelor	clopidogrel	ticagrelor
medical	4.5%	2.7%	3.6%	2.2%
PCI≥12h or CABG	1.8%	1.1%	1.4%	1.9%
PCI<12h	1.4%	2.1%	2.0%	1.9%

Table 7: Percentages of Patients with Sponsor's PEP within 1st 30 Days by Non-Study Thienopyridine Use Day 1 and Invasive Management

Thienopyridine d1:	no		yes	
Invasiveness	clopidogrel	ticagrelor	clopidogrel	ticagrelor
medical	5.5%	3.5%	4.9%	2.9%
PCI≥12h or CABG	7.2%	6.3%	7.3%	7.2%
PCI<12h	4.1%	4.1%	4.7%	4.1%

Medically managed patients always fared better with ticagrelor regardless of clopidogrel pretreatment. Patients with early PCI without clopidogrel pre-treatment fared slightly better with clopidogrel for MI and CV death and all cause mortality and neutral by the sponsor's MACE. The results for the sponsor's MACE always favor ticagrelor with the exception of the latter neutral result and virtually neutral results for patients with later invasive management with clopidogrel pre-treatment.

COMMENT: These findings suggest to me that ticagrelor is not a better, faster platelet inhibitor. I would expect that patients with the very early invasive strategy would have the greatest need for good platelet inhibition, but ticagrelor fared worse for short term outcomes in these patients. The short term outcomes also suggest that clopidogrel pre-treatment is beneficial regardless of later P2Y$_{12}$ inhibitor.

7.1.6.9. Relationship to type of MI by ECG presentation

STEMI is the other medical condition, besides PCI, for which we believe good platelet inhibition is important—and for STEMI we believe earlier is better. I show the results for site-reported MI and CV death by type of MI by ECG presentation, invasiveness, and non-study thienopyridine use day 1 in Table 8.

Table 8: Percentages of Patients with Site-Reported MI or CV Death within 1ˢᵗ 30 Days by MI Type by ECG Presentation, Invasive Management, and Non-Study Thienopyridine Use Day 1

Non-study thienopyridine d1:		no		yes	
ECG	Invasiveness	clopidogrel	ticagrelor	clopidogrel	ticagrelor
NSTEMI	medical	3.5%	3.2%	3.3%	2.2%
	PCI≥12h or CABG	4.2%	4.4%	2.8%	2.9%
	PCI<12h	2.3%	2.4%	2.1%	1.8%
STEMI	medical	9.4%	3.4%	5.2%	2.3%
	PCI≥12h or CABG	5.2%	3.9%	4.8%	5.3%
	PCI<12h	2.8%	3.3%	2.9%	3.3%

Note that in Table 8 for STEMI about 75% of patients were managed with a very early invasive approach, i.e., PCI < 12h, while for NSTEMI the invasiveness was fairly evenly distributed, with the most for medical management at 38%. For STEMI clopidogrel performed better than ticagrelor with an early invasive approach, while it performed poorly with medical management. For NSTEMI ticagrelor was about the same as clopidogrel with invasive management but moderately better for medical management. Patients usually fared better with clopidogrel pre-treatment with the exception of STEMI patients managed with very early PCI. The other subgroup in Table 8 that appears to be a second exception, ticagrelor STEMI patient with clopidogrel pre-treatment and a later invasive strategy, is the subgroup with the fewest patients, i.e., <200.

COMMENT: Patients with STEMI managed with very early PCI, e.g., with primary PCI as is the standard of care in the US, do better short term with clopidogrel. It is precisely this situation for which we presume that faster, better platelet inhibition is critical. Hence these results seem inconsistent with the ex vivo platelet inhibition results in the ONSET/OFFSET study.

I explored further the thienopyridine pre-treatment benefit and the possible clopidogrel superiority for STEMI managed with an early invasive approach for both short term and long term results. I show the results for various endpoints for these categorizations and for both short-term and long-term results in Table 9.

Table 9: Percentages of Patients with Short-term and Long-term Efficacy Endpoints by STEMI with PCI < 12h and Non-study Thienopyridine Use

Non-study thienopyridine d1:			no		yes	
Period	Endpoint	STEMI & PCI<12h	clopidogrel	ticagrelor	clopidogrel	ticagrelor
1st 30 days	MI + CV death	no	4.1%	3.4%	3.0%	2.5%
		yes	2.8%	3.3%	2.9%	3.3%
	death	no	2.8%	1.8%	2.0%	1.7%
		yes	1.8%	2.7%	2.6%	2.6%
	sponsor's PEP	no	6.1%	4.4%	5.9%	4.5%
		yes	3.3%	4.3%	4.4%	5.0%
entire study	site MACE	no	9.3%	8.3%	8.3%	7.0%
		yes	6.4%	6.4%	6.6%	6.5%
	death	no	6.8%	4.8%	5.0%	3.9%
		yes	3.6%	4.1%	4.7%	4.4%
	sponsor's PEP	no	11.8%	9.6%	11.8%	8.9%
		yes	7.4%	7.6%	8.7%	7.9%

COMMENT: STEMI patients with early PCI fared better with clopidogrel for 30-day endpoints. For the entire study endpoints STEMI patients with early PCI have similar results between the two treatments. With this more refined analysis I don't see a clear effect of clopidogrel pre-treatment.

7.1.6.10.   US vs. OUS

The major issue regarding the efficacy of ticagrelor as perceived by many reviewers and at the advisory committee meeting is the quandary of the unfavorable results in the US that are inconsistent with the results in most other countries. The funnel plot from the FDA Statistical Review reproduced in Figure 14 depicts the inconsistency well.

Figure 14: Funnel Plot of Log Hazard Ratio by Events per Country (from FDA Statistical Review)
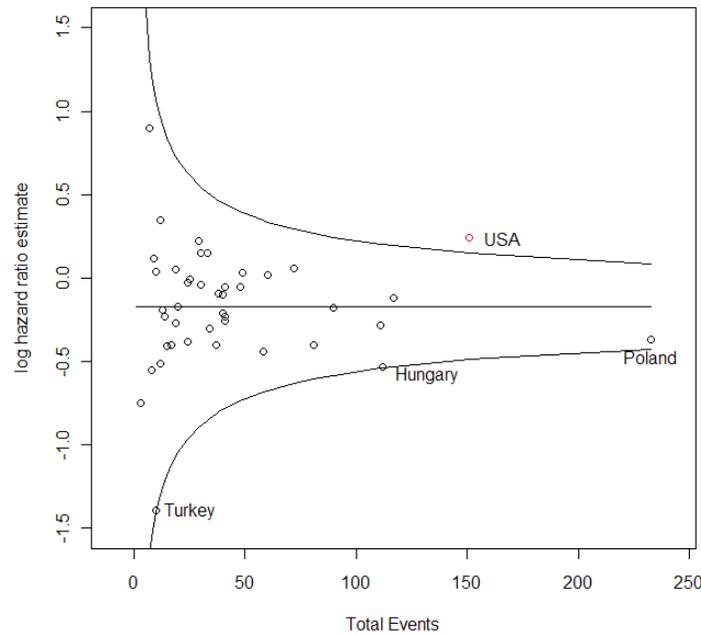
The US has worse results with ticagrelor for all efficacy measures, including MACE, MI, stroke, CV death, and all-cause mortality and is an outlier for all of them except stroke. Stroke rates are at least numerically higher with ticagrelor in all regions.

The sponsor has proposed one mechanism for explaining the disparate US vs. OUS results: aspirin dosage. Aspirin dosages in the US were split between 325 mg and 82 mg while OUS the vast majority of the dosing was 75 or 100 mg (after a loading dose of 500 or 1000 mg). The sponsor proposes that ticagrelor patients did worse with the high 325 mg dosage. Please see the FDA primary clinical efficacy and statistical reviews for exhaustive analyses of the aspirin dosage. They conclude that, because of multiple problems with the analyses (aspirin dosage and region are highly correlated, the sponsor's analyses are sensitive to reclassification of small numbers of cases regarding loading vs. maintenance aspirin dosing and events in high dose aspirin OUS, biologic plausibility, etc.) aspirin dosing does not explain the disparate results. I examine US vs. OUS differences for the factors discussed above first and then address the ASA effects in the next section.

I show the percentages of patients with site-reported MI or CV death within the first 30 days by region and STEMI with PCI < 12h in Table 10 and the same breakdown for site-reported MACE during the entire study in Table 11.

Table 10: Percentages of Patients with Site-Reported MI or CV Death within 1st 30 Days by Region and STEMI with PCI<12h

STEMI & PCI<12h	OUS		US	
	clopidogrel	ticagrelor	clopidogrel	ticagrelor
no	3.8%	3.1%	2.5%	2.3%
yes	2.9%	3.2%	1.8%	5.0%

Table 11: Percentages of Patients with Site-Reported MACE for the Entire Study by Region and STEMI with PCI<12h

STEMI & PCI<12h	OUS		US	
	clopidogrel	ticagrelor	clopidogrel	ticagrelor
no	9.5%	8.2%	5.5%	7.9%
yes	6.7%	6.3%	4.6%	14.0%

The short-term results in Table 10 are more consistent between OUS and US than the long term results in Table 11. While the short-term results roughly show clopidogrel better than or equal to ticagrelor for STEMI with PCI<12h and ticagrelor better than or equal to clopidogrel for the rest of the patients, the long-term results show that clopidogrel was better than ticagrelor in the US while ticagrelor was better than clopidogrel OUS.

COMMENT: These two tables illustrate well the quandary of PLATO. While the short-term results are not drastically different, the long-term results are completely disparate in the US vs. OUS. I tend to trust US results more and they do represent the most relevant population and practice patterns for our approval, but the bulk of the data are from OUS. It is also striking in Table 11 that clopidogrel in STEMI patients with PCI<12h in the US has the lowest rate and ticagrelor the highest rate in the same subgroup..

One factor that could be informative to explore for the US vs. OUS discrepancy is the timing of study drug with relation to the start of the PCI. US practitioners tend to delay administering the antiplatelet drug until after performing angiography and delineating the coronary anatomy; OUS practitioners are more likely to give antiplatelet drug early. The time of first study drug and the time of the PCI were captured in PLATO. However, times (like dates) are problematic in clinical trials and PLATO appears to have substantial problems with its times. The following are some statistics that confirm that analyzing the time from study drug to PCI is futile:

- For 725 patients the first study drug time is prior to the randomization time. Only for one of these patients did the sponsor confirm that study drug was actually administered prior to randomization. The rest must be time errors.

- For 335 patients the PCI time is prior to randomization. These cases are either protocol violations or time errors.

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- For 730 patients the study drug time is after the PCI. These cases are not protocol violations but they could be contrary to the intent of the study to administer study drug immediately after randomization or they could be time errors.

7.1.6.11. Aspirin dosage and other factors

The sponsor has proposed aspirin dosage as having a substantial and significant interaction with ticagrelor efficacy. The sponsor alleges that the lower efficacy with ticagrelor in the US is the result of lower efficacy of ticagrelor with higher dosages of aspirin, i.e., 100 mg or below works well with ticagrelor while 300 mg or above interferes. (b) (4)

(b) (4)

I scrutinized the aspirin administration records. There is one difference in aspirin administration practices between US and OUS that may confound the analyses: OUS investigators frequently administered a loading dose of aspirin of 500 or 1000 mg and then reduced the dosage to 80-100 mg after a few doses for maintenance while US investigators tended to use either ASA 325 or 81 mg consistently for the short term. For OUS patients who suffered an endpoint shortly after the administration of the loading dose it is not obvious what dosage to use for analyses correlating aspirin dosage with outcomes. Because about 20% of patients had a primary endpoint within the first three days, we can not ignore this problem. The sponsor performed analyses both including and excluding the loading dose. However, some patient only received a loading dose, so the sponsor excluded them from some analyses. I favor analyzing all dosing for short and long term outcomes and then separately analyzing events after day 3.

I show the short-term results in Table 12 , the long-term results in

Table 13, and the events after day 3 in Table 14**Error! Reference source not found.**.

Table 12: Percentages of Patients with Sponsor's PEP within 1st 30 Days by Region, Aspirin Dosage, and Treatment

	ASA	clopidogrel	ticagrelor
OUS	none	13.5%	16.1%
	≤100	4.3%	3.6%
	101-299	8.0%	6.7%
	≥300	18.8%	15.8%
US	none	3.7%	10.0%
	<300	5.1%	3.1%
	≥300	5.5%	7.0%

Table 13: Percentages of Patients with Sponsor's PEP by Region, Aspirin Dosage, and Treatment

	ASA	clopidogrel	ticagrelor
OUS	none	18.0%	20.3%
	≤100	9.9%	7.8%
	101-299	15.9%	13.5%
	≥300	29.4%	25.9%
US	none	*	*
	<300	10.2%	7.9%
	≥300	8.9%	15.4%

* <20 patients

Table 14: Percentages of Patients with Sponsor's PEP after 3 Days by Region, Aspirin Dosage, and Treatment

	ASA	clopidogrel	ticagrelor
OUS	none	17.3%	19.0%
	≤100	8.9%	6.8%
	101-299	10.8%	10.8%
	≥300	11.0%	11.7%
US	none	*	*
	<300	9.1%	7.0%
	≥300	6.4%	11.3%

* <20 patients

COMMENT: The OUS and US results are inconsistent for ASA as well as for efficacy results. The OUS results are easier to explain: The high rates both for no ASA and for the high dosages suggest that the ASA dosages are consequences of outcomes rather than predictors, e.g., patients were not down-titrated to a lower dosage before having an event. Note that OUS there is a similar gradient of risk with increasing ASA dosage both short and long term for both clopidogrel and ticagrelor. For MACE after 3 days OUS there are no differences between rates by treatment for the higher ASA dosages. This pattern is inconsistent with the US pattern and suggests to me that the OUS results for higher ASA dosages are outcome consequences rather than causes.

The US ASA results I believe are a combination of small numbers leading to random variation and some risk or outcome consequences similar to the OUS effects. The clopidogrel and ticagrelor gradients with increasing ASA dosage are in opposite directions for the longer follow-up durations while ASA dosage with clopidogrel shows little effect upon short-term outcomes.

The sponsor's and the primary reviewers' approach to exploring the US-OUS discrepancy has been to determine how the addition of a single factor affects the region-treatment interaction term in a Cox regression. The only additional single factor that minimizes the region-treatment interaction is the ASA dosage. I argue that there are many limitations of this approach:

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- *ASA dosage is highly correlated with region. With two highly correlated factors in the same regression it is impossible to predict which one will be significant.*

- *As I presented above, the US and OUS appear to be heterogeneous for ASA dosage and for outcomes related to ASA dosage. I have no confidence that a Cox regression including both regions appropriately models the relationships between the various factors and outcomes.*

- *The cofactors and covariates tested have almost exclusively been baseline covariates. However, ASA dosage as defined is not a baseline covariate. It does appear to be related OUS to whether an endpoint occurred prior to the usual down titration after the loading doses. Its explanation also may be related to factors or covariates that are not baseline and have not been collected. The critical explanatory factor or factors may not have been collected or recognized.*

That the factors determining ASA dosage differed by region is easy to demonstrate. I show the percentages of patients receiving ASA ≥ 300 mg by selected factors and region in Table 15.

Table 15: Percentages of Patients Receiving ASA ≥ 300 mg by Selected Factors and Region

Factor		OUS	US
gender	female	3%	45%
	male	3%	56%
age	<65	3%	56%
	≥65	3%	48%
index event	ua	2%	46%
	nstemi	3%	53%
	stemi	3%	58%
stent	no	3%	45%
	yes	3%	57%
stent thrombosis	none	3%	53%
	definite	13%	54%
heart failure	no	3%	53%
	yes	6%	55%

STEMI patients were slightly more likely to get ASA ≥ 300 mg in both regions. However, in the US stented patients were more likely to get the higher dose while OUS patients with stent thrombosis or heart failure were more likely to get it.

COMMENT: The latter two findings confirm my suspicion that OUS higher risk patients received higher ASA dosages. In the US higher risk alone does not appear to be driving the use of the higher ASA dosage. Stent thrombosis, of course, can

part of a primary MI or CV death endpoint and heart failure can be the
consequence of a primary endpoint so these associations could be the
consequences of the endpoints rather than caused by the higher ASA dosages.

I analyzed the interaction between treatment and aspirin dosage in the US patients
only. I did so for both the sponsor's MACE primary endpoint and for site-reported
MACE. The results were similar, so I present only the site-reported MACE
analyses here because the treatment effect is statistically significant in the US for
site-reported MACE. I show the basic Cox regression of treatment for site-reported
MACE in US patients in Figure 15.

Figure 15: Cox Regression of Treatment for Site-reported MACE in US Patients

```
. stcox rx if us

        failure _d:  pepsite
  analysis time _t:  pepsiteday/30

Iteration 0:   log likelihood = -706.11496
Iteration 1:   log likelihood = -703.04428
Iteration 2:   log likelihood = -703.04321
Refining estimates:
Iteration 0:   log likelihood = -703.04321

Cox regression -- Breslow method for ties

No. of subjects =          1413                 Number of obs   =       1413
No. of failures =           100
Time at risk    =   13994.13333
                                                LR chi2(1)      =       6.14
Log likelihood  =    -703.04321                 Prob > chi2     =     0.0132


------------------------------------------------------------------------------
         _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
         rx |   1.653682    .3407089     2.44   0.015     1.104278    2.476426
------------------------------------------------------------------------------
```

Note that treatment is statistically significant, with a hazard ratio of 1.7 for
ticagrelor vs. clopidogrel, for site-reported MACE in the US subgroup. I add my
ASA dosage ≥ 300 mg and the interaction term for this dosage and treatment in
Figure 16.

Figure 16: Cox Regression of Treatment and ASA Dosage for Site-reported MACE in US Patients

```
. stcox rx##aspge300 if us

        failure _d:  pepsite
  analysis time _t:  pepsiteday/30

Cox regression -- Breslow method for ties

No. of subjects =          1339                 Number of obs   =       1339
No. of failures =            94
Time at risk    =   13521.63333
                                                LR chi2(3)      =       9.93
Log likelihood  =    -654.26927                 Prob > chi2     =     0.0192


------------------------------------------------------------------------------
         _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
```

35

```
       1.rx |   1.100529   .3535202     0.30   0.766    .5863702    2.065527
  1.aspge300 |    .899422   .2998799    -0.32   0.751    .4679085    1.728885
             |
  rx#aspge300 |
         1 1 |    1.97722   .8521954     1.58   0.114    .849535     4.60181
-----------------------------------------------------------------------------
```

For US patients alone the interaction term is not statistically significant, although the hazard ratio for the combination of ticagrelor and ASA dosage ≥ 300 mg is 2.0. I add selected other common factors, e.g., age and gender, and some factors that are significant in Figure 17.

Figure 17: Cox Regression of Treatment, ASA Dosage, and Selected Factors for Site-reported MACE in US Patients

```
. stcox rx##aspge300 age male pci##rx i.indexev mihx hfhx strkhx if us

       failure _d:  pepsite
  analysis time _t:  pepsiteday/30

Cox regression -- Breslow method for ties

No. of subjects =          1258              Number of obs   =       1258
No. of failures =            92
Time at risk    =       12780.3
                                             LR chi2(12)     =      46.06
Log likelihood  =    -617.16186             Prob > chi2     =     0.0000


-----------------------------------------------------------------------------
         _t | Haz. Ratio   Std. Err.     z    P>|z|    [95% Conf. Interval]
------------+----------------------------------------------------------------
       1.rx |   .5549913   .2675053    -1.22   0.222    .2157783    1.427462
  1.aspge300 |  1.007043   .3410821     0.02   0.983    .5185001    1.955902
             |
 rx#aspge300 |
         1 1 |   1.751283   .7667678     1.28   0.201    .7424602    4.130852
             |
        age |    1.01951   .0093628     2.10   0.035    1.001324    1.038027
       male |   1.026268   .2425497     0.11   0.913    .6457834    1.630929
      1.pci |   1.015407   .3526054     0.04   0.965    .5141097    2.005508
             |
     pci#rx |
         1 1 |   2.543781   1.282501     1.85   0.064    .946953     6.83331
             |
    indexev |
          4 |   2.305917   1.061753     1.81   0.070    .9352124    5.685609
          5 |   1.724679   .6961301     1.35   0.177    .7818779    3.804326
             |
       mihx |   1.563234   .3677625     1.90   0.058    .985763     2.478994
       hfhx |    2.72703   .8028708     3.41   0.001    1.531391    4.856172
     strkhx |   2.078409   .9068002     1.68   0.094    .8838035     4.88772
-----------------------------------------------------------------------------
```

All of the significant or close to significant factors seem sensible. Increasing age increases risk, as do history of MI, heart failure, or stroke, and STEMI and NSTEMI relative to unstable angina. With the addition of these and other factors the significance and hazard ratio of the ASA-treatment interaction term is further reduced. Conversely the hazard ratio of the treatment term decreases to less than one and its significance increases (although not to nominal statistical significance.) However, this change is accompanied by a significant interaction (if one considers interactions to be significant at P<0.1) between ticagrelor and PCI, with increased risk for that combination.

I also examined various statistics for the US sites. I did not find any obvious patterns with regard to endpoints and aspirin, clopidogrel, PCI, or stent use that could explain the negative US results with ticagrelor.

COMMENT: The interaction between PCI and treatment is reminiscent of the short-term results suggesting that clopidogrel is preferable for STEMI with a PCI < 12h. For the US alone the interaction with PCI appears to be stronger than the interaction with ASA dosage.

Because multiple factors appear to influence PLATO outcomes, it should be informative to analyze PLATO outcomes using multivariate statistical techniques. I show the simple Cox regression of treatment for site-reported CV death or MI within the first 30 days in Figure 18 and of treatment and selected other factors in Figure 19. I show the Cox regression of treatment and selected other factors for deaths within the first 30 days in Figure 20 and the same for the STEMI subgroup in Figure 21.

Figure 18: Cox Regression of Treatment for Site-reported CV Death or MI within 1st 30 Days

```
. stcox rx

        failure _d:  micvd30
  analysis time _t:  micvd30day

Cox regression -- Breslow method for ties

No. of subjects =        18624               Number of obs   =      18624
No. of failures =          610
Time at risk    =       531986
                                             LR chi2(1)      =       1.45
Log likelihood  =   -5977.8534               Prob > chi2     =     0.2285

------------------------------------------------------------------------------
        _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+------------------------------------------------------------------
        rx |   .9070426   .0735277    -1.20   0.229     .7737963    1.063234
------------------------------------------------------------------------------
```

Figure 19: Cox Regression of Treatment and Selected Other Factors for Site-reported CV Death or MI within 1st 30 Days

```
. stcox rx##us age male proclt12h##rx ecgstemi mihx hfhx strkhx

        failure _d:  micvd30
  analysis time _t:  micvd30day

Cox regression -- Breslow method for ties

No. of subjects =        18622               Number of obs   =      18622
No. of failures =          609
Time at risk    =       531979
                                             LR chi2(11)     =     157.92
Log likelihood  =   -5889.7633               Prob > chi2     =     0.0000

------------------------------------------------------------------------------
        _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------+------------------------------------------------------------------
      1.rx |   .8070838   .0856909    -2.02   0.044     .6554561    .9937879
      1.us |   .8168985   .2044402    -0.81   0.419     .5001993    1.334115
           |
```

```
       rx#us |
         1 1 |    1.245215    .4290543      0.64   0.524     .6337997      2.44645
              |
          age |    1.038255    .0040705      9.58   0.000     1.030308     1.046264
         male |    .9903591    .0879733     -0.11   0.913     .8321099     1.178704
   1.proclt12h |    .5856983    .0738407     -4.24   0.000     .4574677     .7498725
              |
  proclt12h#rx |
         1 1 |    1.320211    .2196895      1.67   0.095      .952795     1.829311
              |
      ecgstemi |    1.617888     .151529      5.14   0.000     1.346562     1.943886
         mihx |    .9868015    .1007122     -0.13   0.896     .8078985     1.205321
         hfhx |    1.033767    .1667123      0.21   0.837     .7536194     1.418055
        strkhx |    1.777293    .2722232      3.75   0.000     1.316385      2.39958
-------------------------------------------------------------------------------
```

Figure 20: Cox Regression of Treatment and Selected Other Factors for Deaths within 1st 30 Days

```
. stcox rx##us age male proclt12h##rx ecgstemi mihx hfhx strkhx

        failure _d:  died30
   analysis time _t:  died30day

Cox regression -- Breslow method for ties

No. of subjects =        18622                   Number of obs   =       18622
No. of failures =          410
Time at risk    =       545060
                                                LR chi2(11)     =      204.03
Log likelihood  =    -3922.281                  Prob > chi2     =      0.0000


-------------------------------------------------------------------------------
          _t |  Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+-----------------------------------------------------------------
        1.rx |    .6960885    .0910996     -2.77   0.006      .538598     .8996306
        1.us |    1.037912    .2875154      0.13   0.893     .6030685     1.786301
             |
       rx#us |
         1 1 |    .7689475    .3380706     -0.60   0.550     .3248349     1.820248
             |
         age |    1.051869    .0051136     10.40   0.000     1.041894     1.061939
        male |    .9190501    .0975233     -0.80   0.426     .7464754     1.131522
  1.proclt12h |    .4780598    .0727023     -4.85   0.000     .3548407     .6440671
             |
 proclt12h#rx |
         1 1 |    1.667986    .3403373      2.51   0.012     1.118182     2.488126
             |
     ecgstemi |    2.293471    .2574004      7.40   0.000     1.840608     2.857756
         mihx |    .9335184    .1178472     -0.54   0.586      .728899     1.195579
         hfhx |    1.318869    .2359879      1.55   0.122     .9287405     1.872875
        strkhx |    1.704465    .3163558      2.87   0.004     1.184682     2.452306
-------------------------------------------------------------------------------
```

Figure 21: Cox Regression of Treatment and Selected Other Factors for Deaths within 1st 30 Days in the STEMI Subgroup

```
. stcox rx##us age male proclt12h##rx mihx hfhx strkhx if ecgstemi

        failure _d:  died30
   analysis time _t:  died30day

Cox regression -- Breslow method for ties

No. of subjects =         7541                   Number of obs   =        7541
No. of failures =          207
Time at risk    =       219926
                                                LR chi2(10)     =      107.43
Log likelihood  =    -1790.7983                 Prob > chi2     =      0.0000
```

```
-------------------------------------------------------------------------------
         _t |  Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+------------------------------------------------------------------
       1.rx |   .5118339    .1307792    -2.62   0.009     .3101971    .8445402
       1.us |   1.348004    .5662893     0.71   0.477     .5917056    3.070976
            |
      rx#us |
        1 1 |   .6529754    .4715071    -0.59   0.555     .1585815    2.688692
            |
        age |    1.05552    .0069981     8.15   0.000     1.041893    1.069325
       male |   .8733519    .1330311    -0.89   0.374      .647936     1.17719
 1.proclt12h |   .5041226    .0984388    -3.51   0.000     .3438145    .7391765
            |
proclt12h#rx |
        1 1 |   2.429008    .7447203     2.89   0.004      1.33185    4.429989
            |
       mihx |    .917128    .1850989    -0.43   0.668     .6174995    1.362145
       hfhx |   1.179087    .3839955     0.51   0.613     .6227782     2.23233
      strkhx |   1.855599    .5024344     2.28   0.022     1.091458    3.154722
-------------------------------------------------------------------------------
```

For the Cox regression of treatment alone in Figure 18 treatment is not a significant factor. However, it becomes significant when other risk factors are incorporated into the analysis as shown in Figure 19. Note the following: (1) For short term outcomes there is no significant US effect or US-OUS interaction. (2) Having a PCI within 12 hours (proclt12h) is associated with a significantly lower risk. There appears to be an interaction with treatment, with ticagrelor use and early PCI associated with higher risk. (Because of the insensitivity of interaction analyses, a significance level of 0.10 rather than 0.05 is frequently used for them.)

The interaction between ticagrelor use and early PCI is more pronounced for deaths within 30 days as shown in Figure 20. Treatment remains highly significant and US and the US-treatment interaction insignificant. The interaction between ticagrelor use and early PCI remains highly significant if the STEMI subgroup alone is analyzed as shown in Figure 21, while it is not significant in the NSTEMI subgroup alone (not shown).

COMMENT: For short term results the US does not appear to behave significantly differently than OUS. Any crude differences between outcomes in the two regions may be related to differences in invasive practices, including ones that were not captured. The most consistent short-term subgroup result appears to be reduced effectiveness of ticagrelor in STEMI patients undergoing early PCI.

I show a Cox regression of treatment for site-reported MACE for the entire study in Figure 22 and of treatment and selected other factors in Figure 23.

Figure 22: Cox Regression of Treatment for Site-reported MACE for the Entire Study

```
. stcox rx

        failure _d:  pepsite
  analysis time _t:  pepsiteday/30

Cox regression -- Breslow method for ties
```

```
No. of subjects =         18624                      Number of obs   =      18624
No. of failures =          1493
Time at risk    =      185606.6
                                                     LR chi2(1)      =       3.16
Log likelihood  =    -14435.241                      Prob > chi2     =     0.0753


------------------------------------------------------------------------------
         _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
         rx |   .9120105   .0472485    -1.78   0.075     .8239515    1.009481
------------------------------------------------------------------------------
```

Figure 23: Cox Regression of Treatment and Selected Other Factors for Site-reported MACE for the Entire Study

```
. stcox rx##us age male stented##us clopprior ecgstemi mihx hfhx strkhx

       failure _d:  pepsite
  analysis time _t:  pepsiteday/30

Cox regression -- Breslow method for ties

No. of subjects =         18622                      Number of obs   =      18622
No. of failures =          1492
Time at risk    =   185606.3667
                                                     LR chi2(12)     =     467.39
Log likelihood  =    -14193.268                      Prob > chi2     =     0.0000


------------------------------------------------------------------------------
         _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
       1.rx |   .8840479    .047494    -2.29   0.022     .7956946     .982212
       1.us |   .4400139   .1017503    -3.55   0.000     .2796608    .6923108
            |
      rx#us |
        1 1 |   1.826349    .388978     2.83   0.005     1.203078    2.772513
            |
        age |   1.035595   .0025986    13.94   0.000     1.030515    1.040701
       male |   .9801411   .0559052    -0.35   0.725     .8764716    1.096073
  1.stented |   .8051195   .0470564    -3.71   0.000     .7179771    .9028386
            |
  stented#us |
        1 1 |   1.821984   .4146184     2.64   0.008     1.166384    2.846083
            |
   clopprior |   1.373469   .1150881     3.79   0.000      1.16545    1.618617
     ecgstemi |   1.277647   .0730119     4.29   0.000     1.142269    1.429069
         mihx |   1.431006   .0862904     5.94   0.000     1.271492    1.610532
         hfhx |   1.438207   .1253764     4.17   0.000     1.212321    1.706182
       strkhx |   2.083655   .1903202     8.04   0.000     1.742117     2.49215
------------------------------------------------------------------------------
```

As for site-reported short-term outcomes, treatment is not a significant factor for long-term site-reported outcomes in a Cox regression limited to it alone but becomes significant when other risk factors are incorporated into the regression. For long-term site-reported outcomes there is the inexplicable interaction between treatment and region. There is also an interaction between stenting and region but not stenting and treatment (not shown). Other factors, such as types of stent, were also not significant, although I do not show them here.

COMMENT: For long term results there is also the suggestion that invasive factors are influential and differ between US and OUS.

Because the Cox regressions above may be hard for some to visualize, I have included Kaplan-Meier failure plots of what I consider to be the most relevant analyses in Figures 24 to 26.

Figure 24: Time to Death from Any Cause for STEMI Patients with PCI≤12h
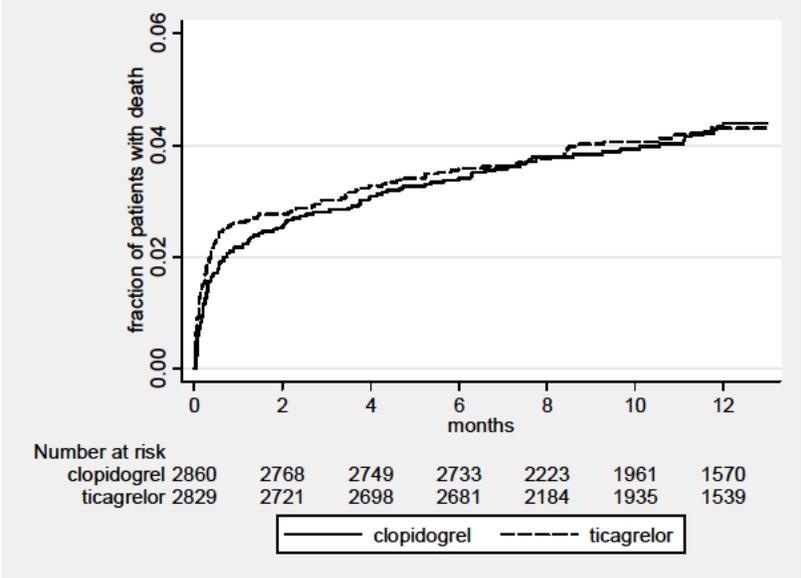
Figure 25: Time to Sponsor's PEP for US STEMI Patients with PCI≤12h
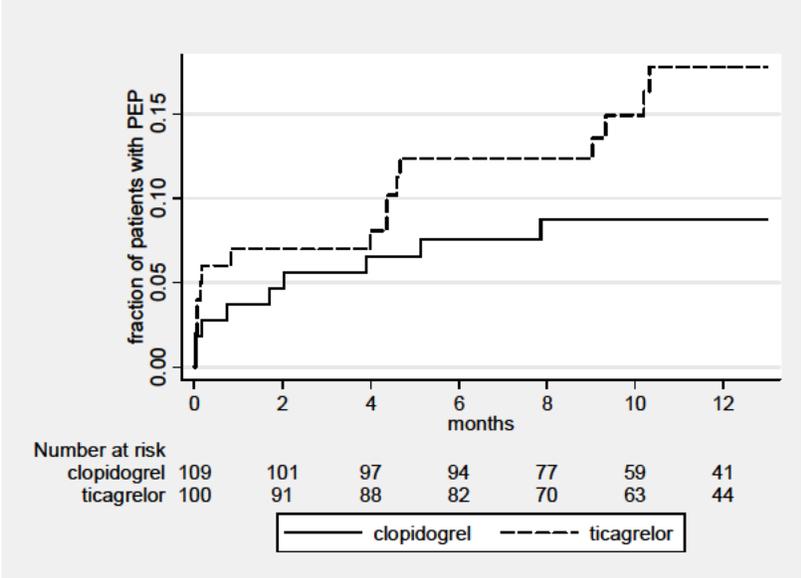
Figure 26: Time to Sponsor's PEP for Other US Patients (no STEMI with PCI≤12h)
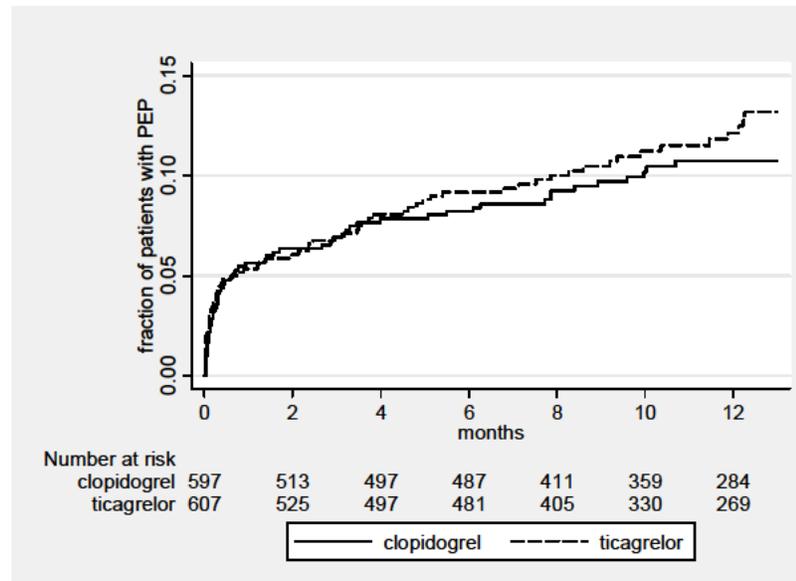
While the failure plots can not portray all of the interactions suggested by the Cox regressions, they do confirm what I consider to be the major points: Figure 24 suggests that there is a problem with increased events, including deaths, with ticagrelor in the subgroup of STEMI patients with PCI≤12h in the entire study population. While the death rates in the entire population appear to equalize later, the event rates for this subgroup in the US do not as shown in Figure 25. (I show the sponsor's PEP rates for the US because the low numbers of patients and low death rates in the US produce death rate estimates that appear to be unstable compared to the PEP rates.) Overall the PEP rates for US patients without STEMI and PCI≤12h are neutral as shown in Figure 26.

COMMENT: The Cox regression results and the failure plots above are my justifications for approval of ticagrelor except in STEMI patients undergoing early invasive management.

7.1.6.12.   Efficacy conclusions

After reviewing all of the data I am left with one overarching impression: PLATO tried to include so many variations that it leaves some important questions only partially answered. I summarize my conclusions regarding efficacy as follows:

- PLATO claims to have won on its primary MACE endpoint. However, this claim is severely challenged by two facts: (1) The completeness of follow-up for CV events is poor for a study of less than one year median follow-up. (2) PLATO does not win by site-reported MACE analyzed alone. However, the point estimate is still favorable, the hazard ratio is significant in Cox

regressions including other risk factors, and the control is an active drug with proved efficacy.

- More impressive than reduced MACE is the alleged all-cause mortality benefit. This benefit too is challenged by problems with incomplete follow-up, although follow-up for vital status in PLATO was better than follow-up for CV events—although still not good. My concerns regarding vital status follow-up were reinforced by the sponsor's misrepresentations of facts at the Advisory Committee meeting—see Section 8. More concerning is the fact that mortality, as well as MACE, went the wrong way in the population of most interest to us, i.e., the US population. Finally, I have concerns that this late mortality benefit is inconsistent with all of our prior experiences with $P2Y_{12}$ inhibitor trials. Ticagrelor fails to show an impressive early benefit and appears to fail in the condition for which rapid, high platelet inhibition is critical (STEMI with early PCI.) Yet it has this late mortality benefit that we did not see with the other consistent $P2Y_{12}$ inhibitor (prasugrel) that produced platelet inhibition clearly superior to clopidogrel.

- I do not agree with the sponsor's conclusion that ASA dosage explains the US-OUS discrepancy. The pattern of ASA dosage effects is different OUS than US. (b) (4)

- While my last analyses do not confirm a major problem, I still have concerns that half of the patients in PLATO were treated differently than the (b) (4), i.e., they received pre-treatment with clopidogrel. My analyses may not have revealed the full impacts of this clopidogrel pre-treatment.

- The data suggest that there may be an interaction between ticagrelor and invasive management. The difficulty in proving this interaction is that PLATO was not designed to address specifically invasive vs. medical management, and the US-OUS discrepancy and lack of relevant details (such as good timing data) make dissecting them extremely difficult. The early (30-day) results are much more consistent between US and OUS than the entire study results. I also have more reason to distrust the later results because of the problems with late follow-up. The early results appear to be consistent that ticagrelor efficacy is lower than clopidogrel for STEMI patients undergoing early PCI.

I believe that we cannot ignore the interactions with invasive management and the apparent reduced efficacy of ticagrelor compared to clopidogrel in STEMI patients undergoing early PCI. I base this latter conclusion on a subgroup analysis, the type we ordinarily do not use for approval decisions. However, I assert that there are two reasons why we should consider it: (1) As I have discussed previously, $P2Y_{12}$ inhibitors show differing benefits in STEMI vs. NSTEMI and with medical

management vs. invasive management. While PLATO's primary design did not address these variations, our analyses of it must. (2) My analyses of STEMI patients undergoing PCI are based on our need expressed in (1) to understand how ticagrelor behaves in the major ACS subgroups and with the two management approaches. They are typical and not arcane and unanticipated like the sponsor's aspirin dosage analyses.

7.2. Safety

7.2.1. General safety considerations

Ticagrelor is a platelet inhibitor such that its primary safety concern is bleeding. It has unique adverse effects of dyspnea and increased rates of ventricular pauses identified in earlier clinical studies. These latter adverse effects may be related to adenosine-like activity.

7.2.2. Safety findings

7.2.2.1. Bleeding

The safety issue common to platelet inhibitors is bleeding. Ticagrelor did produce more bleeding than clopidogrel as shown by the sponsor's statistics in Figure 27.

Figure 27: Sponsor's Hazard Ratio Estimates of Non-procedural Bleeds
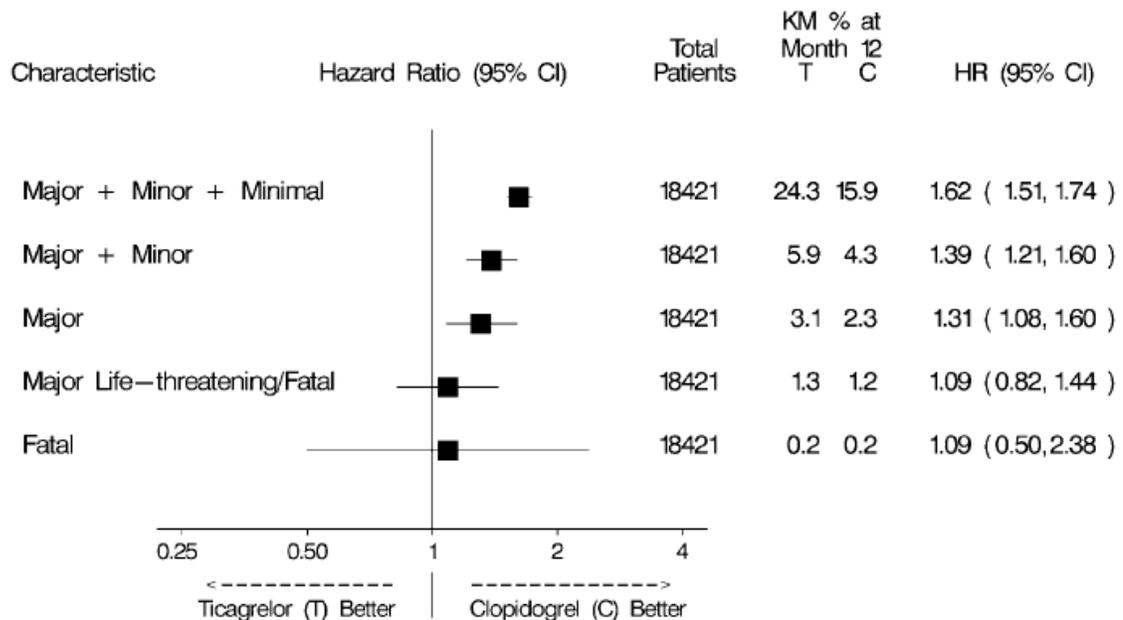
Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 T	C	HR (95% CI)
Major + Minor + Minimal		18421	24.3	15.9	1.62 (1.51, 1.74)
Major + Minor		18421	5.9	4.3	1.39 (1.21, 1.60)
Major		18421	3.1	2.3	1.31 (1.08, 1.60)
Major Life−threatening/Fatal		18421	1.3	1.2	1.09 (0.82, 1.44)
Fatal		18421	0.2	0.2	1.09 (0.50, 2.38)

0.25   0.50   1   2   4

<--------------- --------------->
Ticagrelor (T) Better | Clopidogrel (C) Better

CI Confidence interval; HR Hazard ratio; KM% Kaplan-Meier estimate of % of patients with an event at 12 months.

While major bleeds and less serious bleeds were substantially increased with ticagrelor, life-threatening and fatal bleeds were not significantly increased. The FDA primary clinical safety reviewer, Dr. Melanie Blank, commented that most patients with major bleeds had major CABG-related bleeds (~ 67%) and most CABG bleeds were major (~80%). However, this latter statistic appears inflated by the criterion that transfusing two or more units of blood or packed cells defined a major bleed. The risk of CABG-bleeding was increased in ticagrelor patients who did not wait until day 5 after stopping treatment to have CABG.

COMMENT: Besides confirming that the offset for ticagrelor is substantially longer than the pharmacokinetics predict, these statistics suggest that delaying CABG and other major surgery for five days or more after stopping ticagrelor is the most important management principle for dealing with the increased bleeding risk of ticagrelor.

7.2.2.2. Strokes, intracerebral hemorrhages, and embolism

Strokes were included in the sponsor's primary efficacy endpoint but, because rates of stroke were higher with ticagrelor, they are also safety issues. Site-reported stroke rates were higher, but not significantly higher, with ticagrelor (1.5% vs. 1.2%). One possibility is that higher platelet inhibition could convert a small, subclinical ischemic stroke into a clinically apparent hemorrhagic one. The sponsor reported that with ticagrelor more patients had non-procedural intracranial hemorrhage (ICH, 26 vs. 14) and fatal ICH (11 vs. 2). The FDA primary clinical safety reviewer has raised the possibility of another mechanism: Pulmonary embolism and embolic events in general were slightly more frequent with ticagrelor. She also observes that strokes and pulmonary emboli were very slightly more frequent with prasugrel than clopidogrel in the TRITON trial. She hypothesizes that higher platelet inhibition might lead to clots that are more friable and likely to embolize.

COMMENT: While the stroke rate is slightly higher with ticagrelor, the lower MACE rate (including the strokes) mitigate any concerns that I have about strokes.

7.2.2.3. Dyspnea

Dyspnea events in PLATO were reported more frequently in ticagrelor patients than in clopidogrel patients, about 14% vs. 8% by the sponsor's statistics. Dyspnea leading to discontinuation was uncommon but more frequent with ticagrelor (0.9% vs. 0.1%) as were dyspnea serious adverse events (SAEs, 0.9% vs. 0.6%). About half of the dyspnea AEs resolved within one week while a third were continuing at study termination. PLATO included a pulmonary function substudy that did not reveal any differences between treatment groups, although Dr. Blank questions that it was designed, conducted and analyzed in such ways that might have obscured differences if they existed. The sponsor hypothesizes that dyspnea may be another AE, like ventricular pauses, potentially related to adenosine. The sponsor proposes

that if a patient reports dyspnea, physicians should evaluate the patient for underlying causes of dyspnea. If no cause is identified, patients should continue on ticagrelor treatment unless they cannot tolerate the dyspnea.

COMMENT: I agree that this proposal is reasonable.

7.2.2.4. Ventricular pauses and ventricular arrhythmias

Phase 2 studies suggested ticagrelor increased slightly the rate of sinus pauses. Because of this observation PLATO included a Holter monitoring substudy. The Holter monitoring confirmed that more ticagrelor patients had ventricular pauses ≥3 seconds and ≥5 seconds compared to clopidogrel; this difference was statistically significant for ventricular pauses ≥3 seconds at visit 1 only (relative risk 1.7, 95% confidence limits 1.15 to 2.64).

Reported AEs also do not suggest a clinical problem from ventricular pauses or bradycardia. Sinus pause AEs were uncommon and only slightly more frequent with ticagrelor (20 vs. 17). Bradycardia was similarly slightly more frequent (4.3% vs. 4.0%). Because of the slightly higher rate of stroke with ticagrelor, I recoded all atrial fibrillation events. By my recoding patients with atrial fibrillation events were virtually perfectly balanced between the two arms (both 5.2%). (My rates of atrial fibrillation are higher than those coded by the sponsor because I included reports of "absolute arrhythmia" and "arrhythmia", European terms for atrial fibrillation, as well as the reports of atrial fibrillation.)

I also recoded ventricular tachycardia and ventricular fibrillation events. Both types of serious ventricular arrhythmias appear to be less frequent with ticagrelor, combined about 1.5% of ticagrelor patients and 1.8% of clopidogrel patients. Only about 13% of these arrhythmias were reported in patients who also suffered an MI, so the slightly lower rate of MIs with ticagrelor may not explain the difference.

COMMENT: The lower rate of ventricular arrhythmias may be another adenosine-related effect of ticagrelor and one that could contribute to the long term benefit.

7.2.2.5. Sex hormonal adverse effects

Ticagrelor has signals of sex hormonal activity from its pre-clinical animal studies. The short summary from the FDA pharmacology and toxicology review is the following: There were reported drug-related effects on the reproductive organs of both sexes. In male mice, very high doses caused seminiferous epithelial degeneration of the testes. Female mice had an absence of corpora lutea at very high doses. In rats, endocrine effects were manifested as dose-related decreases in regular estrus cycles at relatively low doses ≥10 mg/kg. The relatively non-specific finding of irregular estrus cycles became more important in light of the carcinogenicity study where female rats showed statistically significant incidences of uterine adenocarcinoma and uterine squamous cell carcinoma.

Because of these findings we scrutinized all adverse effects that could be related to sex hormonal activity, including malignancies of sexual organs. The one signal we found was regarding gynecomastia. For more details see the FDA primary clinical safety review, but the K-M plot of time to first gynecomastia is striking, as shown in Figure 28.

Figure 28: Time to First Gynecomastia in Men

Note that the absolute rate of gynecomastia is low, about 3 per 1,000 men at one year. The sponsor has commented that the use of other drugs associated with gynecomastia, such as spironolactone, confounds some of these cases. However, this is still a randomized comparison and, that ticagrelor may potentiate gynecomastia effects of other drugs, is not reassuring.

On the other hand, in this relatively short study we did not find any evidence for effects upon rates of sex organ malignancies. One testicular cancer was reported in a ticagrelor patient while prostate cancer was evenly balanced (13 vs. 12). Breast cancer events favored ticagrelor (4 vs. 10) while ovarian cancer was relatively balanced (2 vs. 1) and no uterine or cervical cancer events were reported.

COMMENT: Given an observed favorable overall impact of ticagrelor upon CV events and total mortality, a potential increased risk of some sex hormone-related adverse effects is acceptable.

7.2.3. Safety update

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The 120-day safety update did not provide any new safety data.

7.2.4. Immunogenicity

Immunogenicity is not a significant concern for this small molecule.

7.2.5. Special safety concerns

Please see Section 7.2.2 regarding dyspnea, ventricular pauses, and sex hormonal adverse effects.

7.2.6. Primary reviewers' comments and conclusions

The primary clinical safety reviewer, Dr. Melanie Blank, recommends non-approval. However, she bases her recommendation on efficacy concerns, primarily the US-OUS discrepancy, rather than safety concerns. Overall she characterizes the drug as having a "favorable safety profile."

7.2.7. Discussion of notable safety issues

Please see Section 7.2.2.

8. Advisory Committee Meeting

We presented ticagrelor at the July 28, 2010, meeting of the Cardiovascular and Renal Drugs Advisory Committee. The members voted 7 to 1 for approval for both invasive and medical management of ACS.

COMMENT: I believe the advisory committee proceedings were marred by a major problem: misrepresentation of some facts by the sponsor's representatives. I present two of the misrepresentations below followed by my comments.

1. *PLATO randomization was not stratified by invasive intent.* In the sponsor's main presentation on PLATO results, the presenter (one of the two PLATO principal investigators) made the following statement: "As I said, when you first see this group of patients, there are two basic care paths that one can go down. One can go down an invasive treatment strategy or a medical treatment strategy. We were interested in both of those groups of patients, because clinicians were making decisions at the point of contact, when they decide to initiate dual anti-platelet therapy, as to one of those two care paths. We, in fact, stratified randomization to allow us to draw inference between ticagrelor and clopidogrel in each of those subgroups." Because PLATO randomization was not stratified, I prompted Dr. Temple to have the stratification issue clarified. The interchange between Dr. Temple and Dr. Jonathan Fox, the sponsor's representative, was as follows:

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"DR. TEMPLE: Dr. Harrington said that there was stratification by the intent to intervene or not intervene. Tom Marciniak showed me a statement in what appeared to be the protocol that said it was not stratified by that. It may not matter, because there's large numbers in both, but can you make -- which was it?

DR. FOX: The way the trial was run, when patients presented for their urgent medical care for their ACS event, and if they were deemed eligible for the trial, the study site staff contacted the automatic randomization system either over a Web-based link or telephone link. And all they had to do was state that they had a patient that was eligible, willing to provide informed consent. And the only other information they had to provide at that time was the intent to manage invasively or medically, and then they were given a randomization code.

DR. TEMPLE: And stratified by that question.

DR. FOX: That's correct. So those initial data from the automatic randomization system were used."

Because the protocol, statistical analysis plan, and study report do not mention stratification of the randomization, I queried the sponsor in writing after the meeting. The sponsor responded as follows:

"With respect to invasive intent, AstraZeneca provided a response to the committee stating that, to randomize a patient, the IVRS system required information on whether the patient was to be medically or invasively managed as a prerequisite of randomization. However, this is not equivalent to stratification. While there was no intent whatsoever to misguide the committee, AstraZeneca acknowledge it would have been helpful to have been more precise in this regard, to avoid any confusion."

COMMENT: This misrepresentation is very concerning for several reasons:

(1) The principal investigator either did not understand the PLATO design or misrepresented it. In either case, one must distrust all other statements made by this presenter—the sponsor's primary presenter of the study results. See also the second misrepresentation below.

(2) At the meeting we asked the sponsor and the sponsor could have—and should have— responded simply, "No, the randomization was not stratified by invasive intent." Being "more precise" was simple and should have been honest. Hence the sponsor has cast a shadow of doubt on all of its assertions, whether at the AC meeting or elsewhere in its submission.

(3) The misrepresentation seems superfluous. Because invasive intent was a randomization time specification, we would consider it to be advantageous for analyses from that perspective regardless of its use for stratification. I believe the assertion about stratification was made to promote "invasive intent" as the best delineator of usefulness of antiplatelet drugs in invasive vs. medical management. To the contrary, I argue that it is a poor delineator for these reasons: (a) One doesn't need an antiplatelet drug because someone else intends to do angioplasty on you. You

need one if someone <u>does</u> do angioplasty on you. (b) Invasive intent includes intent to do CABG, for which one does not want an antiplatelet drug administered recently.

I believe the better discriminator for value with invasive procedures is the fact of doing an early angioplasty, regardless of whether the decision for it was at randomization time or slightly thereafter. While the sponsor's analyses with invasive intent suggest that ticagrelor benefit was similar regardless of type of management, my analyses above using the fact of angioplasty suggest that ticagrelor may not be as effective with early angioplasty. Whether ticagrelor is useful for early invasive management is a critical question for US practice unanswered by PLATO.

2. *PLATO did not have only five patients with missing vital status at study end.* The sponsor's presenter also made the following assertion: "First, I will point out that on this 18,000-plus clinical trial involving 43 countries, almost 1,000 centers, we have vital status at the end of the trial for all but five patients. This is a tremendous achievement that I think many of you are well aware who do these kinds of trials." This "tremendous achievement" stands at odds with the poor reported follow-up for CV events, with about 17% of living patients not having a final visit on or after their scheduled time or about 8.6% having incomplete CV follow-up by any type of contact.

   That there are some problems with the vital status follow-up is easy to demonstrate: Three patients allegedly withdrew consent after they died. According to the CONTACT file, another 12 patients reported their own deaths by telephone, with the reported causes of death "unknown" for only 3 of them. Another patient survived a "fatal" bleed—but was counted as dead in some sponsor analyses. While such miscues are not uncommon in large trials like PLATO, neither are they supportive of a "tremendous achievement."

   If one considers having vital status "at the end of trial" to be having it on or after the targeted study completion date for a patient—the only definition that I consider valid—then the sponsor reports 54 ticagrelor and 52 clopidogrel patients as not having vital status known at the end of the trial. So by the sponsor's count 106 patients—not 5— are missing follow-up at the end of the study. The 106 patients constitute about 0.6% of those randomized and the distribution is roughly equal between the two groups, so these statistics are also reassuring and not unreasonable for this large, less than one- year median follow-up study. Why did the sponsor's presenter extol the bogus number 5? One possibility is that the sponsor did not want questions about ascertainment to detract from the impressiveness of the overall mortality statistics.

COMMENT: The net effect of the sponsor's misrepresentation at the advisory committee meeting is that I have reduced confidence that the sponsor's data reports and assertions regarding PLATO are accurate. I am most distrustful of the long term results because, with longer time, there are more opportunities for manipulation. This distrust is unfortunate for the sponsor because the alleged long term mortality benefit is the most impressive finding in PLATO. I do note that the misrepresentation regarding vital status follow-up, while seemingly trivial, is directly relevant to the validity of the mortality benefit. The misrepresentation

regarding stratification by invasive management is directly relevant to the question of whether ticagrelor is as effective for invasive management.

Some might argue that the level of misrepresentation by Astra Zeneca is not unusual. While that argument is probably accurate, some of the fault lies with us. I believe we have not been aggressive enough in admonishing sponsors for such indiscretions or publicizing them. We actually have the statutory authority to withdraw approval of an application if "the application contains any untrue statement of a material fact." While in this case I would not exercise that authority, I believe that discounting the "substantial evidence" that PLATO might otherwise provide is appropriate.

9. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

10. Financial Disclosure

The primary clinical review describes the financial disclosures. There are no financial involvements that should adversely affect the overall integrity of the studies.

11. Labeling

11.1.   Proprietary name

The proprietary name Brilinta is acceptable.

11.2.   Physician labeling

I have a number of changes to recommend. We will discuss these changes with the sponsor during label negotiations.

11.3.   Carton and immediate container labeling

The primary reviewers did not note any problems with carton or immediate container labeling.

11.4.   Patient labeling/medication guide

A medication guide is needed and proposed by the sponsor. We will negotiate changes during labeling discussions.

12. DSI Audits

DSI audited six sites in Hungary and Poland. The DSI inspectors did not identify any major problems that would invalidate use of the data to support the application.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

I recommend that ticagrelor be approved for the treatment of ACS except for STEMI patients undergoing early PCI. I also recommend a post-marketing requirement for a US study addressing STEMI patients undergoing early PCI because, if ticagrelor is approved, practitioners will likely use ticagrelor in these patients regardless of labeling. The available data suggest safety concerns in these patients, i.e., increased mortality.

My primary recommendation is a difficult one and not the only action that I would support. I recommended approval primarily based on the short term results that appear consistent between US and OUS—I consider them to be the more reliable results. If one judges that the long term results, i.e., the study as a whole, are the more reliable, than I would have to side with the primary reviewers who recommend disapproval because the US-OUS discrepancy has not been explained adequately and the overall US results for ticagrelor are detrimental. Hence I would also support disapproval of ticagrelor until a confirmatory study is done or approval of ticagrelor for medical management alone. I would not support unrestricted approval of ticagrelor for all ACS patients. I do have concerns about the US-OUS discrepancy and about ticagrelor's effectiveness with early invasive vs. medical management. These concerns must be mitigated by a restricted approval and addressed promptly with an appropriate trial. With an unrestricted approval, regardless of the description of the trial in labeling, I project that the confirmatory trial would never be completed.

13.2. Safety concerns to be followed postmarketing

I do not have any safety concerns that require special postmarketing surveillance. I believe surveillance of postmarketing reports will be useful for determining whether dyspnea, ventricular pauses, and interactions with CYP3A4 inhibitors are more problematic in general use than they were in the clinical trials. I am also recommending a postmarketing study as described in Section 13.4.

13.3. Risk Minimization Plan

 Ticagrelor does not require any special risk minimization plan beyond a medication guide.

13.4. Postmarketing studies

I believe that PLATO left questions unanswered regarding the efficacy of ticagrelor in the US; with invasive procedures, particularly for early PCI in STEMI patients; and for the long term mortality benefit given the mortality trend in the wrong direction in PLATO in the US. Because mortality trends the wrong way in the US, there are safety issues as well as efficacy issues. Hence I believe that we should require the sponsor to conduct an outcomes trial in STEMI patients treated with primary PCI in the US.   We should consider the following requirements for that trial:

- Conduct the trial in the US in STEMI patients undergoing primary PCI
- Exclude patients with recent $P2Y_{12}$ inhibitor use
- Do not restrict statin dosages; consider using a statin not metabolized by CYP3A such as rosuvastatin; capture statin dosages and measure LDL-C
- Use a 1:1 split of clopidogrel and prasugrel as the controls
- Avoid overencapsulated controls and use matching tablets instead
- Administer study drug as soon as possible after randomization
- Randomize to high vs. low aspirin dosage
- Follow and treat all patients until study end

13.5. Comments to be conveyed to the applicant

The proposed labeling changes will be discussed with the sponsor during label negotiations.

References

Berger, P. B. and S. Steinhubl (2002). "Clinical Implications of Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) Study: A US Perspective." <u>Circulation</u> **106**(17): 2284-2287.

Bhatt, D. L., A. M. Lincoff, et al. (2009). "Intravenous Platelet Blockade with Cangrelor during PCI." <u>New England Journal of Medicine</u> **361**(24): 2330-2341.

Group, C. C. (2005). "Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial." <u>The Lancet</u> **366**(9497): 1607-1621.

Harrington, R. A., G. W. Stone, et al. (2009). "Platelet Inhibition with Cangrelor in Patients Undergoing PCI." <u>New England Journal of Medicine</u> **361**(24): 2318-2329.

Investigators, C.-O. (2010). "Dose Comparisons of Clopidogrel and Aspirin in Acute Coronary Syndromes." <u>New England Journal of Medicine</u> **363**(10): 930-942.

Investigators, C. (2001). "Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation." <u>New England Journal of Medicine</u> **345**(7): 494-502.

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/s/

THOMAS A MARCINIAK
09/17/2010

Review Addendum

FDA

Clinical Efficacy Review
Robert Fiorentino, MD, MPH
CDER/ODE1/DCRP
NDA: 022433
Drug: Brilinta, ticagrelor
Date of Review: August 25, 2010

Background

My initial NDA efficacy review, dated June 25, 2010, was submitted to file on that same date. An FDA Advisory Committee was held on July 28, 2010 to discuss this application. The committee voted 7-1 in favor of approval of ticagrelor. Significant discussion surrounded the disparate outcome in the US compared to the overall results. I noted the following points of discussion during the AC related to the PLATO study and ticagrelor (not entirely inclusive):

- Despite some concerns regarding subjects lost to follow-up and the unique method of censoring subjects at the time of their study termination/completion, the committee in general did not express strong concerns that the study was poorly-conducted or that the overall results were invalid. The committee suggested resolution of apparent differences between the sponsor's and FDA's tabulation of subjects without adequate follow-up.
- There was some debate surrounding the appropriateness of dividing the ACS population into NSTEMI, STEMI and UA that were determined at the end of the index hospitalization, as well as the clinical implications related to a claim
- Comments from the committee, in general, suggested that committee members were not entirely convinced of a potential aspirin-treatment interaction
- There was concern, particular held by the one dissenting vote, that baseline and treatment characteristics in the US may [somehow] have contributed to the US outcome
- There were comments raised regarding the appropriateness of including a reduction in stent thrombosis in the indication given the nature in which data for this exploratory endpoint was collected (discussed in my initial efficacy review)
- The committee suggested a few minor additional analyses for clarification that are addressed in this review addendum

My views on these issues are discussed herein.

Results of Analyses Subsequent to Initial Review

A number of analyses were performed by both the FDA and sponsor following the AC meeting. The major analyses that I believe to be most relevant are discussed below.

Outcome according to initial findings on ECG:

Table 1 presents my analysis of the number of subjects according to initial ECG findings and final Index ACS Event as STEMI or not (No=0 or Yes=1).

Table 1. Subjects by Initial ECG finding and Final Index ACS Event=STEMI

Index ACS STEMI	Persistent ST Segment Elevation (>=1 mm)		Total
	0	1	
0	10,647	921	11,568
1	937	6,088	7,025
Total	11,584	7,009	18,593

Index ACS STEMI	Persistent STE or new LBBB		Total
	0	1	
0	10,163	1,405	11,568
1	885	6,140	7,025
Total	11,048	7,545	18,593

STE = ST elevation, LBBB = left bundle branch block
Source: R. Fiorentino, Clinical Reviewer

Table 2 presents the sponsor's tabulation:

Table 2.

Table 1	Patients without STE/LBBB by ECG but with STEMI final diagnosis and patients with STE/LBBB by ECG but not STEMI final diagnosis – PLATO full analysis set	
Category	Ticagrelor 90 mg bd	Clopidogrel 75 mg od
No STE/No LBBB and STEMI	449	438
STE/LBBB and Not STEMI	705	699

AZRO: T12.188 (pnatsa2053ai).
bd Twice daily; ECG Electrocardiogram; LBBB Left bundle branch block; od Once daily; STE ST segment elevation

It is not entirely clear to me how subjects could have persistent ST elevation on the initial ECG yet not have STEMI as the final event, although it is possible that it could be investigator error (data entry) or possibly subsequent comparisons to later ECGs that demonstrated the findings were not new. Regardless, I do not consider this an issue that would invalidate the efficacy results since there is close agreement in outcomes between the initial STE population by ECG and those later classified as having an index event of STEMI.

Table 3 and Figure 1 present outcomes according to initial ECG and shows that the results of my analysis (based on an original dataset) agree with the sponsor's.

Table 3. Primary Outcome by Initial ECG

Initial ECG: Persistent ST Elevation (≥1mm) or new LBBB?	Clopidogrel	Ticagrelor	HR (95%CI)
Yes	10.8% (384/3792)	9.4% (331/3752)	0.87 (0.75, 1.01)
No	12.3% (630/5499)	10.2% (533/5581)	0.83 (0.74, 0.93)

LBBB = left bundle branch block
Source: R. Fiorentino, Clinical Reviewer

Figure 1. Primary Outcome by Initial ECG (SPONSOR)

Figure 1   Forest plot of primary efficacy endpoint for patients with or without new ST elevation/LBBB at randomisation – PLATO full analysis set
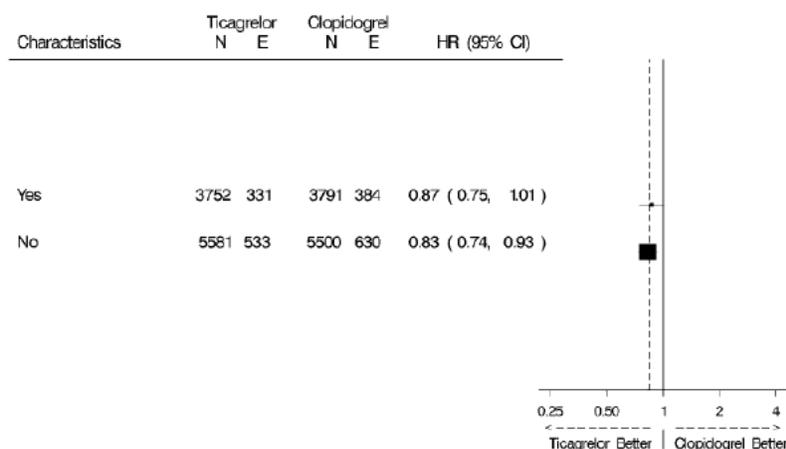
These analyses suggest that the outcomes based on initial ECG closely mirror those in the final ACS definitions [STEMI: HR = 0.84 (0.72, 0.98)].

As discussed later, when dividing up the ACS population into subtypes, it may make more sense to focus on the initial ECG findings (STE vs. non-STE) as apposed to STEMI vs. NSTEMI determined at later timepoints.

Outcomes by initial troponin (+ vs. -) and MI rates in those who had negative initial troponin

In PLATO, baseline troponin was defined as first *central* troponin measurement. Troponin positive was defined as being above the central laboratory upper limit of normal (ULN) or negative troponin I value within 12 hours of the index event.

According to the sponsor's analysis, for patients with a positive baseline troponin, 9.8% (738/7525) ticagrelor patients vs. 11.5% (871/7564) clopidogrel patients had a primary endpoint event. For patients with a negative baseline troponin, 6.5% (99/1525) ticagrelor patients vs. 6.5% (94/1443) clopidogrel patients had a primary endpoint event. The HR (95% CI) for patients

with positive baseline troponin was 0.85 (0.77, 0.94) and for patients with negative baseline troponin was 1.00 (0.75, 1.32).

Ana analysis of time to first MI is presented in Figure 2.

Figure 2.

Figure 2   Forest plot of time to first MI by baseline troponin – PLATO full analysis set

Characteristics	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
Positive	7525	434	7564	517	0.84 (0.74, 0.95)
Negative	1525	60	1443	62	0.92 (0.64, 1.31)

```
       0.25   0.50    1     2    4
       <---------   --------->
       Ticagrelor Better | Clopidogrel Better
```
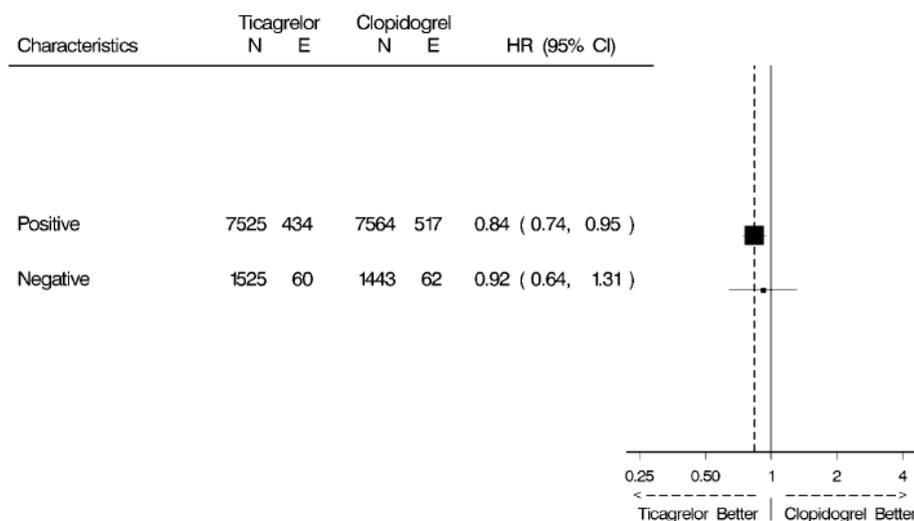
Source: Sponsor

The results of this analysis are limited by the small number of subjects who had negative troponins; however the troponin negative group appears to correlate strongly with the unstable angina population in which no comparative benefit was observed with ticagrelor.

Baseline characteristics of high dose ASA group in US vs. non-US & low dose group US vs. non-US

The sponsor has provided an extensive tabulation of the baseline variables stratified by US/non-US and high/low dose ASA (above or below 300mg).

On review, it appears that the baseline characteristics that were originally identified as varying across the US and non-US regions also have characteristic imbalances when sub-stratified by high or low dose aspirin. In general there is not much additional insight gained from this breakdown.

However, of note is that 73% of subjects in the *high dose* ASA (≥300mg) group in the US had a PCI and 74% had a drug or bare metal stent vs. 59% and 59% (respectively) in the US *low dose* group. This agrees with my earlier analyses and impression that in the US, subjects with more invasive treatments tended to get higher doses of aspirin.

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In comparison, 60% of subjects in the high dose ASA (≥300mg) group in the non-US had a PCI and 75% had a DES/BMS vs. 51% and 62% (respectively) in the non-US low dose group.

Otherwise the differences in baseline factors between high and low aspirin groups across US vs. non-US status are unremarkable. However, substantial differences in event rates between these subgroups are discussed later and suggest to me that non-US subjects who received high dose aspirin are clinically distinct to the similar group in the US.

Sensitivity analyses presented by sponsor at the Advisory Committee with respect to CV follow-up status

Sponsor has provided a summary slide of the requested analysis and is presented in Figure 3. The slide represents a type of sensitivity analysis that estimates the HR that must be observed in 50 and 100 events and the impact on the study outcome. By this analysis, one could have 50 additional MI and strokes in ticagrelor and 0 in clopidogrel and still win. Death outcome is not included in this analysis since vital status follow-up was more definitive. 50 events represent the number of non-fatal MI or strokes that would be expected if the observed event rates were the same in the subjects with inadequate follow-up (a presumption).

Figure 3. Sponsor's Backup Slide for AC Meeting

CV Event Follow-up Sensitivity Analysis

Non-fatal MI + Non-fatal Stroke	HR amongst new events	Ticagrelor events	Clopidogrel events	Overall new HR	P-value
	1.6	31	19	0.863	0.00125
50	10	46	4	0.889	0.010
	>10	50	0	0.897	0.017
	1.19	55	45	0.865	0.00125
100	2.2	70	30	0.890	0.010
	4.9	84	16	0.916	0.05

Corrected Version

NU-16

It remains my view that given the observed outcome in the trial, it *seems unlikely* that the study outcome would be invalidated by potential imbalances in events among "missed" events, although I admit one never can know. The statistical review addendum is pending at the time of this review and may address this issue more definitively.

Analyses of subjects who had clopidogrel use at time of index event (or before) and open label clopidogrel before or on the day of randomization.

Sponsor has performed the described analysis and provided datasets that contain the above indicator variable. The results of the analysis are presented in Table 4. There did not appear to be differences in overall outcome when the data was stratified by use of open label (OL) clopidogrel before randomization.

Table 4. Primary efficacy endpoint events (composite of CV death, MI or stroke) in patients *with or without* open-label clopidogrel use

		Ticagrelor 90 mg bd		Clopidogrel 75 mg od		
		N	Patients with events n (%)	N	Patients with events n (%)	Hazard ratio (95% CI)
Any OLC before the date of randomisation	Yes	3422	330 (9.6%)	3401	370 (10.9%)	0.89 (0.76, 1.03)
	No	5911	534 (9.0%)	5890	644 (10.9%)	0.82 (0.73, 0.92)
Any OLC before or on the date of randomisation	Yes	4441	410 (9.2%)	4410	493 (11.2%)	0.82 (0.72, 0.94)
	No	4892	454 (9.3%)	4881	521 (10.7%)	0.87 (0.76, 0.98)
Any OLC before or on the date of index event	Yes	3748	330 (8.8%)	3701	408 (11.0%)	0.80 (0.69, 0.92)
	No	5585	534 (9.6%)	5590	606 (10.8%)	0.88 (0.78, 0.99)

AZRO: T 6.7.1, 6.7.2, 6.7.10, 6.7.11, 6.7.12, 6.7.13.
bd Twice daily; CI Confidence interval; CV Cardiovascular; HR Hazard ratio; MI Myocardial infarction; od Once daily; OLC Open-label clopidogrel.
Source: Sponsor.

Figure 4 is a sponsor's slide that was presented in the AC meeting. It only presented outcomes in patients *without* prior or open label clopidogrel and demonstrates a benefit for ticagrelor, with the exception of strokes.

Figure 4. Sponsor's AC Backup Slide

PLATO: Efficacy Results in Patients Without Prior or OL Clopidogrel

Characteristic	Ticagrelor 90 mg bid N = 5911		Clopidogrel 75 mg qd N = 5890		Hazard Ratio (95% CI)	p-value
	Patients with Events	KM %	Patients with Events	KM %		
Composite of CV death/MI (excl. silent MI)/stroke	534 (9.0%)	9.4%	644 (10.9%0	11.5%	0.82 (0.73, 0.92)	0.0008
Composite of CV death/MI (excl. silent MI)/stroke – Intent to Invasively Manage*	347 (8.2%)	8.5%	425 (10.1%)	10.6%	0.80 (0.70, 0.93)	0.0026
Composite of all cause mortality/MI (excl. silent MI)/stroke	562 (9.5%)	9.9%	685 (11.6%)	12.2%	0.81 (0.73, 0.91)	0.0003
Composite of CV death/total MI/stroke/Severe recurrent cardiac ischemia/recurrent cardiac ischemia/transient ischemic attack/other arterial thrombotic events	754 (12.8%)	13.3%	870 (14.8%)	15.5%	0.86 (0.78, 0.95)	0.0022
MI (excl. silent MI)	259 (4.4%)	4.7%	314 (5.3%)	5.7%	0.82 (0.69, 0.96)	0.0162
CV death	281 (4.8%)	5.0%	341 (5.8%)	6.1%	0.82 (0.70, 0.96)	0.0146
Stroke	86 (1.5%)	1.6%	74 (1.3%)	1.4%	1.16 (0.85, 1.58)	0.3562
All cause mortality	315 (5.3%)	5.6%	392 (6.7%)	7.1%	0.80 (0.69, 0.93)	0.0033

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EF-147

I performed a number of analyses following the AC meeting to further investigate the association between prior clopidogrel use, early pci within 24hrs, index ACS event and outcomes. The purpose of this analysis was to investigate outcomes in subgroups and across timepoints where the need for adequate antiplatelet therapy is most critical (PCI), including the effect that any prior use of clopidogrel may have had on benefit. Select results of these analyses are presented below.

Figure 5 and Figure 6 illustrate that, for subjects who did not have a PCI within 24hrs of randomization, the use of open label clopidogrel (non-study) on or before randomization did not make a substantial difference in outcome compared with those who did received clopidogrel. Although the benefit in those who received OL clopidogrel was somewhat attenuated.

Figure 5. Subjects <u>WITHOUT</u> PCI < 24hrs and <u>NO</u> Open Label Clopidogrel on or before Randomization Date

KM Primary Event
Subjects without PCI <24hrs and NO O.L. Clopidogrel on or Before Rand. Date

Number at Risk (events)

CLOP	2523	(218)	2244	(48)	2143	(38)	1665	(17)	1071
TICAG	2519	(166)	2277	(48)	2171	(26)	1686	(14)	1048
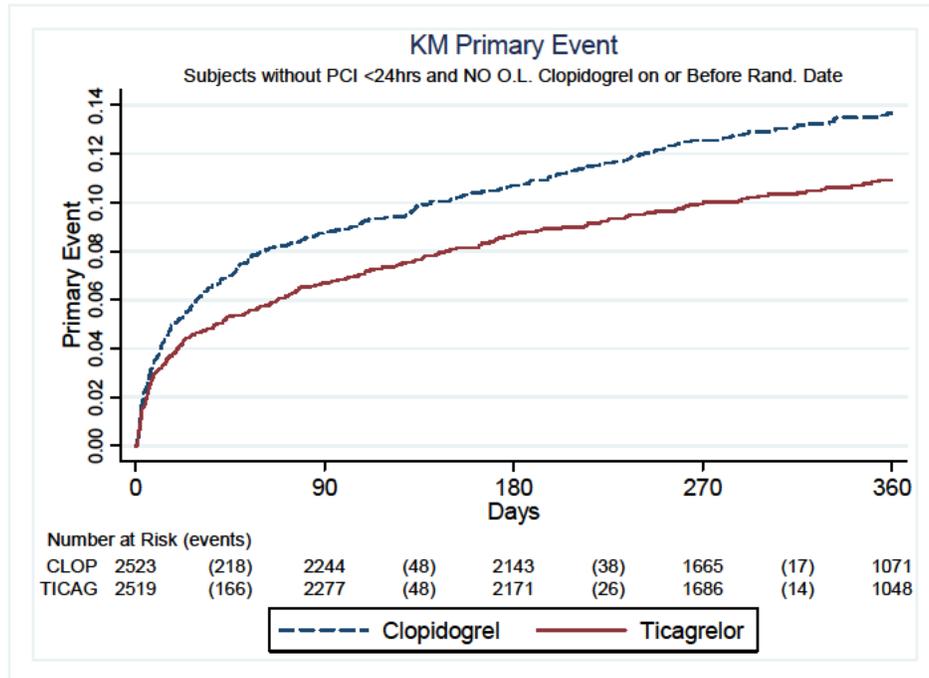
HR=0.80 (0.68, 0.94)

Source: R. Fiorentino, Clinical Reviewer

Figure 6. Subjects <u>WITHOUT</u> PCI<24hrs and *Received* Open Label Clopidogrel on or before Randomization Date

KM Primary Event
Subjects without PCI <24hrs and O.L. Clopidogrel on or Before Rand. Date

Number at Risk (events)								
CLOP	2032	(173)	1803	(49)	1726	(27)	1357	(17)	836
TICAG	2078	(172)	1835	(36)	1765	(17)	1409	(13)	895

Clopidogrel ---- Ticagrelor
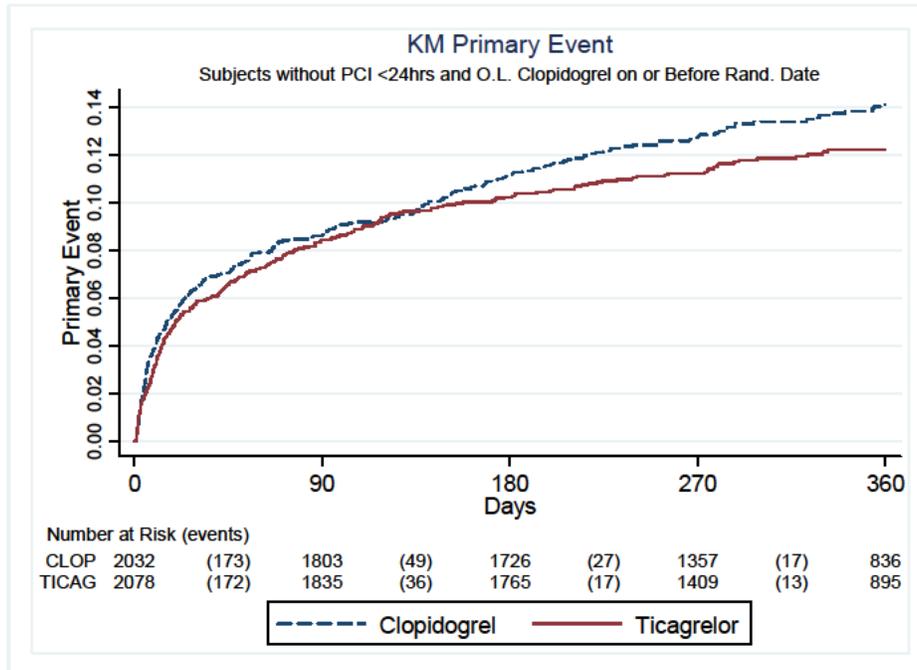
HR = 0.88 (0.74, 1.04)
Source: R. Fiorentino, Clinical Reviewer

Similarly, in subjects <u>who received PCI within 24hrs</u> and also <u>had OL clopidogrel</u> on or before the day of randomization, ticagrelor also had a comparative benefit over on-study clopidogrel. Results were similar by index ACS event type (STEMI vs. NSTEMI) as shown in Figure 7.

Figure 7. Subjects WITH PCI <24hrs and Open Label Clopidogrel on or Before Randomization Date [including stratified by STEMI or NSTEMI]
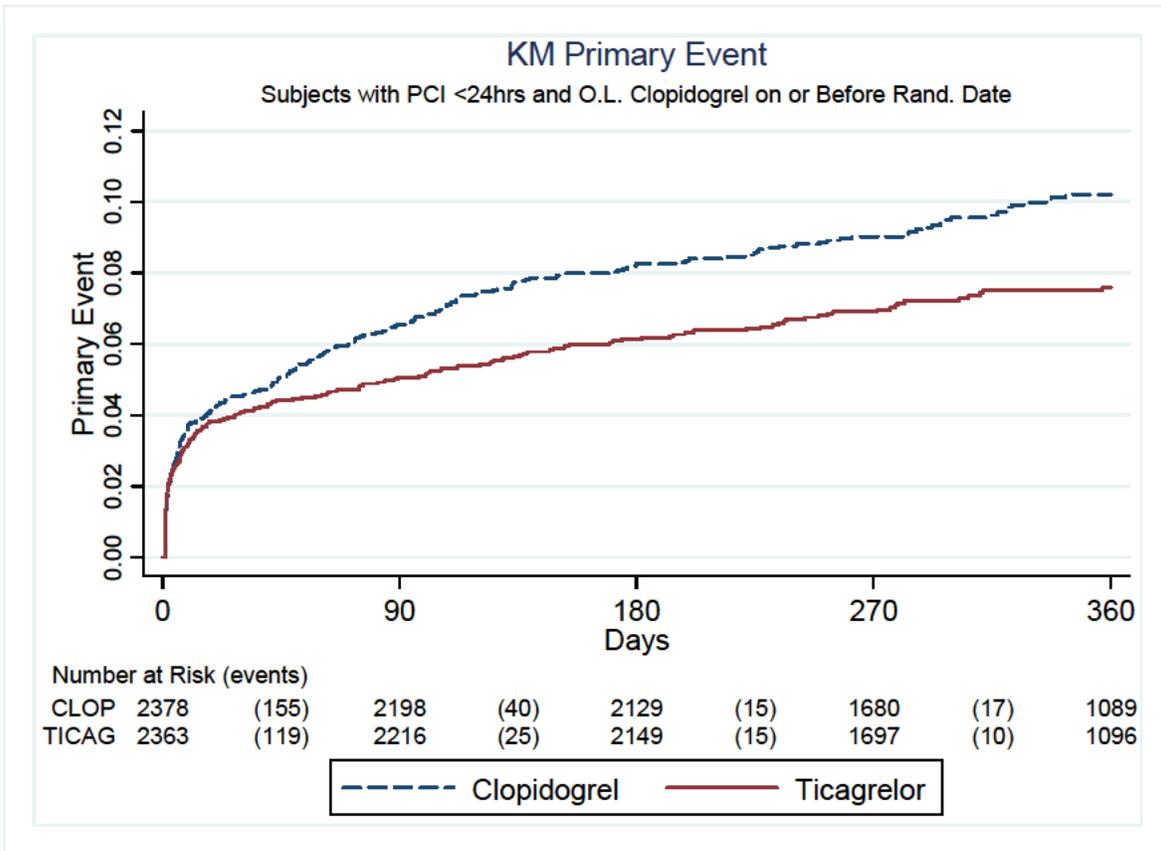
STEMI   **NSTEMI**
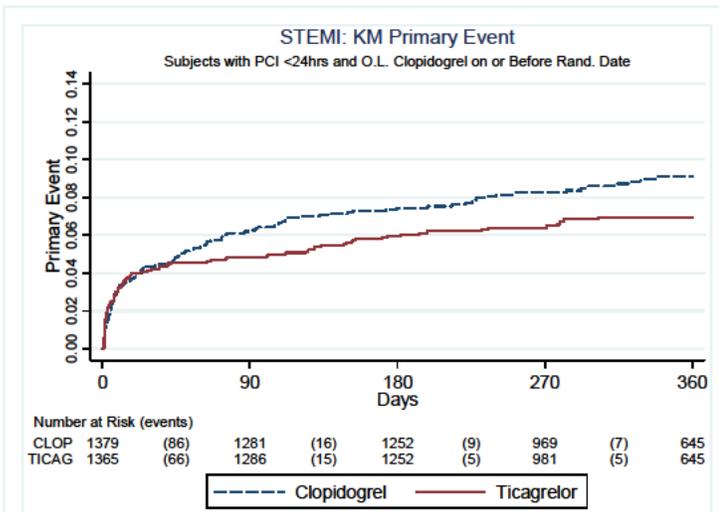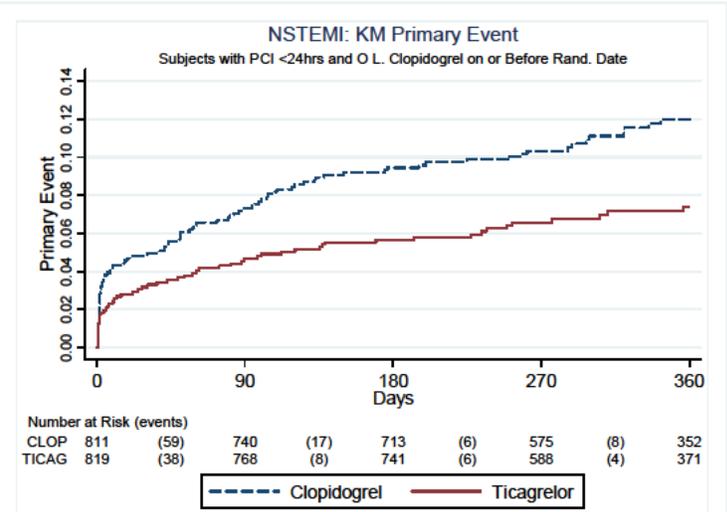
Source: R. Fiorentino, Clinical Reviewer

In contrast to these findings, post-hoc analyses showed that ticagrelor had no apparent benefit over clopidogrel (n=4,731) in subjects with PCI <24hrs and who <u>did not</u> receive open label clopidogrel on or Before Randomization Date. The lack of comparative benefit in subjects with early PCI who did not receive open label clopidogrel was entirely explained by worse outcomes in the STEMI group, as shown in Figure 8.

Figure 8. Subjects WITH PCI <24hrs and <u>NO</u> Open Label Clopidogrel on of Before Randomization Date [including stratified by STEMI or NSTEMI]

KM Primary Event
Subjects with PCI <24hrs and NO O.L. Clopidogrel on or Before Rand. Date

Number at Risk (events)

CLOP	2358	(137)	2192	(28)	2126	(19)	1677	(14)	1078
TICAG	2373	(133)	2215	(30)	2134	(17)	1688	(15)	1108

HR = 0.98 (0.80, 1.19)

STEMI

STEMI: KM Primary Event
Subjects with PCI <24hrs and NO O.L. Clopidogrel on or Before Rand. Date

Number at Risk (events)

CLOP	1510	(75)	1421	(18)	1376	(12)	1075	(8)	685
TICAG	1529	(88)	1428	(16)	1373	(10)	1059	(8)	703

HR = 1.07 (0.83, 1.38)

NSTEMI

NSTEMI: KM Primary Event
Subjects with PCI <24hrs and NO O.L. Clopidogrel on or Before Rand. Date

Number at Risk (events)

CLOP	657	(49)	598	(6)	585	(6)	473	(5)	318
TICAG	662	(35)	618	(12)	595	(4)	483	(6)	308

HR = 0.86 (0.60, 1.22)

Source: R. Fiorentino, Clinical Reviewer

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Finally, as presented in Figure 9, these outcomes are very similar if the findings on initial ECG were used (new and persistent STE/LBBB or not) instead of STEMI and NSTEMI. This approach may make more sense in the context of an ACS population when only early data can be used to make clinical care decisions.

Figure 9
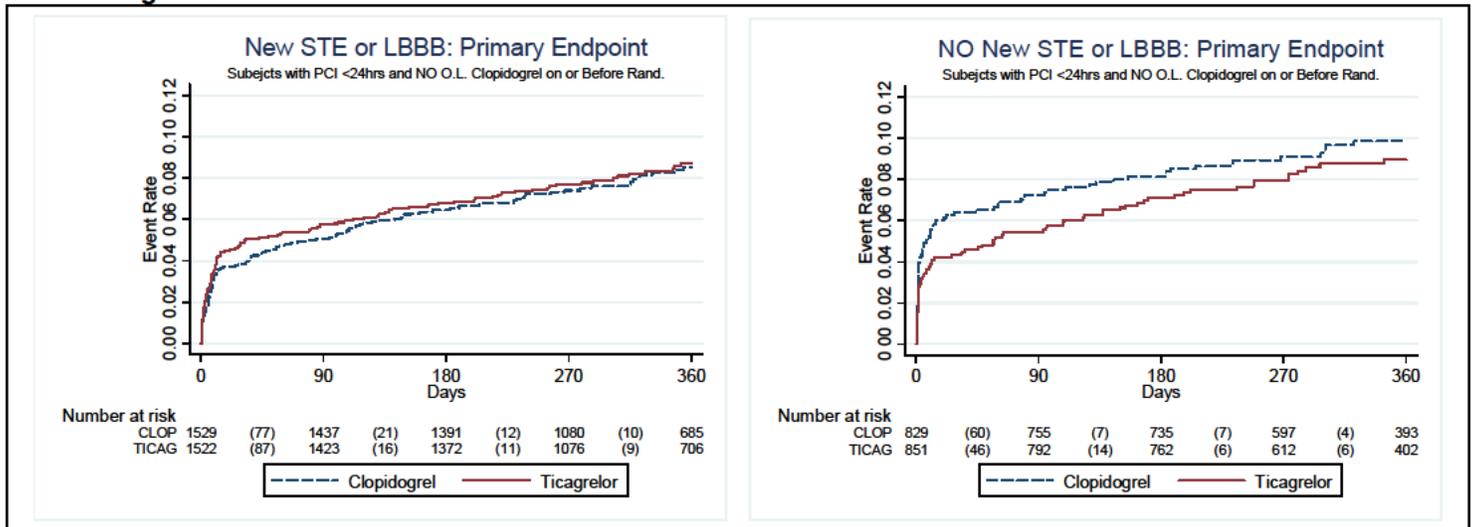
An explanation for the outcomes in these subgroups is not entirely clear. One could speculate that ticagrelor has a delayed effect/benefit or even early harm that is somehow masked when clopidogrel is onboard, but I do not believe there is any definitive PK/PD evidence to support this. These may simply represent indeterminate *post hoc* findings. I am not sure how this information could be used to help guide therapy in an urgent ACS population or how it should be presented in a label, if at all.

Outcomes by ASA dose at baseline and prior to randomization

ASA dosing records prior to randomization were not consistently captured. Therefore the sponsor could not provide the data to reliably assess outcomes by prior ASA use. However, ASA dosing on the day of randomization was collected; Figure 10 shows the forest plot of primary efficacy endpoint by ASA dose at baseline (on the day of randomization).

Figure 10.

Forest plot of primary efficacy endpoint by ASA dose on the day of randomisation – PLATO full analysis set

Characteristics	Ticagrelor N	E	Clopidogrel N	E	HR (95% CI)
Low:< 300mg	5529	514	5389	618	0.80 (0.72, 0.90)
High:> = 300mg	3138	270	3065	281	0.94 (0.79, 1.11)
Unknown	666	80	837	115	0.88 (0.66, 1.17)
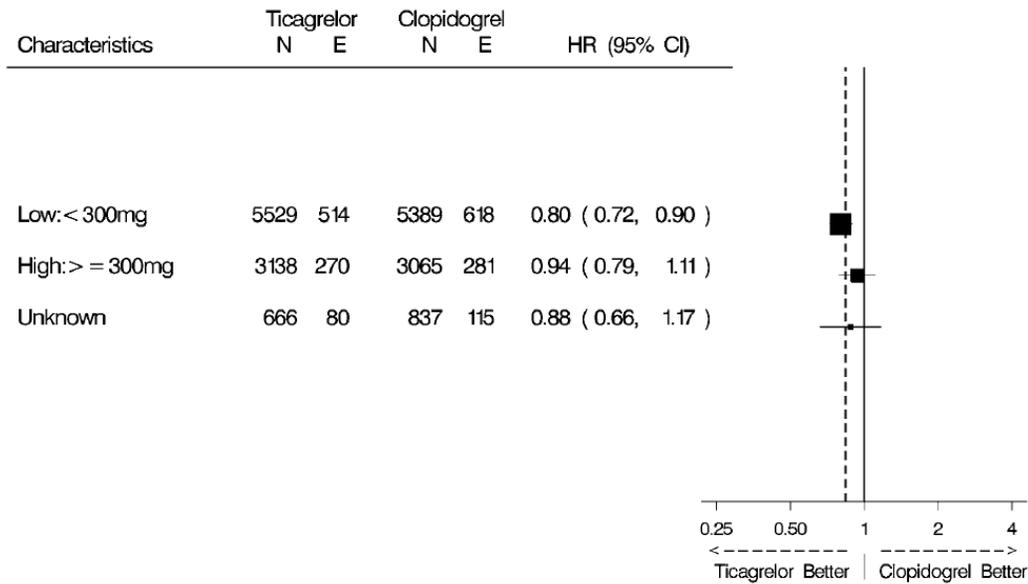
AZRO: F12.221 (pnatsa3200).
CI Confidence interval; HR Hazard Ratio.
Source: Sponsor

There have been additional analyses performed by the statistical review (Jialu Zhang) to further evaluate subjects who received only loading doses; however these analyses appear confounded by high event rates at very early timepoints in subjects who may not have continued the study thereafter. For instance, the median time to event for those subjects with a primary endpoint in the "ASA loading only" group is 1.28 days; subjects in the "ASA loading only" group who had a primary event tended to have it quickly. For those who did not have events, the median censoring time is 302 days. At this time, I am not confident that subdividing subjects into very early aspirin dose subgroups provides any further insight into the potential ASA-ticagrelor treatment interaction.

Other Review Issues Related to Efficacy

Comparison of Events by US vs. non-US and high/low dose ASA Use

Table 5 presents the cumulative event rates using the aspirin dosage cutoffs used by the sponsor (300mg) and stratified by US vs. non-US.

This comparison is relevant in that the sponsor has presented data that suggests it is more the ASA dose strata that predicts outcome as apposed to US vs. non-US status. That is, the sponsor has presented hazard ratios that are similar in the US and non-US when stratified by ASA dose group. The sponsor's AC slide on this matter is presented in Figure 11.

Figure 11. Sponsor's Slide
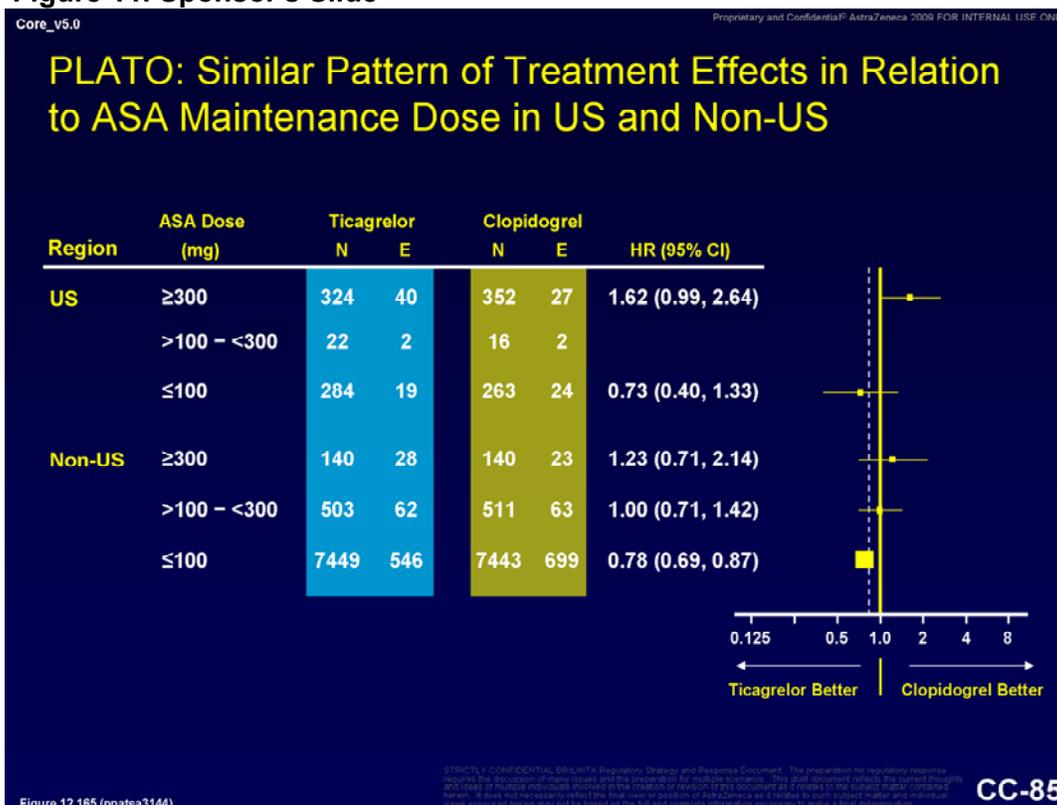
However, when one looks at the actual cumulative events between these groups, one can see clearly that the high-dose (≥300mg) aspirin group outside the US has much higher cumulative event rates compared to the high dose US groups (see Table 5). This suggests to me that subjects who received higher doses of aspirin outside the US were more heterogeneous than the other groups. This, combined with the very small number of subjects in this subgroup, raises concerns regarding the validity of conclusions that can be drawn by comparing outcomes (HRs) across these strata in a way that might supports an aspirin-ticagrelor interaction hypothesis. Also, we should recall that the initial analysis of the data showed no numerical benefit in the US in the <100mg group. Subsequently, the sponsor made revisions and corrections to the ASA dataset after unblinding, including additional events in the smaller subgroups, which then revealed the results seen above in Figure 11. I advise that this comparison not be presented in the draft label.

Table 5. Cumulative Event Rates by Median ASA Dose Group and Region

	ASA ≤ 100mg		ASA ≥ 300mg	
	US	Non-US	US	Non-US
Primary Endpoint	C: 9.1% (24/263) T: 6.7% (19/284)	C: 9.4% (699/7443) T: 7.3% (546/7449)	C: 7.7% (27/352) T: 12% (40/324)	**C: 16% (23/140)** **T: 20% (28/140)**
CV Death	C: 2.7% (7/263) T: 2.1% (6/284)	C: 4.1% (302/7443) T: 2.8% (209/7449)	C: 1.7% (6/352) T: 3.7% (12/324)	**C: 7.1% (10/140)** **T: 7.9% (11/140)**
MI	C: 6.8% (18/263) T: 4.6% (13/284)	C: 5.5% (413/7443) T: 4.5% (335/7449)	C: 5.7% (20/352) T: 9.6% (31/324)	**C: 10% (14/140)** **T: 14% (19/140)**
Stroke	C: 0.0% (0/263) T: 0.7% (2/284)	C: 1.1% (81/7443) T: 1.2% (91/7449)	C: 0.9% (3/352) T: 1.2% (4/324)	**C: 2.9% (4/140)** **T: 0.7% (1/140)**

ASA dose = median55 derived definition.
Source: R. Fiorentino, Clinical Reviewer

Timing of Benefit

Since the time of my initial clinical efficacy review, I've performed additional analyses to more clearly elucidate the timing of benefit seen in PLATO. The observed accrual of benefit in the overall PLATO population has been previously discussed, however the timing of early benefits in specific populations was further investigated.

Figure 12 and Figure 13 present the KM curve for the primary study endpoint in NSTEMI and STEMI subjects, respectively. For subjects with STEMI, there was no comparative benefit for ticagrelor over clopidogrel observed in the first 30 days; in fact, the overall benefit in the 1st 30 days was driven entirely by the NSTEMI population (the UA population showed no difference).

Figure 12. NSTEMI
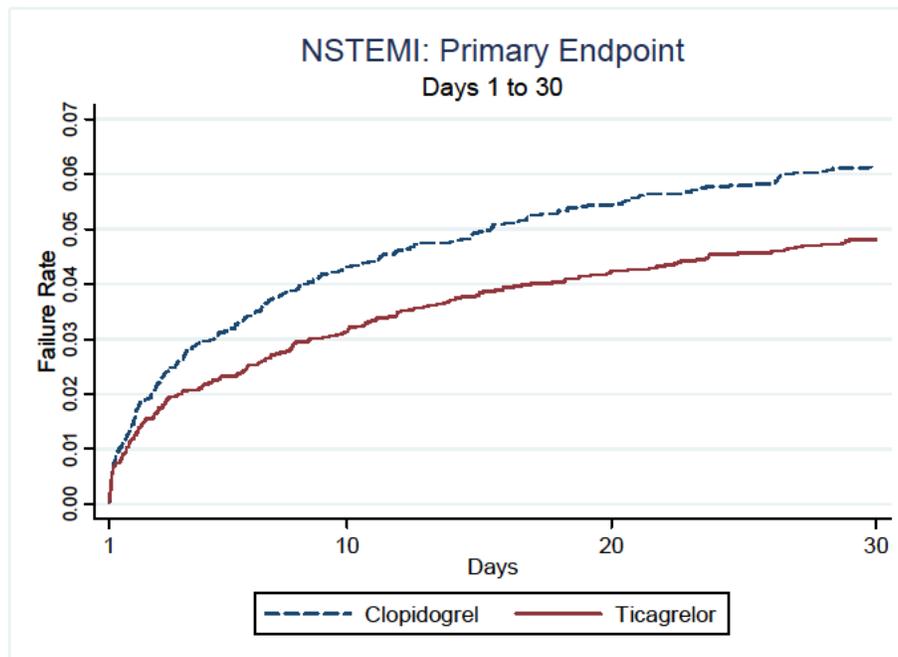
HR = 0.78 (0.65, 0.95)

Figure 13. STEMI

STEMI: Primary Endpoint
Days 1 to 30
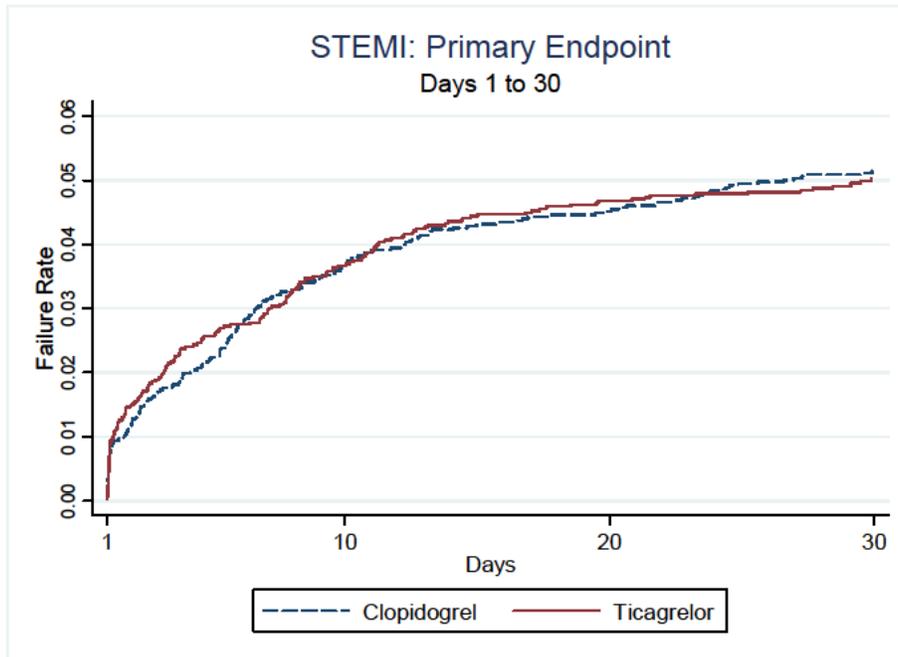
HR = 0.98 (0.79, 1.20)

The results of additional 30 day "landmark" analyses are provided below:

Primary Endpoint: Day 0-30		
	HR	**95% CI**
UA	1.12	(0.76, 1.64)
NSTEMI	0.78	(0.65, 0.95)
STEMI	0.98	(0.79, 1.20)
Invasive	0.89	(0.77, 1.04)
Medical	0.84	(0.66, 1.07)
Primary Endpoint: Day 30-365		
	HR	**95% CI**
UA	0.86	(0.62, 1.19)
NSTEMI	0.87	(0.73, 1.03)
STEMI	0.68	(0.53, 0.87)
Invasive	0.78	(0.66, 0.93)
Medical	0.86	(0.71, 1.05)

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Further analysis in the STEMI plus early PCI group (within 24 hrs of rand.) showed a slight trend towards worse outcomes early in the ticagrelor arm, a crossover in the curves at approximately 60 days and a (non-significant) difference in this subgroup at 360 days (see Figure 14).

Figure 14. STEMI + PCI within 24 hrs of Randomization

Primary Endpoint
Subejcts with STEMI + PCI within 24hrs of Randomization

Number at risk

CLOP	2889	(161)	2702	(34)	2628	(21)	2044	(15)	1330
TICAG	2894	(154)	2714	(31)	2625	(15)	2040	(13)	1348

Clopidogrel ----- Ticagrelor
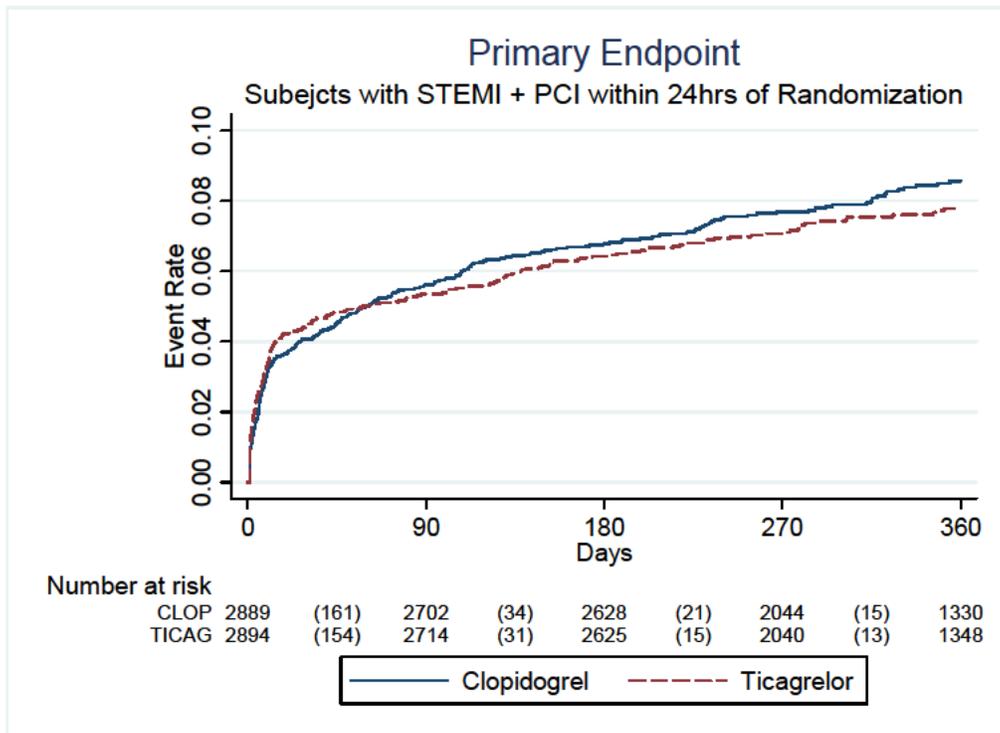
HR = 0.92 (0.76, 1.11)

The interpretation of these analyses, including the clopidogrel subgroups discussed previously, could suggest that there may be an attenuation of the relative benefit for ticagrelor or potentially worse outcomes in subjects with STEMI who have early PCI and/or did not have thienopyridine (clopidogrel) therapy on-board early in the course of randomization.

The results of these *post hoc* subgroup analyses are interesting, but the robustness of the findings remain uncertain, in part because pharmacodynamic data does not demonstrate that ticagrelor has a delay in onset compared to clopidogrel, or conversely, has any harmful (agonist) or early pro-thrombotic effects.

The implications of these findings are also unclear in an ACS population in which one would want to maximize antiplatelet therapy as soon as possible. In practice, it may be harmful to require that an ECG clearly demonstrate persistent ST elevation (≥1mm) or not prior to making the determination to administer ticagrelor. Regardless, at a minimum these analyses would seem to provide some lingering uncertainties regarding how to use ticagrelor across ACS subtypes or invasive management strategies, including what role, if anything, that prior clopidogrel use has on outcome. This is discussed further in my recommendations.

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Revised Follow-Up and Vital Status Data

The sponsor has provided revised vital status data, as presented in part in Table 6.

Table 6. Vital status ascertainment versus target[a]

	Ticagrelor	Clopidogrel
Total	9333	9291
All deaths	444	542
Total not known to have died	8889	8749
---Last date of contact ≥ target	8838 (99.4%)	8699 (99.4%)
---Last Date of contact < target	54 (0.6%)	52 (0.6%)

[a]   Target = Vital status ascertained via contact on or after the final scheduled visit (with a window of -10 days).

I note 106 subjects who were known alive at a last contact date that was less than the planned target date (based on study close-out). These rates were balanced between the two arms (0.6%). According to the sponsor, the median time from last contact to target contact date was 24 days in ticagrelor arm and 23.5 in the clopidogrel arm.

In addition, the sponsor has provided clarification of deaths in PLATO. The key results and tabulations from these interactions are presented below in Table 7,
Table 8 & Table 9.

Table 7. All deaths reported in PLATO by status of adjudication, relation to intended treatment period, and whether found during follow-up contact (FULL)

	Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291
All deaths	**444 (4.8%)**	**542 (5.8%)**
All adjudicated deaths	418 (4.5%)	520 (5.6%)
In intended treatment period	400 (4.3%)	506 (5.4%)
After withdrawal of consent	1 (0.0%)	0
Not after withdrawal of consent (counted toward formal 'all-cause mortality' endpoint)	**399 (4.3%)[a]**	**506 (5.4%)[a]**
After intended treatment period	18 (0.2%)	14 (0.2%)
Adjudicated deaths not found by follow-up	390 (4.2%)	478 (5.1%)
Adjudicated deaths found by follow-up	28 (0.3%)	42 (0.5%)
Non-adjudicated deaths	26 (0.3%)	22 (0.2%)
In intended treatment period	25 (0.3%)	19 (0.2%)
After withdrawal of consent	25 (0.3%)	19 (0.2%)
Not after withdrawal of consent	0	0
After intended treatment period	0	1 (0.0%)
Unknown date of death	1 (0.0%)	2 (0.0%)
All deaths in intended treatment period (all known deaths)	**425 (4.6%)**	**525 (5.7%)**
All deaths in intended treatment period or with unknown dates (all known deaths incl those with unknown death date)	**426 (4.6%)**	**527 (5.7%)**
All deaths after intended treatment period	18 (0.2%)	15 (0.2%)

/csre/dev/azd6140/d5130reg201001/sp/prog/tlf/efficacy/eff2212a.lst eff2212.sas 06AUG2010:07:56 kpjq838
(Table 6.2.51)

[a]   Deaths that were included in the analysis of the formal all-cause mortality endpoint, reported in the CSR, Table 28 (v): all adjudicated deaths occurring in the intended treatment period and not after withdrawal of consent.

In my view, this table provides a fairly complete accounting of the deaths in PLATO, including characterization of the various categories of death as defined in the study.

Table 8 and Table 9 provide a tabulation of the various clinical event assessments according to adequacy of CV follow-up. Full CV event follow-up is defined as either the patient died, had an primary event, or last "Clinical Events Form" date was no more than 10 days before target date.

As noted previously, the US population had worse CV follow-up; 99 subjects in the ticagrelor arm and 98 in the clopidogrel arm (~14% incomplete CV follow-up). This contrasts with the better CV follow-up seen in the non-US population (~8% incomplete CV follow-up).

Table 8. US CV Follow-Up

```
                        Ticagrelor Regulatory Response

            Table 6.7.25   Clinical events accessment vs target date US
                                      FULL
_____

                                              Randomized Treatment
                                       _____
                                          Ticagrelor           Clopidogrel
                                           90 mg bd              75 mg od
      Description                          N = 707               N = 706
      _____

      Total Randomized                  707 ( 100%)          706 ( 100%)

          Died                           32 ( 4.5%)           26 ( 3.7%)

      No Death Record                   675 (95.5%)          680 (96.3%)
          Had Primary Composite Event    62 ( 8.8%)           49 ( 6.9%)
          Did Not Have Primary Composite Event  613 (86.7%)  631 (89.4%)
              Full CV event follow-up*   514 (72.7%)          533 (75.5%)
              Incomplete/Early CV event follow-up  99 (14.0%)  98 (13.9%)

      Full CV event follow-up*          608 (86.0%)          608 (86.1%)

      Incomplete/Early CV event follow-up  99 (14.0%)         98 (13.9%)
```

Source: Sponsor

Table 9. Non-US CV Follow-Up

```
                        Ticagrelor Regulatory Response

            Table 6.7.26   Clinical events accessment vs target date Non-US
                                      FULL
_____

                                              Randomized Treatment
                                       _____
                                          Ticagrelor           Clopidogrel
                                           90 mg bd              75 mg od
      Description                          N = 8626              N = 8585
      _____

      Total Randomized                 8626 ( 100%)         8585 ( 100%)

          Died                          412 ( 4.8%)          516 ( 6.0%)

      No Death Record                  8214 (95.2%)         8069 (94.0%)
          Had Primary Composite Event   464 ( 5.4%)          517 ( 6.0%)
          Did Not Have Primary Composite Event  7750 (89.8%)  7552 (88.0%)
              Full CV event follow-up*  7000 (81.2%)         6838 (79.7%)
              Incomplete/Early CV event follow-up  750 ( 8.7%)  714 ( 8.3%)

      Full CV event follow-up*         7876 (91.3%)         7871 (91.7%)

      Incomplete/Early CV event follow-up  750 ( 8.7%)        714 ( 8.3%)
```

Source: Sponsor

Although it is concerning that the incomplete follow-up is overall as large as it is, I am not convinced that this invalidates the *overall* study outcome, particularly given the sensitivity analyses discussed previously. However, it is conceivable that the higher rate of incomplete follow-up in the US (perhaps coupled with the poorer treatment compliance and other baseline/treatment factors noted previously) may have contributed to the disparate outcomes observed in the US. However, an argument against the US results being an artifact due to worse study compliance and/or poorer follow-up is that these observations are generally balanced between the two treatment arms.

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Discussion

In general, the PLATO trial appears to have been well-conducted and I accept the outcome to be valid for the overall study population. The issue of the significance of the lack of complete follow-up has been discussed in my initial review and previous comments herein.

Other than the concerns discussed in this document, the primary issue for me after studying the results of the PLATO trial is whether or not the best estimate of the true treatment effect for the US should be the overall effect observed in the trial. This is important because the *overall* results of PLATO are encouraging and appear to support a benefit for ticagrelor over clopidogrel in ACS, including a mortality benefit. As noted previously, the magnitude of benefit at earlier timepoints or in specific post-hoc subgroups may be a matter of debate.

There have been a number of discussions regarding the contribution that chance could have played in accounting for the US outcome and, by extension, to the related aspirin interaction. Obviously the possibility of chance cannot be ruled out, but there are a number of observations that suggest to me that factors other than chance contributed to the US outcome. This is relevant in that, for me, believing that the results in the US are due to chance in some ways means accepting that the overall outcome of PLATO is the best estimate of how ticagrelor would perform in the US. Conversely, if chance is rejected, then one must admit there is something about the US subgroup (known or not) which could have contributed to the observed outcome. It's my view that there are a number of reasons why one might not expect ticagrelor to perform in the US as it has in the non-US population.

First, it should be noted that the US was the second largest country enrolled (n=1,413 randomized) into PLATO, however it represented less than 8% of the analysis population. Although not a statistically robust point of discussion, it is notable that the 95% confidence intervals around the US and non-US subgroups do not overlap. How likely is it that the second biggest country by enrollment in PLATO would also have the most divergent outcome and that this would be *entirely* explained by chance? According to the statistical review, if the overall study population's hazard ratio of 0.84 represents the true HR in the US, the probability of observing an HR ≥ 1.27 (as observed in the US) is less than 1%. Even if the true HR = 1.0 in the US (i.e., no difference between ticagrelor and clopidogrel), the probability of observing an HR ≥ 1.27 in the US is only 7%.

It should be noted that he 95%CI of the US outcome HR=1.27 (0.92, 1.75) does include 1.0, suggesting that although there may be no comparative benefit with ticagrelor over clopidogrel observed in the US, one still cannot definitively conclude that it is comparatively worse overall.

Secondly, outcomes in the US appeared consistent across multiple subgroups as shown in the slides produced by the statistical reviewer (with some interpretability limitations due to sample size; see Appendix). In fact, they appear to be fairly consistently the "mirror image" of the non-US forest plot. Univariate and multivariate evaluation across these subgroups (ignoring the aspirin interaction hypothesis for now) has offered little to no explanation for the divergent US outcome. It seems to me that had less consistent results been observed across subgroups in the US or had a single subgroup accounted for the US discrepancy, then attribution to a chance event would have seemed more defensible.

Thirdly, as discussed, the US population itself appeared to differ somewhat on baseline and treatment characteristics compared to the overall non-US population. This has been discussed previously in my initial review, in this addendum and also in my AC presentation (see the

Appendix for my AC slides). In brief, the US population was heavier, had more diabetes, more significant cardiac disease and interventions, fewer STEMIs, differences in invasive strategies and lower treatment compliance. It seems somewhat doubtful to me that these differences would be explained by chance alone; they could represent a combination of sampling from a broader US population with inherently different characteristics at baseline and/or some type of selection bias on the part of US investigators. For the latter, this may be an explanation for why relatively more NSTEMI patients were enrolled in the US (67% US vs. 41% non-US), such that investigators were more selective of who they enrolled compared their non-US counterparts. Other than investigator selection, I can't offer an explanation for why the US population should have had different rates of NSTEMI or STEMI than the non-US population. In addition, the worse compliance to therapy and greater inadequate follow-up seen in the US also suggests that the conduct of the US study may have played a part in the outcomes, albeit to an unknown extent. If it's true that the US had a more selected study population, then this raises additional questions about what the true benefit of ticagrelor will be in the "real-world" ACS populations in the US (i.e., closer to the overall estimate or even worse?). Further, the fact that none of the population differences between the US and non-US has been shown to be acting as a significant effect modifier has not reassured me, given that if we had had more statistical power for our methodologies, we may have found one.

Clearly no one would accept that the differences in aspirin dose between the US and non-US are explained by chance, so by what degree could any of the other observed differences, whether baseline characteristics, treatment strategies, or study conduct be attributable to chance? We simply don't know if these differences in the US vs. non-US populations are "real" (based in actual practice patterns) and contributing to the divergent outcomes. It is possible that any of these factors are confounding the relationship between treatment and outcome and potentially acting as effect modifiers in manner we can't understand.

Additionally, the results for each of the *component* endpoints of the primary composite, with the exception of stroke, are all consistently and qualitatively different between the US and non-US groups. For stroke, the difference is primarily quantitative, but regardless, the comparative benefit in the US was worse *across all endpoints* (including death). If the results had been more inconsistent with that seen outside the US (i.e., MI went one way and CV-death another), this would have been more likely explained by chance; but they did not.

The discussion is further complicated by the apparent aspirin-ticagrelor interaction. My views on the potential aspirin-ticagrelor interaction hypothesis remain unchanged from my initial NDA review document (June 25, 2010) in that I remain unconvinced that concomitant aspirin dosing in itself, explains the disparate US outcomes. In addition, although it is interesting that the US and non-US outcomes appear more similar when compared within the same aspirin dose strata, I can't accept these comparisons as valid (as addressed previously). Regardless of whether or not the aspirin interaction is true, this suggests that there may be other patient or treatment factors that contributed to the observed aspirin interaction and US outcome in a manner we do not yet understand.

For the sake of discussion, there was a somewhat similar outcome observed in an unrelated CV trial that has been mentioned over the course of this review. MERIT-HF was a large-scale randomized placebo-controlled survival trial designed to investigate whether metoprolol succinate controlled/extended release (CR/XL) once daily added to optimum standard therapy lowers total mortality (first primary outcome) and the combined outcome of total mortality plus all-cause hospitalization (second primary outcome) in patients with chronic heart failure. Overall, MERIT-HF demonstrated a hazard ratio of 0.66 for total mortality and 0.81 for mortality plus all-

cause hospitalization. The hazard ratio of the first secondary end point of mortality plus *hospitalization for heart failure* was 0.69. However, the post-hoc US subgroup showed a mortality hazard of 1.05 (Am Heart J 2001;142:502-11). In the end it was concluded by the study investigators that the US results were likely due to chance.

For purpose of comparison, this study contrasts with the results of PLATO in a number of ways that are illustrative of why I feel it's more difficult to attribute the US findings in PLATO to chance alone:

1. In the US, MERIT-HF failed on the first primary endpoint of mortality, but it also won on the other two endpoints that included hospitalization. This inconsistency was proposed as supporting the possibility of a chance occurrence. In contrast, in PLATO there were consistency worse outcomes in the US across the major composite endpoint and all component endpoints (CV death, MI and stroke).
2. Within the MERIT-HF US subgroup, there was consistency across all predefined risk subgroups in all 3 outcomes, except for the NYHA class II patients (which did worse). The investigators could not find any imbalance in baseline risk factors or background therapy that could account for this discrepancy (per the authors, this was "not consistent with causality by biologic gradient"). In contrast, no subgroup in PLATO (other than aspirin dose) explains or largely accounts for the worse outcome observed in the US.
3. Finally, there were plenty of consistent external data available that demonstrated B-blockers to be effective in reducing mortality and mortality due to all-cause hospitalization. In PLATO's case, the only practical alternative antiplatelets are clopidogrel and prasugrel, but these have different properties than ticagrelor and were not studied in the same ACS population as in PLATO.

In summary, it seems easier to attribute the US results of MERIT-HF to chance than it is for PLATO, for some of the reasons outlined above.

Conclusion & Recommendations

It is my view that the outcome in the US is unlikely to be an entirely random occurrence. The evidence suggests to me that it is a real possibility that ticagrelor may behave differently in the US than in the non-US population, for reasons already addressed. There are other uncertainties, as discussed, that casts some doubt that the best estimate of treatment effect for the US should be the same as the overall effect observed in the trial. In my view, it would be a matter of faith to accept the overall study results as the best estimate of outcome in the U.S.

Therefore, I recommend that ticagrelor not be approved.

A separate study in the US could be designed to address some of these uncertainties. In fact, I think that given the findings I've discussed, there exists sufficient justification to ask for more data in the US, since this was a relatively minor subset of the total PLATO population. Such a trial, briefly, should address the following key items:

1. It would seem most reasonable to utilize the same primary endpoint as in PLATO in a similar ACS population. This would be a similarly sized trial. I understand that the sponsor has suggested that a currently planned study (PEGASUS) in subjects who are 1 to 3 years out from an MI could be used to provide additional efficacy data in the US population. However, it does not seem appropriate that outcomes in this population

should be generalized to an ACS population, particularly after reviewing the timing of benefit observed across ACS subtypes in PLATO.

2. If ticagrelor is expected to demonstrate a benefit over clopidogrel in an ACS population, in which adequate antiplatelet therapy is to be initiated as soon as possible following presentation, it may be useful to determine if benefit is shown in specific subgroups. As such, subjects could be stratified by *initial* ECG findings (STE vs. non-STE) if it could be justified that this would not substantially delay effective treatment (e.g., clopidogrel given as soon as possible). These issues should be discussed further if additional US studies are considered.

3. A new study should strive towards a design that limits investigators selecting a study population that is not representative of the "real world" ACS patient population in the US.

4. The study could incorporate prespecified analyses regarding whether or not the use of clopidogrel before randomization or concomitant aspirin has an effect on the benefits of ticagrelor. This may be important if subjects are enrolled at later timepoints, such as after STEMI vs. UA/NSTEMI is confirmed, before which they may have received varying doses of open label clopidogrel.

5. If the sponsor seeks an indication to reduce stent thrombosis, the study should prospectively incorporate this into the design and plan on use of a central core (angio) lab and appropriate adjudication of all suspected stent thromboses.

APPENDICES

1. Statistical reviewer's (Jialu Zhang) BACKUP slides

US / Non US forest plots of hazard ratios by Baseline Antiplatlet Use, Index Event Characteristic, sex, time to 1st dose, open label cpd, simvastatin during trial, clopidogrel naive, 80% compliance, and prior stroke.

USA / Non US forest plots of hazard ratios by bare metal stent, drug eluting stent, TIMI Score, Age, index hosp days, Days on treatment, index event to early PCI, and Days on ASA.

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2. Clinical Efficacy Review: AC Meeting Slides

Slide 1

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health   www.fda.gov

NDA 22-433 Brilinta® (ticagrelor)

Efficacy Review

Cardio-Renal Advisory Committee Meeting
July 28, 2010

Robert P. Fiorentino, MD, MPH
CDER, DCRP

Slide 2

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health   www.fda.gov

Proposed Indication:

Reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be:
- managed medically
- managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG

BRILINTA as compared to clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes. BRILINTA as compared to clopidogrel has also been shown separately to reduce the rate of:
- CV death
- MI

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Slide 3

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health   www.fda.gov

Outline

- Regulatory context of PLATO
- Subgroups relevant to the proposed indication
  - Outcome by Index ACS Event
  - Outcome by Medical *vs.* Invasive Management
  - Accrual & Timing of benefit compared to clopidogrel
- Regional Differences (US *vs.* non-US)
- ASA-ticagrelor treatment interaction hypothesis

3

Slide 4

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health   www.fda.gov

PLATO

- One strength of PLATO was that subjects were to take the first dose of study medication as soon as possible after randomization and before any PCI
- Subjects could also be medically managed without a planned intervention (PCI) for the index event
- Goal was to reflect current clinical management of ACS, with early initiation of dual antiplatelet therapy, irrespective of whether patients are medically managed or invasively managed
- PLATO enrolled STEMI, NSTEMI and UA (without stratification)

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Slide 5

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health   www.fda.gov

Prior Antiplatelet Studies: Clopidogrel & Prasugrel

CURE (clopidogrel)
- ACS within 24 hours after the onset of symptoms
- No STEMI
- *Some without ECG changes*
- *...vs.* placebo (ASA background)
- Primary Endpoint: CV death, nonfatal MI, or stroke

TRITON-TIMI 38 (prasugrel)
- ACS with scheduled percutaneous coronary intervention
- UA/NSTEMI & STEMI
- IP delayed until after angiography (except STEMI ≤12hr)
- *...vs.* clopidogrel (ASA background)
- Primary endpoint: CV death, nonfatal MI, or stroke

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Slide 6

CLOPIDOGREL IN ADDITION TO ASPIRIN FOR ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

Figure 1. Cumulative Hazard Rates for the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) during the 12 Months of the Study. The results demonstrate the sustained effect of clopidogrel.

1

TRITON TIMI-38

Primary Efficacy End Point

Clopidogrel 12.1

Prasugrel 9.9

End Point (%)

Hazard ratio, 0.81;
95% CI, 0.73–0.90;
P<0.001

UA/NSTEMI: 74%   PCI: 99%   N. America: 32%
STEMI: 26%

Days after Randomization

No. at Risk
Clopidogrel 6795 6169 6036 5835 5043 4369 3017
Prasugrel   6813 6305 6177 5951 5119 4445 3085

TRITON TIMI-38: Index ACS Event

UA/NSTEMI   Clopidogrel   STEMI   Clopidogrel

Effient   Effient

p=0.002   p=0.017   p=0.02   p=0.05

Days from Randomization   Days from Randomization

The KM curves show the adjudicated primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke over time in the UA/NSTEMI and STEMI populations.

In the **UA/NSTEMI** population, the curves continue to diverge throughout the 15 month follow-up period.

In the **STEMI** population, the early separation was maintained throughout the 15 month follow-up period, but there was no progressive divergence after the first few weeks.

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PLATO

Ticagrelor (T) [864/9333]
Clopidogrel (C) [1014/9291]

11.67%
9.80%

Kaplan-Meier Percentage (%)

UA: 17%
NSTEMI: 43%
STEMI: 38%

	HR	95% CI	p-value
T vs C	0.84	0.77, 0.92	<0.001

Days from Randomisation

N at risk
T 9333 8628 8460 8219 6743 5161 4147
C 9291 8521 8362 8124 6650 5096 4074

Primary Endpoint
Days 1 to 30

5.4%
4.8%

Failure Rate

HR = 0.88 (0.77, 1.00)

Days

Clopidogrel   Ticagrelor

Primary Endpoint: 30-day landmark

Ticagrelor (T) [413/8763]
Clopidogrel (C) [510/8688]

6.60%
5.28%

Kaplan-Meier Percentage (%)

	HR	95% CI	p-value
T vs C	0.80	0.70, 0.91	<0.001

Days from Randomisation

N at risk
T 8763 8543 8397 7028 6480 4822
C 8688 8437 8286 6945 6379 4751

Final Diagnosis of Index Event

"At enrolment, a preliminary diagnosis of non-ST or ST segment elevation ACS was made based on initial ECG.

By the end of the initial hospitalisation (Visit 1 discharge), the availability of laboratory data allowed the index event to be classified as UA, NSTEMI, or STEMI."
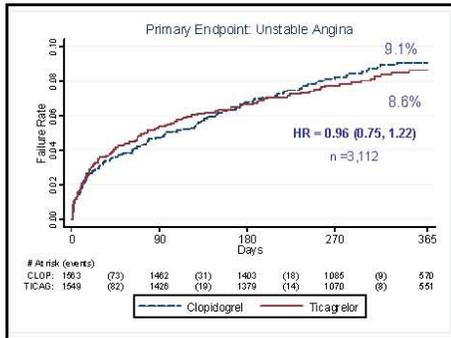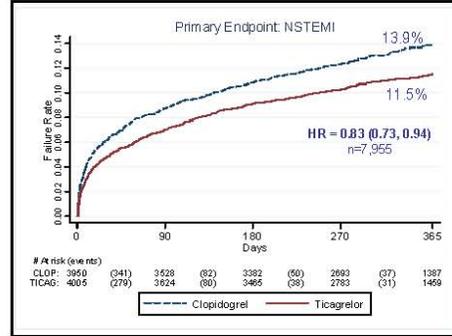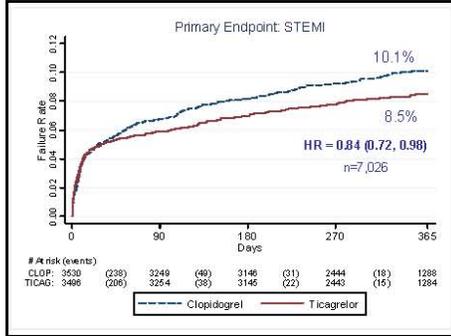
12

2

Primary Endpoint: STEMI

10.1%

8.5%

HR = 0.84 (0.72, 0.98)
n=7,026

At risk (events)
CLOP: 3630 (238) 3249 (49) 3146 (31) 2444 (18) 1288
TICAG: 3496 (206) 3254 (38) 3145 (22) 2443 (15) 1284

- - - Clopidogrel —— Ticagrelor

Primary Endpoint: NSTEMI

13.9%

11.5%

HR = 0.83 (0.73, 0.94)
n=7,955

At risk (events)
CLOP: 3950 (341) 3528 (82) 3382 (50) 2693 (37) 1387
TICAG: 4005 (279) 3624 (80) 3465 (38) 2783 (31) 1459

- - - Clopidogrel —— Ticagrelor

Primary Endpoint: Unstable Angina

9.1%

8.6%

HR = 0.96 (0.75, 1.22)
n =3,112

At risk (events)
CLOP: 1563 (73) 1462 (31) 1403 (18) 1085 (9) 570
TICAG: 1549 (82) 1426 (19) 1379 (14) 1070 (8) 551

- - - Clopidogrel —— Ticagrelor

PLATO: Unstable Angina Population

ACS within 24 hours before randomization and documented cardiac ischemic symptoms of ≥10 minutes duration at rest.

If ST segment changes on ECG indicative of ischemia, but no STEMI or NSTEMI, had to have at least 1 of the following risk factors:

- Aged 60 or over
- Previous MI or CABG
- Known multi-vessel coronary artery disease (CAD)
- Previous ischemic stroke, TIA, carotid stenosis (≥ 50%) or cerebral revascularization
- Diabetes mellitus
- Peripheral arterial disease
- Chronic renal dysfunction

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Outcome by Index ACS Event

- There was no relative benefit in subjects with Unstable Angina
  - *What is the clinical significance in an ACS population?*
- The index ACS event itself was associated with planned (and actual) treatment strategy at randomization

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Invasive vs. Medical Management

- IP + ASA given irrespective of whether patients were medically managed or invasively managed (with PCI or CABG)

- Reflecting current guidelines, initiation of treatment in PLATO was to occur as soon as possible after symptom onset, prior to the assessment of coronary anatomy by angiography

18
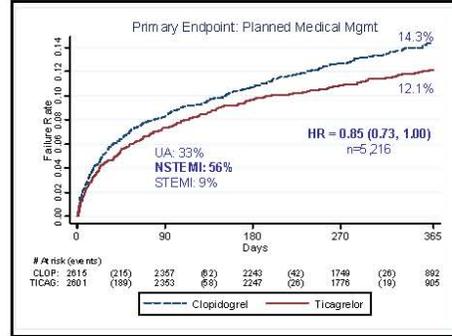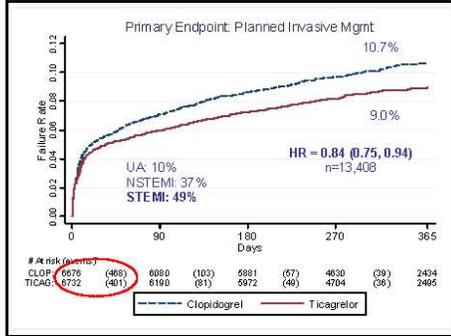
3

Primary Endpoint: Planned Invasive Mgmt

Primary Endpoint: Planned Medical Mgmt

Primary Endpoint:
Planned Treatment Approach at Randomization
vs. Index ACS Event

	STEMI		NSTEMI		UA	
Medical Mgmt	T: 14.7% (31/218)	0.73 (0.46, 1.16)	T: 14.0% (190/1441)	0.85 (0.70, 1.02)	T: 8.1% (66/813)	0.97 (0.69, 1.37)
	C: 19.5% (44/233)		C: 16.6% (226/1469)		C: 8.6% (67/863)	
Invasive Mgmt	T: 8.1% (260/3278)	0.86 (0.72, 1.01)	T: 10.2% (242/2564)	0.82 (0.70, 0.97)	T: 9.3% (59/676)	0.95 (0.67, 1.35)
	C: 9.5% (293/3297)		C: 12.2% (284/2481)		C: 9.7% (66/710)	

T = ticagrelor, C = clopidogrel; % are KM% at 365 days; HR (95% CI)

Are there 6 subgroups in the proposed indication?

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US v. non-US
Outcomes

	Ticagrelor (n/N)	Clopidogrel (n/N)	HR (95% CI)
PLATO Overall N=18,624	9.8% (864/9333)	11.7% (1014/9291)	**0.84** (0.77, 0.93)
Non-US n=17,211	9.6% (780/8626)	11.8% (947/8585)	**0.81** (0.74, **0.90**)
US n=1,413	12.6% (84/707)	10.1% (67/706)	**1.27** (**0.92**, 1.75)

- 95% CIs of the US and non-US subgroups do not overlap
- In the US, clopidogrel did 'better' and ticagrelor did 'worse'

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US *vs.* non-US

- Significant interaction between region and treatment (p=0.045) due to "North America"

- The United States comprised 78% of subjects in North America

- Both US and Canada had primary outcomes unfavorable towards ticagrelor
  US: HR = 1.27 (0.92, 1.75), n=1,413
  Canada: HR=1.17 (0.59, 2.31), n=401

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US: Primary Endpoint

12.9%

10.1%

HR = 1.27 (0.92, 1.75)

Clopidogrel — Ticagrelor

US ONLY

MI: 1.38 (0.95, 2.01)
CV Death: 1.26 (0.69, 2.31)
Strokes: 1.75 (0.51, 5.97)

U.S. Only: Myocardial Infarction (excl. silent)

U.S. Only: CV Death

U.S. Only: Strokes
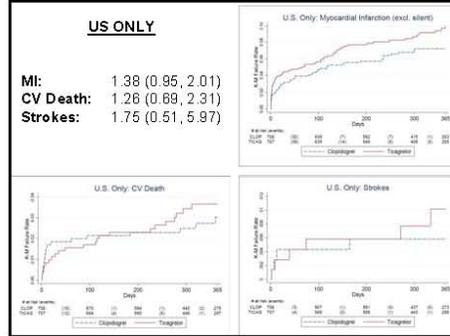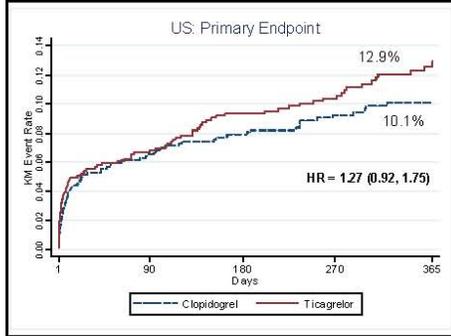
Factor	US	Non-US
Weight (median)	87kg	80kg
Diabetes	33%	24%
Prior MI	27%	20%
Prior PCI	29%	12%
Prior CABG	17%	5%
STEMI	16%	40%
NSTEMI	67%	41%
UA	10%	17%
≥ 12 hrs index event to study drug	63%	46%
Planned Invasive Mgmt	94%	70%
PCI < 24hr after randomization	62%	50%
PCI w/ Drug eluting stent	46%	19%
Ave. # DES implanted	1.8	1.6
PCI w/ Bare Metal stent	23%	46%
Ave. # BMS implanted	1.5	1.5
ASA dose, mg Median	325	100
Mean	217	99
Compliance	86%	95%

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- The US population had different baseline factors at the time of enrollment and subsequently underwent different treatment strategies compared to the general non-US population

- …including the use of concomitant higher-dose aspirin

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ASA Interaction

- The most pronounced initial observation explaining the regional differences in outcome was that of a potential treatment interaction between aspirin (ASA) and study treatment, such that higher-dose aspirin was associated with comparatively unfavorable outcomes for ticagrelor.

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ASA Interaction

- On average, the US took a substantially higher dose of concomitant aspirin compared to the rest of the world

- Avg. ~220mg US vs. ~100mg non-US

- Over half of the US study population received concomitant median daily doses of 325mg aspirin, with a lesser number receiving 81mg

30

5

Median ASA Dose: US vs. non-US

ASA Dose over time
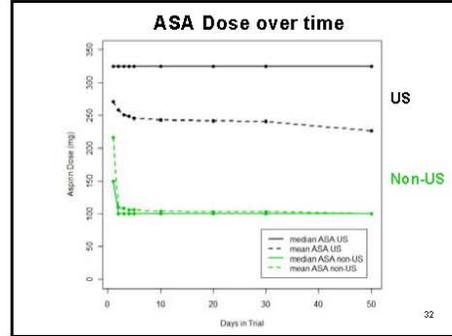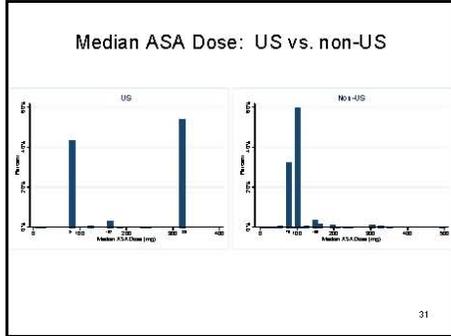
ASA Interaction

- Further analyses suggested that US subjects who received ASA 81mg had numerically better outcomes than those on 325mg

- It was not clear if effect modifiers related to higher dose aspirin could explain these differences *independently*

ASA Interaction (cont'd)

- US subjects who received higher-dose, 325mg ASA (n=667) when compared to those with 81mg (n=545), were more likely to have:
  - PCI on-study (77% vs. 61%)
  - More stents implanted (74% vs. 58%)
  - More frequent use of GPIIb/IIIa inhibitors during index hospitalization (57% vs. 45%)

ASA Interaction (cont'd)

- However, no specific factor was highly correlated with higher ASA dose in the US

- Overall, there was no other single factor identified that appeared to be acting as a *surrogate* for higher-dose ASA that was the true causal factor for the regional interaction

- Possible that the baseline and treatment characteristics of US population, including the use of higher-dose aspirin, were confounded with outcome in a manner that could not be teased apart by *post hoc* multivariate analyses (*multicollinearity*)

Conclusion

- There are potentially multiple confounders and/or effect modifiers that complicate these post hoc analyses

- Imbalances in study populations may create fertile ground for an as yet uncharacterized effect modification

- It seems unlikely that the unfavorable US outcome can be explained entirely by any single factor alone, including aspirin

- The possibility of a chance outcome cannot be excluded

6

Conclusion (cont'd)

- No clear biological or pathophysiological explanation for a ticagrelor effect modifier, ASA or otherwise, has been indentified...

- But there has been speculation

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Thank you

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BACK UP SLIDES

Ticagrelor PD profile mimics its PK profile

Ticagrelor concentration does not track geographic difference in efficacy
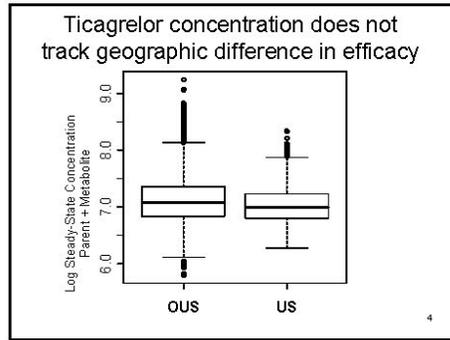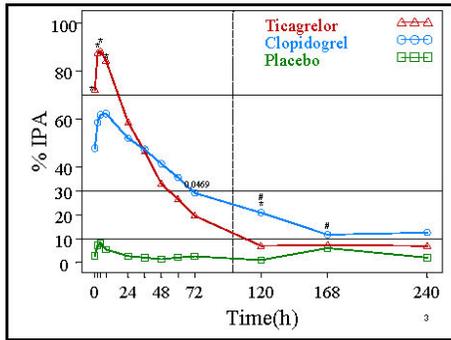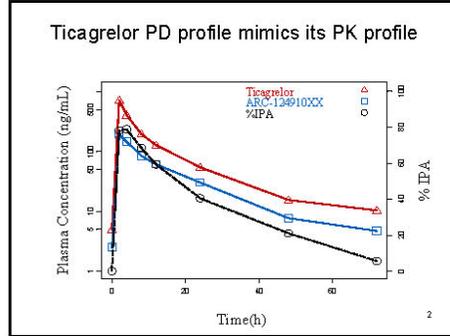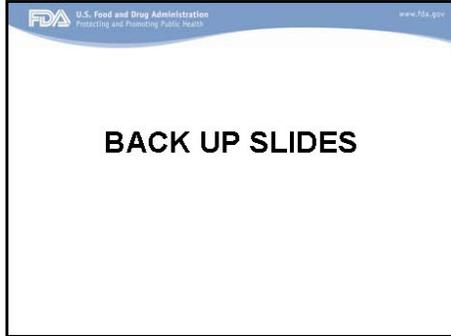
Landmark Analyses

Day 0-30

	HR	95% CI
UA	1.12	(0.76, 1.64)
NSTEMI	0.78	(0.65, 0.95)
STEMI	0.98	(0.79, 1.20)
Invasive	0.89	(0.77, 1.04)
Medical	0.84	(0.66, 1.07)

Day 30-365

	HR	95% CI
UA	0.86	(0.62, 1.19)
NSTEMI	0.87	(0.73, 1.03)
STEMI	0.68	(0.53, 0.87)
Invasive	0.78	(0.66, 0.93)
Medical	0.86	(0.71, 1.05)

US: Primary Endpoint
Days 1 to 30

STEMI: Primary Endpoint
Days 1 to 30

5.2%
5.0%

HR = 0.98 (0.79, 1.20)

Clopidogrel — Ticagrelor

NSTEMI: Primary Endpoint
Days 1 to 30

6.1%
4.8%

HR = 0.78 (0.65, 0.95)

Clopidogrel — Ticagrelor

Cumulative Outcome Event Rates by FDA-defined Regions

Reclassified FDA Region	Primary Endpoint HR (Cox)	Arm	Primary Endpoint	MI (exc. Silent)	CV Death	Stroke
USA N=1,413	1.27 (0.92, 1.75)	TIC n=707	84 (12%)	64 (9%)	24 (3%)	7 (1%)
		CLOP n=706	67 (9%)	47 (7%)	19 (3%)	4 (1%)
E. Europe N=7,645	0.76 (0.65, 0.88)	TIC n=3820	299 (8%)	162 (4%)	150 (4%)	41 (1%)
		CLOP n=3825	394 (10%)	242 (6%)	173 (5%)	38 (1%)
W. Europe N=5,429	0.84 (0.71, 1.00)	TIC n=2725	240 (9%)	157 (6%)	60 (2%)	40 (1%)
		CLOP n=2704	281 (10%)	169 (6%)	101 (4%)	36 (1%)
Asia N=1,631	0.77 (0.58, 1.01)	TIC n=619	90 (11%)	37 (5%)	58 (7%)	13 (2%)
		CLOP n=612	114 (14%)	45 (6%)	75 (9%)	10 (1%)
L. America N=1,237	0.86 (0.65, 1.13)	TIC n=621	91 (15%)	48 (8%)	43 (7%)	15 (2%)
		CLOP n=616	104 (17%)	52 (8%)	57 (9%)	13 (2%)
Other N=1,269	1.11 (0.77, 1.60)	TIC n=641	60 (9%)	36 (6%)	20 (3%)	9 (1%)
		CLOP n=628	54 (9%)	38 (6%)	17 (3%)	5 (1%)

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EVENT	Region	Ticagrelor 90 mg bd N=9333			Clopidogrel 75 mg od N=9291			Hazard Ratio (95% CI)	p-value	p-value (int)
		n	Patients with Events	KM%	n	Patients with Events	KM%			
CV DEATH/ MI (EXC SILENT)/ STROKE	US	707	84 (11.9%)	12.6%	706	67 (9.5%)	10.1%	1.27 (0.92, 1.75)	0.1459	0.0092
	Non-US	8626	780 (9.0%)	9.6%	8585	947 (11.0%)	11.8%	0.81 (0.74, 0.90)	<0.0001	
CV DEATH	US	707	24 (3.4%)	3.7%	706	19 (2.7%)	2.7%	1.26 (0.69, 2.31)	0.4458	0.1190
	Non-US	8626	329 (3.8%)	4.0%	8585	423 (4.9%)	5.3%	0.77 (0.67, 0.89)	0.0005	
MI (EXC SILENT)	US	707	64 (9.1%)	9.6%	706	47 (6.7%)	7.2%	1.38 (0.95, 2.01)	0.0966	0.0065
	Non-US	8626	440 (5.1%)	5.5%	8585	546 (6.4%)	6.9%	0.80 (0.70, 0.90)	0.0004	
STROKE	US	707	7 (1.0%)	1.0%	706	4 (0.6%)	0.6%	1.75 (0.51, 5.97)	0.3730	0.5089
	Non-US	8626	118 (1.4%)	1.5%	8585	102 (1.2%)	1.3%	1.15 (0.88, 1.50)	0.2964	
ALL CAUSE MORTALITY	US	707	28 (4.0%)	4.2%	706	24 (3.4%)	3.6%	1.17 (0.68, 2.01)	0.5812	0.1406
	Non-US	8626	311 (4.3%)	4.6%	8585	482 (5.6%)	6.1%	0.77 (0.67, 0.89)	0.0001	

Table 1   ASA dose during first 4 days of study drug: US and non-US – Full PLATO analysis set

Region	Treatment	Day	N	Mean	Median
Non-US	Ticagrelor 90 bd	1	8149	221	150
		2	7974	110	100
		3	7882	107	100
		4	7779	105	100
	Clopidogrel 75 mg od	1	8109	218	150
		2	7995	111	100
		3	7899	109	100
		4	7798	106	100
US	Ticagrelor 90 bd	1	648	261	325
		2	624	243	325
		3	611	237	325
		4	604	234	325
	Clopidogrel 75 mg od	1	635	283	325
		2	625	278	325
		3	599	269	325
		4	590	265	325

US

Percent
Median ASA Dose (mg)

2

Non-US

Percent — Median ASA Dose (mg)

TT38

1. UA/NSTEMI ≤72 hours after symptom onset (TIMI Risk Score ≥3)
2. STEMI >12 hours and ≤14 days after symptom onset
   Spontaneous or provoked ischemia
   Catheterization/PCI in stable patient

STEMI ≤12 hours after symptom onset

Eligibility Assessment and Informed Consent
Pre-catheterization medication

Diagnostic Catheterization

Medication or CABG planned

PCI planned (aspirin ≤24 hours prePCI)

Do NOT randomize

Randomize (stratified)

Loading dose of study drug

Investigator Discretion:
1. Choice of antithrombin
2. Use/choice of IV GP IIb/IIIa
3. PCI device

PCI

No PCI

Daily maintenance dose of study drug (long-term follow-up)

Daily maintenance dose of study drug (long-term follow-up)

Abbreviations: CABG = coronary artery bypass graft surgery;
GP = glycoprotein; IV = intravenous; NSTEMI = Non-ST-segment elevation
myocardial infarction; PCI = percutaneous coronary intervention;
STEMI = ST-segment elevation myocardial infarction; TIMI = The TIMI
Study Group; UA=unstable angina

US Population
Distribution of Mean ASA Dose*

Percent of Sample — Mean ASA Dose (mg)

* for subjects with >= 5 days of ASA; graph restricted to doses <500mg

Non-US Population
Distribution of Mean ASA Dose*

Percent of Population — Mean ASA dose (mg)

* All available data

US Primary Endpoint STEMI

US Primary Endpoint NSTEMI

US Primary Endpoint Unstable Angina

Clopidogrel — Ticagrelor

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Primary Endpoint
Day 1 to 7

Failure Rate — Days

3.2%

2.7%

Clopidogrel — Ticagrelor

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Cox regression analysis of the primary endpoint (non-US)

US Primary Endpoint: NSTEMI Subgroup
Days 1 to 30

US Primary Endpoint: STEMI Subgroup
Days 1 to 30

Primary Endpoint: NSTEMI — Primary Endpoint: Planned Medical Mgmt

37% 2910 / 7955

Primary Endpoint: STEMI — Primary Endpoint: Planned Invasive Mgmt

94% 6575 / 7026

Clopidogrel — Ticagrelor

ASA Interaction (cont'd)

Events on Ticagrelor in NA region	Treatment-by-region interaction	HR & 95% CI in NA	Overall HR & 95% CI
Original data (102 for T vs. 82 for C)	0.046	1.25 (0.93, 1.67)	0.84 (0.77, 0.92)
1 event switching (101 for T vs. 83 for C)	0.065	1.22 (0.91, 1.63)	0.84 (0.77, 0.92)
2 events switching (100 for T vs. 84 for C)	0.091	1.19 (0.89, 1.59)	0.84 (0.76, 0.92)
3 events switching (99 for T vs. 85 for C)	0.123	1.16 (0.87, 1.55)	0.83 (0.77, 0.91)

C Clopidogrel; CI Confidence interval; HR Hazard ratio; NA North America; T Ticagrelor.

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CURE 2001

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US vs. non-US Population (cont'd)

Factor	US (N=1,413)	Non-US (N=17,211)
Time ≥12 hrs from index event to first dose of study drug	893 (63.2%)	7,961 (46.3%)
Intended invasive management	1,323 (93.6%)	12,085 (70.2%)
Early PCI (w/in 24hrs)	866 (61.3%)	8,388 (48.8%)
Drug eluting stent, n(%) Ave. # DES implanted	653 (46%) 1.8	3,339 (19.4%) 1.6
Bare Metal stent, n(%) Ave. # BMS implanted	331 (23%) 1.5	7993 (46%) 1.5
GP IIb/IIIa use during index hospitalization	709 (50.2%)	4,353 (25.3%)
β-blocker use on day of randomization	1,226 (86.8%)	12,834 (74.6%)
At least 80% compliance	1,210 (85.6%)	16,310 (94.8%)
ASA dose, mgᵃ Median Mean	325 217	100 99
Subjects with median ASA doseᵃ (median) ≥300 mg	618 (44%)	239 (1.4%)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT FIORENTINO
08/25/2010

FINAL CLINICAL SAFETY REVIEW

Application Type	NDA
Application Number(s)	22433
Priority or Standard	Standard
Submit Date(s)	November 18, 2009
Received Date(s)	November 18, 2009
PDUFA Goal Date	September 16, 2010
Division / Office	Division of Cardiovascular and Renal Products/ ODE 1
Reviewer Name(s)	Melanie Blank, MD
Review Completion Date	August 25, 2009
Established Name	Ticagrelor
(Proposed) Trade Name	Brilinta
Therapeutic Class	cyclopentyltriazolopyrimidine
Applicant	AstraZeneca
Formulation(s)	Tablet
Dosing Regimen	90 mg bd
Indication(s)	Acute Coronary Syndrome
Intended Population(s)	Acute Coronary Syndrome Population

Clinical Review
Melanie J. Blank, MD
NDA 22433
Ticagrelor (Brilinta)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendations on RegulatoryAction

I recommend a nonapproval decision for ticagrelor.

1.2 Risk benefit Assessment

PLATO demonstrated that the world-wide performance outside of North America of ticagrelor was superior to an active comparator for reducing the frequency of myocardial infarction, and cardiovascular death in patients who presented with acute coronary syndrome. PLATO was successful on its primary endpoint: MACE (myocardial infarction, stroke, cardiovascular death), despite no demonstrable benefit in stroke prevention. Ticagrelor is the first drug in its class to show a mortality benefit.

The safety profile of ticagrelor was better than expected given the enormous benefit found. As shown in Table 1, for every all-cause 10 deaths avoided by ticagrelor, there was 1 hemorrhagic stroke death. According to the sponsor, for every 1000 patients, there were 17 MACE events avoided.

Table 1: Events per 1000 patients by treatment (negative numbers favor ticagrelor)

	Ticagrelor N=9235 patients with events	Clopidogrel N=9186 patients with events	RR	Increase or decrease in events/1000 patients treated
Death (All-cause)	408 (4.4%)	505 (5.5%)	0.8	-10
Major Bleed	961 (10.4%)	929 (10.1%)	1.03	3
Major Fatal/Life-threatening	491 (5.3%)	480 (5.2%)	1.02	1
Fatal Bleed	21 (0.2%)	23 (0.3%)	0.91	0
TIMI defined Major Bleed	657 (7.1%)	638 (6.9%)	1.02	2
Non-procedural Major Bleed	235 (2.5%)	180 (2.0%)	1.3	6
Intracranial Bleed	27 (0.3%)	14 (0.2)	1.9	1
Deaths from Intracranial Bleed	11 (0.1)	2 (0.0)	5.47	1
CABG	**N= 770**	**N=814**		
CABG-related bleed Major Bleed	619 (80.4%)	654 (80.3%)	1	0
CABG-related fatal Bleed	6 (0.8%)	6 (0.7%)	0	0

There were statistically more overall bleeds (PLATO-defined major, life-threatening/fatal, fatal, minor and minimal), in the ticagrelor arm. For PLATO-defined major bleeds alone, there were numerically more major bleeds in the ticagrelor arm but this difference did not reach statistical significance except in the subgroup of patients with PLATO-defined nonprocedural major bleeds.

Hemorrhagic stroke was the most concerning safety signal. There were 27 hemorrhagic strokes in the ticagrelor treatment arm and 14 in the clopidogrel treatment arm. 11 of the hemorrhagic strokes in the ticagrelor arm were fatal, compared to 1 fatality from hemorrhagic stroke in the clopidogrel arm.

Overall risk of stroke was greater in the ticagrelor arm compared to the clopidogrel arm (1.5% vs. 1.3%; p=0.2249). Of note, 8/99 (8.1%) patients who had a history of cerebrovascular disease (including carotid and vertebrobasilar disease) upon study entry had cerebrovascular events during the trial compared to 4/99 (4.0%) patients in the clopidogrel arm. Of those patients, 2 of the ticagrelor treated patients had

hemorrhagic cerebral events compared to 1 of the clopidogrel-treated patients. 1/8 died after stroke in the ticagrelor group and ¼ died after stroke in the clopidogrel group. This means that patients with a history of cerebrovascular d

The observation of increased ventricular pauses in the Holter Substudy and increased dyspnea in the ticagrelor arm did not translate into concerns regarding longterm safe use.

Despite the favorable safety profile and the impressive overall efficacy of ticagrelor, it is very troublesome that ticagrelor trends toward doing harm in the U.S. population. This trend cannot be explained sufficiently by aspirin dose or other known modifiable condition. Because the population of patients enrolled in the U.S. was substantial (1413 patients), it seems highly unlikely that chance would have created the disparity in efficacy between the U.S. and the rest of the world, particularly because the different aspects of the composite endpoint all trended in the wrong direction. Whether it was due to practice differences or another as of yet unidentifiable difference between the U.S. and the rest of the world, ticagrelor's effect on U.S. patients is at best no better than clopidogrel's effect and possibly worse. What this means is that we cannot even feel confident that the effect of ticagrelor is better than placebo in the U.S. population.

When assessing a drug for approval, one must first evaluate its effectiveness when used for its proposed indication. Without proven efficacy, no drug, particularly drugs that have a high risk of adverse events such as increased overall and non-procedural bleeding, stroke (and fatal hemorrhagic stroke), ventricular pauses and dyspnea, are safe. Without proven effectiveness in the U.S., and with other known to be effective alternative treatments available, it appears that it would not be safe to administer ticagrelor to the U.S. population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A medication guide for practitioners has been proposed by the sponsor. If ticagrelor is approved, this guide after modifications are made should be sufficient for informing providers on the main ticagrelor safety issues, contraindications, and administration instructions.

1.4 Recommendations for Postmarket Requirements and Commitments

If ticagrelor is approved, the sponsor should be required to do another long term study; an adequately powered non-inferiority study with a prospectively agreed upon lower bound for the inferiority margin in the U.S. population. The study should use a controlled aspirin dose, no restrictions on statin drug use and use prasugrel or clopidogrel as the comparator.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The submission was an electronic submission that followed the eCTD guidance. There was an adequate index, text was searchable, the data sets and fields were well defined, and the appropriate sections for completing the review were present. Content of Labeling was submitted in SPL format. Additionally, the sponsor was agreeable and prompt when asked to supply datasets or other analyses.

3.2 Compliance with Good Clinical Practices

PLATO was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonization/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics.[1]

3.3 Financial Disclosures
Most of the investigators had no financial disclosures. There were 2 investigators, one in the U.K, and one in Germany who disclosed significant payments over $25,000 above the costs of conducting the trial or other trials, but could include payments made to the investigator or investigator's institution to support activities of the investigator (i.e., including but not limited to grants to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria).One U.S. investigator had equity interest in AstraZeneca exceeding $50,000. Since these investigators either served on the adjudication committee that was blinded and/or had low numbers of adjudicated events at their centers, it is unlikely that any bias on their parts would have affected the overall outcome of the trial.

It is important to note that any amount of payment ≤ $25,000 does not need to be disclosed. If it was common practice to compensate investigators with payments up to $25,000, it is conceivable that bias could have affected the outcome of the trial. It should be noted that it was easy to open the capsules and determine which drug each patient was taking.

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1 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: E14. Adopted by CHMP May 2005, issued as CHMP/ICH/2/04. Available at http://www.ich.org/cache/compo/475-272-1.html#E14.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Ticagrelor is a round, biconvex, yellow, film-coated tablets containing 90 mg of ticagrelor. Ticagrelor is an immediate release (IR) formulation intended for twice-daily (bd) administration. The 90 mg ticagrelor IR tablet formulations were used in the Sponsor's worldwide clinical development program, and the Phase 3 tablet is the proposed commercial formulation of ticagrelor.

4.3 Preclinical Pharmacology/Toxicology

Paraphrased from Dr. Elizabeth Hausner's review:

Ticagrelor toxicology was assessed in mice, rats, rabbits and marmosets. The non-clinical toxicology studies indicated that the target organs of toxicity were the gastrointestinal tract (dogs, rats, marmosets), liver (rats), bone marrow (rats, marmosets), immune system (marmosets, rats), adrenal (rodents) and endocrine system (mice and female rats).

Findings pertinent to the clinical review:

Respiratory System findings: In rats, safety pharmacology studies showed that there were pulmonary function changes after administration of ticagrelor. There was increased respiratory rate (up to 20% of pre-dose baseline, p<0.01), increased peak inspiratory flow (up to 35% of pre-dose baseline, p>0.05) and increased expiration time (decreased by up to 20% from pre-dose baseline, p<0.01). Other studies showed that foamy alveolar macrophages were present in the lungs of rats at doses ≥180 mg/kg/day. These were described as minimal changes. Similar changes were not reported for marmosets.

Hematology findings: Across species, the hematology findings were relatively consistent with minor blood loss associated with regeneration.

Hepatic findings: Liver effects in rats occurred at doses ≥80 mg/kg and included indications of altered function or damage evidenced by decreased triglycerides (67%, p<0.001), increased AST (20%, p<0.001) or ALP (31%, p<0.001) when compared to the control groups. Centrilobular hypertrophy was inconsistently reported (mice ≥250 mg/kg/day; rats ≥180 mg/kg). Liver effects in marmosets were inconsistent.

Evaluation of Fertility: The main study animals did not show histologic effects on the testes or epididymides.

Embryo-fetal development: Studies showed effects on the liver and the skeletal systems in both rats and rabbits. Delayed development of the gallbladder and incomplete ossification of the hyoid, pubis and sternebrae were seen in rabbits. Supernumerary liver lobes and incomplete ossification of the parietal bone, sternebrae, misshapen/misaligned sternebrae, displaced articulation of the pelvis, and supernumerary ribs were seen in the rats. The pre- and post-natal development study in rats indicated that exposure to ticagrelor in late gestation or during lactation also affected development. Pinna unfolding delays and eye opening delays were common.

Reproductive System findings: There were reported drug-related effects on the reproductive organs of both sexes. In male mice, very high doses caused seminiferous epithelial degeneration of the testes. Female mice had an absence of corpora lutea at very high doses. In rats, endocrine effects were manifested as dose-related decreases in regular estrus cycles at relatively low doses ≥10 mg/kg. The relatively non-specific finding of irregular estrus cycles became more important in light of the carcinogenicity study where female rats showed statistically significant incidences of uterine adenocarcinoma and uterine squamous cell carcinoma. The rat carcinogenicity study also demonstrated a significant decrease in female survival (Cox: p=0.018, Kruskal-Wallis: p=0.0424), possibly due to metastatic uterine neoplasia. Fourteen of the 31 HD females who died ahead of scheduled termination had (metastatic) uterine adenocarcinoma listed as the cause of death.

The salient nonclinical findings formed the basis for much of my in-depth system oriented review. I focused my evaluation on not only the clinical safety issues that were known prior to the phase 3 experience (bleeding, cardiac and respiratory), but also on hepatic safety issues, the potential neoplastic effects and potential hormonally mediated effects of ticagrelor in the human.

4.4   Clinical Pharmacology

4.4.1   Mechanism of Action

Ticagrelor, (also referred to as AZD6140 in my review), substantially reduces platelet aggregation, and purportedly blocks the pathophysiologic process leading to intracoronary thrombosis in ACS. The first of a new chemical class of antiplatelet agents called **cyclopentyltriazolopyrimidines**, it has properties that importantly distinguish it from the thienopyridines. Ticagrelor is rapidly absorbed following oral administration, and binds reversibly to the P2Y12 platelet ADP receptor. In the acute setting, a rapid onset of effect theoretically may provide better protection during a period of particularly high risk for the ACS patient. In the presurgical setting or when there is bleeding, it

could theoretically provide a quicker reversal effect than other currently marketed platelet aggregation inhibitors because of its in vitro reversibility of platelet binding.

4.4.2 Pharmacodynamics

The pharmacodynamic (PD) effect of antiplatelet agents is traditionally assessed in blood samples from patients by measuring IPA. Because ticagrelor is not a prodrug requiring metabolic activation, it promptly achieves both a higher and more consistent inhibition of platelet aggregation (IPA) than clopidogrel. For example, following oral administration of a 600 mg loading dose of clopidogrel, measured IPA increases gradually, reaching a level after 8 hours that is achieved after only 30 minutes following a 180 mg loading dose of ticagrelor, which then continues to increase to 87% to 89% by 2 hours.

Ticagrelor's reversible binding to the P2Y12 receptor permits the return of platelet aggregation upon cessation of therapy. This process does not require the generation of new platelets. In experiments designed to document this, ticagrelor demonstrated a statistically significant, faster rate of IPA offset compared with clopidogrel from 4 to 72 hours following cessation of administration; IPA measurements are similar for ticagrelor at 3 days and for clopidogrel at 5 days following the last dose.

4.4.3 Pharmacokinetics

Ticagrelor undergoes rapid absorption with peak plasma concentrations attained 2 to 3 hours after oral administration to patients with ACS. An active metabolite forms rapidly, attaining peak plasma concentrations 2 to 3 hours after oral ticagrelor ingestion. Ticagrelor's steady-state volume of distribution, 87.5 L, indicates it does not extensively distribute into or bind to tissues. Both ticagrelor and its primary active metabolite bind extensively (>99.7%) to plasma proteins. Age, gender, severe renal impairment, and mild hepatic impairment do not affect protein binding. Both the AUC and Cmax of both ticagrelor and its active metabolite show approximately proportional increases with increasing oral doses, indicating linear PK. Mean terminal elimination half-life (t1/2) for ticagrelor was 6.9 hours (range 4.5 to 12.8 hours). Ingestion of a high-fat meal had no effect on ticagrelor Cmax, but resulted in a 21% increase in the area under the concentration-time curve (AUC). These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food. The primary route of ticagrelor metabolism is via hepatic metabolism. The active metabolite is at least as potent as ticagrelor at blocking the P2Y12 receptor *in vitro*. As CYP3A4 enzymes are mainly responsible for ticagrelor metabolism and the formation of its active metabolite, the potential for important drug-drug interactions involving other substrates, inhibitors or inducers of this common metabolic pathway was assessed in the development program and will be discussed in my review.

The active metabolite most likely undergoes excretion in bile. Neither ticagrelor nor the active metabolite depend on renal excretion, with <1% recovery in urine for parent and active metabolite. Ticagrelor has a mean t½ of 6.9 hours and the t½ of the active metabolite is 8.6 hours.

7 Review of Safety

7.1.1 Safety Summary and Summary of Studies/Clinical Trials Used to Evaluate Safety

There are several safety issues that should to be considered before making an executive decision on whether or not approve ticagrelor, particularly in the light of the finding that ticagrelor did not benefit the U.S. population in PLATO.

There were 9235 patients that received at least one dose of ticagrelor and 9186 patients that received at least one dose of clopidogrel-in PLATO. These patients comprised the "safety set", according to the sponsor, and their data were used for most of my safety review. When I analyzed adverse events I included only those patients who had at least one dose of drug before having an adverse event.

One of the most significant findings from PLATO was the all-cause mortality benefit seen for ticagrelor. There were statistically significant fewer overall deaths in the ticagrelor group compared to the clopidogrel. In total there were 399 (4.28%) adjudicated deaths within the efficacy period in the ticagrelor treatment arm compared to 506 (5.45%) in the clopidogrel treatment arm (RR=0.78). Vascular deaths accounted for most deaths (~ 95% of deaths in both treatment groups). The term "vascular death" includes cardiovascular deaths, cerebrovascular deaths, bleeding deaths and any other death for which there was no clearly documented nonvascular cause. Bleeding deaths were not as common as other causes of death (0.2% of patients died of bleeds). Causes of death were similar between treatment groups. The most common cause of death was myocardial infarction occurring in about 1% of randomized patients. Sudden death, heart failure, other vascular events and stroke were among the more common causes of death. The U.S. population was an outlier when it came to death prevalence. In the U.S., there were more deaths in the ticagrelor treatment group compared to the clopidogrel treatment group [35 (3.8%) vs. 29 (3.2%), respectively.

The most important safety issue for ticagrelor was bleeding. PLATO defined its own definitions of bleeding severity. The PLATO defined bleeding severity scale is included in the full body of the review. There were more patients that met the criteria for PLATO major bleeds than would have met the criteria for TIMI major bleeds, largely because one of the criteria for a PLATO major bleed was transfusion of 2 or more units of packed red blood cells or whole blood, whereas transfusion is not a criterion for having a TIMI major bleed. Ticagrelor –treated patients had a few more major bleeds than clopidogrel-

treated patients ([1031 (11.2%) vs. 997 (10.9%), respectively and this difference was not statistically significant except for the subcategory of patients that had PLATO defined nonprocedural major bleeds. However the frequency of major + minor bleeding (any bleed requiring intervention or treatment) was greater in the ticagrelor treatment group compared to the clopidogrel treatment group [1339 (14.5%) vs. 1215 (13.2%), respectively (log-rank = 0.0083)] .The reason for this increase was primarily the increased frequency of spontaneous (non-procedural/ non-CABG) bleeds in ticagrelor-treated patients. There was no increase in overall major/life-threatening or fatal bleeds in the ticagrelor treatment group compared to the clopidogrel treatment group as a whole.

Most bleeds in PLATO were CABG-related [737(8%) vs. 783 (8.5%) for ticagrelor and clopidogrel, respectively]. There was a numerically lower CABG-related frequency of overall bleeding in most PLATO-defined categories of bleeding for ticagrelor-treated patients. However, within the first several days of stopping drug, the frequency of bleeding was equivalent between the groups or was slightly worse in the ticagrelor arm. Importantly, the all-cause mortality at any time following CABG or at up to two weeks following CABG was less for ticagrelor than for clopidogrel when considering any time interval between the last dose of study treatment and beginning CABG.

Dyspnea was also an important safety issue for ticagrelor. Dyspnea occurred frequently in patients treated with ticagrelor in all clinical phase 2 studies and in PLATO (14.6% of ticagrelor-treated patients vs. 8.7% of clopidogrel-treated patients). Dyspnea SAEs occurred in less than 0.9% of ticagrelor-treated patients and in less than 0.6% of clopidogrel-treated patients. Dyspnea in ticagrelor-treated patients resulted in more discontinuations than dyspnea in clopidogrel-treated patients (0.9% vs. 0.1%, respectively). More impressively, nearly 10% of ticagrelor-treated patients that had dyspnea discontinued treatment for other AEs compared to <6% of clopidogrel-treated patients. An additional concerning observation is that the onset of dyspnea was considerably earlier in the ticagrelor-treated patients compared to the clopidogrel-treated patients, lasted usually >20 days (up to approximately 400 days) and at any length of episode, there were numerically more patients in the ticagrelor treatment group than in the clopidogrel treatment group. A pulmonary function substudy was conducted to see if there were any effects of ticagrelor on pulmonary function tests. The substudy did not reveal any differences between treatment groups but it was designed, conducted and analyzed in such a way that might have obscured differences if they existed.

On the reassuring side, dyspnea is a symptom that resolved in 2/3 of the patients during the study. While two ticagrelor-treated patients with dyspnea AEs died, it is hard to assign the cause of these deaths to ticagrelor because of other comorbidities and confounding circumstances. The subgroup of patients with history of COPD and asthma while having an absolute greater incidence of dyspnea events did not have a difference in relative risk for developing dyspnea compared to all study patients irrespective of

treatment. Most reassuringly, patients with dyspnea know they have it and can discontinue ticagrelor if they are troubled by it. Also, despite its exploratory nature, a retrospective analysis of PLATO outcomes data showed that patients with dyspnea at any time during the trial had favorable clinical outcomes.

Arrhythmias were a concern for ticagrelor because of an increased frequency of arrhythmia related deaths in phase 2 data. In PLATO, the data for ticagrelor is numerically unfavorable for atrial arrhythmias and ventricular pauses but it is favorable for sudden death and ventricular arrhythmias. A limitation of the PLATO study is that patients with an increased risk of bradycardic events (e.g., no pacemaker and known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker) were excluded from the study.

There was a Holter monitor substudy in PLATO that confirmed the increased frequency of ventricular pauses.

Renal effects were a concern because of observations of increased serum creatinine levels during treatment with ticagrelor in the phase 1 and 2 studies. In PLATO, there was an increased frequency of patients that had extreme decreases in eGFR (>30% - 100%) in the ticagrelor group as compared to the clopidogrel group. It is possible that ticagrelor, because of its negative effects on adenosine uptake could alter renal hemodynamics by decreasing tension in the afferent arteriole thereby lowering the glomerular filtration pressure.

While there were no discernable differences between treatment groups for renal AEs, discontinuations for renal AEs or deaths from renal AEs, patients on ticagrelor with baseline eGFRs of < 30 cc/min had numerically more major bleeds than clopoidogrel-treated patients [23 (19%) vs. 16 (11.3%), respectively], and renal failure [12 (13.6%) vs. 5 (5.4%), respectively]. Because of the small numbers of patients in this subgroup, these observations could be chance findings.

However, when patients have poor baseline renal function they rely on hemodynamic changes within the kidney to maintain their GFR. It is possible that ticagrelor is more likely than clopidogrel to lead to the decompensation of renal function in patients who are completely reliant on hemodynamic factors to maintain their GFR. ACS Patients with poor baseline renal function are at higher risk for renal AEs and death. While there are too few data in this subgroup of patients to make firm conclusions, it is possible that ticagrelor might also contribute to the risk of progression to worsening renal failure in these already high risk patients.

A troubling observation in PLATO was the increased frequency and earlier time to overall stroke and intracranial hemorrhagic bleeding events (mostly from strokes) in the ticagrelor-treated patients. Hemorrrhagic bleeds carry a very high mortality. There were

11 patients in the ticagrelor treatment group that died of intracranial hemorrhagic events (almost 1/2 of the patients with intracranial bleeds) while 1/14 patients in the clopidogrel-treatment group died of intracranial bleeding.

An exploration of patients who had histories of carotid, vertebrobasilar and cerebrovascular disease were considerably more likely to have strokes or TIAs while on ticagrelor (5.1 times the risk) and the relative risk of having a stroke or TIA for patients with preexistent disease was 2 times higher for ticagrelor-treated patients than for clopidogrel-treated patients.

Only ~ 400 patients with "history of baseline hepatic disorder" were enrolled. While there were no differences in IPA and no significant difference in plasma binding protein, in PLATO, there was an increase in deaths (3.1% vs. 0.9%), SAEs (20.4% vs. 16.6%) and AEs (84.2% vs. 81.1%) for the ticagrelor-treated patients with a baseline of hepatic disorder compared to similar clopidogrel-treated patients. These patients were more likely to have major bleeds if on ticagrelor (11.2%) vs. 8.7% if on clopidogrel. Clinical outcomes data (MACE), however, were favorable in this subgroup.

Other important safety explorations were uric acid level increases, hepatic events, hormonally mediated events and neoplastic events. An interesting observation was the increased frequency of gynecomastia in the ticagrelor-treated patients. None of these explorations developed into major safety concerns

In addition to the pivotal 3 study, PLATO, I reviewed 4 phase 2 studies that will be considered in the safety review when applicable. In all, there were 960 patients exposed to ticagrelor in the phase 2 studies with doses ranging from 50 mg twice a day to 400 mg once a day. The study names (numbers) are: DISPERSE (Study D5130C00008), DISPERSE2 (Study D5130C00002), OFFSET (Study 5130C00048), and RESPOND (Study D5130C00030).

There were also 41 phase I studies performed that focused on pharmacokinetic (PK) and PD parameters for ticagrelor and its primary metabolite in different populations, and characterization of drug-drug interactions with ticagrelor. The studies were designed to examine specific characteristics of the drug. The Sponsor did not pool the data to address additional safety issues. FDA agreed that pooling of data was not necessary. I reviewed these studies if I felt they were important for my review.

Additionally, I reviewed current literature on ticagrelor and the PLATO study, other literature pertaining to potential safety issues and I familiarized myself with the Prasugrel clinical reviews (Dr. Hicks review and Dr. Unger's review).

The phase 3 and 2 trials are briefly summarized below:

PLATO was a randomized, double-blind, double-dummy, parallel group, international, multicenter study comparing the efficacy and safety of ticagrelor 90 mg administered twice daily twice daily with clopidogrel 75 mg once daily for the prevention of vascular events in patients with non-ST or ST elevation ACS. PLATO included 18624 randomized patients, 13336 males and 5288 females, aged 18 years and over, with a non-ST or ST segment elevation ACS (index event) and with high risk of secondary thrombotic events. Patients were randomized to treatment as soon as possible after presentation but at the latest within 24 hours of the onset of their index event. In PLATO, the overall mean exposure was 248 days, with a median exposure of 277 days. Two substudies were conducted as part of the PLATO study to assess specific safety issues, including a Holter monitoring substudy and a pulmonary function substudy.

DISPERSE was a randomized, double-blind, double-dummy, parallel group, multicenter, multinational study to assess the PD and PK effects of ticagrelor at doses of 50 mg twice a day, 100 mg twice a day, 200 mg twice a day and 400 mg once a day in the presence of ASA compared to clopidogrel 75 mg once a day plus ASA, in subjects with documented atherosclerotic disease, DISPERSE enrolled 146 male and 54 female patients, age 34 to 84 years. In DISPERSE, the overall mean exposure was 27.9 days.

DISPERSE2 was a randomized, double-blind, double-dummy, parallel group, multicenter, multinational trial of 4, 8 or 12 weeks to assess the safety and tolerability of ticagrelor at doses of 90 mg twice a day and 180 mg twice a day, in the presence of ASA, compared with clopidogrel 75 mg once a day plus ASA, in patients with non-ST segment elevation. Patients were evaluated by an Independent Central Adjudication Committee (ICAC) for bleeding events observed within the first 4 weeks of treatment (Day 29). DISPERSE2 treated 632 male and 352 female patients. In DISPERSE2, the overall mean exposure was 54.4 days.

OFFSET was a multi-center, randomized, double-blind, double-dummy, parallel group study of the onset and offset of the antiplatelet effects of 90 mg twice a day ticagrelor (with 180 mg loading dose) compared with 75 mg once a day clopidogrel (with 600 mg loading dose) and placebo with acetylsalicylic acid (ASA) as background therapy with additional detailed assessment of cardiopulmonary function in patients with stable CAD. 93 male and 30 female patients were randomized. They were18 years of age and over and had documented stable CAD. In OFFSET, the overall mean exposure was 40.9 days.

RESPOND was a multi centre, randomized, double-blind, double-dummy crossover study comparing the anti-platelet effects of 90 mg twice a day ticagrelor with 75 mg once a day clopidogrel in patients with stable CAD previously identified as clopidogrel non-responders or responders. In RESPOND a total of 98 patients were randomized, 48 male and 9 female patients to the responder cohort and 28 male and 13 female patients to the non-responder cohort. All patients who participated in RESPOND were18 years

of age and over with documented stable CAD. In RESPOND, the overall mean exposure was 26.9 days, with a median exposure of 29.0 days.

The Phase 1 clinical pharmacology program comprises a diverse range of studies with a focus on formulation development, evaluation of PK and PD parameters for ticagrelor and its primary metabolite in different populations, and characterization of drug-drug interactions with ticagrelor. Individual studies were designed to understand the properties of ticagrelor and provide adequate information for safe use of the drug. One of the caveats from the phase 1 studies is that several formulations were used during that stage of clinical development. The FDA clinical pharmacology reviewer has reviewed this issue thoroughly and thinks that the data from the phase 1 program is fully applicable to the current formulation.

7.1.2   Categorization of Adverse Events

The sponsor used MedDRA 11.1 to categorize adverse events. As a sensitivity test, I combined certain AE terms together that had similar pathophysiological or anatomical characteristics and recoded the adverse event data set to ensure that I would not be missing signals that could be obscured by the MedDRA coding system. In my adverse events sections I specify if the table or graph is from my analysis or the sponsor's analysis.

7.1.3   Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The sponsor provided data from the phase 2 studies. However, they were not pooled with the PLATO data. As necessary, I looked at data values from the phase 2 studies while conducting my review.

7.2   Adequacy of Safety Assessments

7.2.1   Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In PLATO, 9235 patients received ticagrelor, with over 6300 patient-years of exposure. The phase 2 studies, when pooled, included only 960 ticagrelor-treated patients in the safety population. However, the duration of exposure was much shorter, ranging from 4 to 12 weeks. The PLATO exposure is clearly much greater than the phase 2 exposure

and therefore, most of my review concentrates on this trial. The sponsor chose to not pool the safety data and in the minutes from the April 17, 2009 pre-NDA meeting, FDA agreed to this strategy.

Table 2 provides a tabular summary of the exposure to ticagrelor in the safety analysis of PLATO. The safety analysis set for ticagrelor contained 9235 patients and for clopidogrel, the safety analysis set contained 9186 patients. > 70% of patients were exposed to treatment for over 270 days, and >40% were exposed for over 1 year. The numbers of patient-year exposures were 6301 for ticagrelor and 6388 for clopidogrel.

Table 2: Exposure for PLATO (safety analysis set)

Characteristic	Category	Actual Treatment	
		Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Days in Study	N	9235	9186
	Mean	298.6	298.4
	SD	96.31	96.06
	Median	357	356
	Min	1	1
	Max	575	548
	1-30	308 (3.3%)	306 (3.3%)
	31-90	145 (1.6%)	157 (1.7%)
	91-180	299 (3.2%)	290 (3.2%)
	181-270	1840 (19.9%)	1835 (20.0%)
	271-360	2506 (27.1%)	2542 (27.7%)
	>360	4137 (44.8%)	4056 (44.2%)
	>0	9235 (100%)	9186 (100%)
	>30	8927 (96.7%)	8880 (96.7%)
	>90	8782 (95.1%)	8723 (95.0%)
	>180	8483 (91.9%)	8433 (91.8%)
	>270	6643 (71.9%)	6598 (71.8%)
	>360	4137 (44.8%)	4056 (44.2%)
Patient Years		6301	6388

Source: PLATO study report, p.799

Table 3 is a tabular listing of the exposure in the phase 2 studies. As you can see, the exposure in the phase 2 studies equals 211 patient-years compared to the 6301 patient-year exposure in PLATO..

Table 3: Exposure for phase 2 studies

Actual Treatment	Number of Patients	Mean Days of Treatment	Patient-years
Ticagrelor 180 mg bd	360	51.9	51.2
Ticagrelor 90 mg bd	513	44.4	62.4
Ticagrelor 50 mg bd	41	27.9	31.3
Ticagrelor 400 mg od	46	27.5	3.5
Clopidogrel 75 mg od	498	45.2	61.7
Placebo	12	40.7	1.3

Source: Adapted from Integrated Summary of Safety, p.65

7.2.2 Explorations for Dose Response

DISPERSE2 studied the target dose for Phase 3, 90 mg bd, and double that dose, 180 mg bd in patients with NSTEMI-ACS. There was similar total bleeding amongst the 90 mg bd ticagrelor, 180 mg bd ticagrelor, and 75 mg daily clopidogrel groups. These results suggested that the 180 mg bd ticagrelor dose would be best for PLATO. Clinical pharmacology studies, however, played a role in the decision to modify this choice because of greater drug exposure in patients receiving moderate inhibitors of cytochrome P450 isoenzyme 3A (CYP3A4), such as diltiazem. Also, the Holter data from DISPERSE 2 revealed that there were numerically more patients with pauses in the 180 mg bd ticagrelor group. An analysis of the data suggested that there was an apparent dose-related effect of ticagrelor on ventricular pauses. Also, ventricular pauses and adverse events related to bradycardia were observed with ticagrelor, including in a few individual healthy volunteers during the Phase I Single Ascending Dose and Thorough QT studies. Based on these considerations, the 90 mg bd maintenance dose was chosen for PLATO.

Please refer to the clinical pharmacology review for a more detailed discussion.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the pharmacology toxicology review. Important animal data is presented when appropriate in this review.

7.2.4 Routine Clinical Testing

The testing was done in a central laboratory and appeared to be adequate.

I suspect that capture of AEs may have been spotty after drug discontinuation or even prior to drug discontinuation. The reason for my suspicion is that many patients missed their last visits because of the early wrap-up of the trial. While attempts were made to assess the survival of these patients, not much attempt was made to capture the other efficacy endpoint measures or to collect AEs.

7.2.5 Metabolic, Clearance, and Interaction Workup

There was a thorough analysis of these safety issues in the clinical pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Currently Available Related Drugs for Indication:

Clopidogrel bisulfate (PLAVIX and generic) and ticlopidine hydrochloride (TICLID and generic) are ADP receptor antagonists of the thienopyridine class that inhibit platelet activation and aggregation and carry cardiovascular claims.

Prasugrel HCl (Effient) Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets

Ticagrelor differs from the others in the class of platelet inhibitors in that it reversibly binds to the P2Y12 class of ADP receptor on platelets. The clinical importance of this reversibility will be explored in this review.

1. **Clopidogrel** is indicated for the reduction of atherothrombotic events as follows:
Recent MI, Recent Stroke or Established Peripheral Arterial Disease
For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease…to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.
Acute Coronary Syndrome For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Qwave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG…to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia For patients with ST-segment elevation acute myocardial infarction, PLAVIX has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, reinfarction
or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

2. **Ticlopidine** is indicated for the following conditions:
• To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke.
• As adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation.

Ticlopidine carries black box warnings for thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis, and aplastic anemia, and the indication states that the drug "…should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy."

3. **Prasugrel** is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI).

- Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

Effient™ has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death *[see Clinical Studies (14)]*.

It is generally recommended that antiplatelet therapy be administered promptly in the management of ACS because many cardiovascular events occur within hours of initial presentation. In the clinical trial that established the efficacy of Effient, Effient and the control drug were not administered to UA/NSTEMI patients until coronary anatomy was established. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial *[see Warnings and Precautions (5.2)]*. Because the large majority of patients are managed without CABG, however, treatment can be considered before determining coronary anatomy if need for CABG is considered unlikely. The advantages of earlier treatment with Effient must then be balanced against the increased rate of bleeding in patients who do need to undergo urgent CABG.

Since ticlopidine is associated with increased risk for thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis, and aplastic anemia, I examined the ticagrelor data for evidence of these types of adverse events and found none.

Prasugrel provides substantially better (>80%) IPA and clinical efficacy than clopidogrel, but at the cost of a marked increase in major bleeding events, especially in patients over 75 years old, those with body weight <60 kg, those with a history of transient ischemic attack or stroke, and in those undergoing CABG surgery [2]. Like clopidogrel,

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2 Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. NEJM 2007;357:2001-15.
Wiviott SD, Antman EM, Gibson CM, Montalescot G, Riesmeyer J, Weerakkody G, Winters KJ, Warmke JW, McCabe CH, Braunwald E, for the TRITON-TIMI 38 Investigators. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). Am Heart J 2006;152:627-35.

prasugrel inhibits aggregation permanently in circulating platelets. Its greater antiplatelet effect, coupled with the same property of irreversible binding leading to permanent platelet inhibition, seems to translate into a higher bleeding risk. For this reason, bleeding was the main focus of my review and will be discussed in Section 7.5. Since prasugrel also was associated with an excess of new malignant tumors, I also focused on cancer incidence and found no increase.

7.3   Major Safety Results

7.3.1   Deaths

Deaths in Phase 1 and 2

There were 13 (4 in the follow-up period) deaths in the ticagrelor treatment groups in the Phase 1 and 2 programs. These all occurred in the DISPERSE2 (phase 2) study in ACS patients. There were 3 treatment groups in this trial randomized 1:1:1 (ticagrelor 90 mg bd, ticagrelor 180 mg bd and clopidogrel 75 mg od). 11 of the deaths in the ticagrelor treatment arm were categorized as cardiac death (many secondary to arrhythmias). There were 4 deaths (3 in the follow-up period) in the clopidogrel treatment group (no arrhythmias). In DISPERSE2, a study of approximately 1000 patients, there was no suggestion of a death benefit for ticagrelor.

Deaths in PLATO

Conversely, in PLATO, ticagrelor-treated patients had a significantly lower risk of all-cause mortality compared to clopidogrel- treated patients. There are a number of criteria one can use to count deaths as can be seen in Table 4. No matter which criterion one uses to define the numbers of deaths, i.e., total deaths, actual treatment deaths, on treatment deaths, as randomized events, adjudicated deaths, etc., the death benefit of ticagrelor is statistically significant. Please note that one of the adjudicated deaths was found to be alive at the end of the study.

Table 4: Sponsor's Analysis of PLATO: Summary of Deaths adjudicated by the Independent Central Adjudication Committee (ICAC)

Deaths	Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291	Total N=18624	RR
Total known deaths	443 (4.75)	540 (5.81)	983	**0.82**
Discovered after withdrawal of consent, not adjudicated	25 (0.27)	20 (0.22)	45	**1.24**
All adjudicated deaths	418 (4.48)	520 (5.6)	938	**0.8**
Adjudicated deaths within efficacy period (randomisation to last scheduled visit date)	399 (4.28)	506 (5.45)	905	**0.78**
Adjudicated deaths 1 to 30 days after efficacy period (PSOP)	15 (0.16)	12 (0.13)	27	**1.24**
Adjudicated deaths after PSOP	4 (0.04)	2 (0.02)	6	**1.99**
Adjudicated deaths counted in safety analyses	408 (4.37)	505 (5.44)	913	**0.8**
Deaths in safety on-treatment analysis (randomization to 7 days after the last dose of study drug)	283 (3.03)	339 (3.65)	622	**0.83**
Within efficacy period	281 (3.01)	339 (3.65)	620	**0.83**
After efficacy period	2 (0.02)	0 (0.0)	2	
Deaths in safety off-treatment analysis (>7 days after the last dose of study drug)	125 (1.34)	166 (1.79)	291	**0.75**
Adjudicated deaths not counted in safety analyses – patient never took study drug	10 (0.11)	15 (0.16)	25	**0.66**

Source: Source: Adapted from PLATO study report, p. 250

PSOP = Post-study observational period (30-day after the last scheduled visit of the efficacy follow-up study period (60-days off drug).

I have chosen to take the example of the adjudicated all-cause deaths by actual treatment group after one dose of treatment to highlight the ticagrelor death benefit.

The Kaplan-Meier curve in Figure 1demonstrates that 389 (4.21% of ticagrelor-treated patients died compared to 491 (5.34%) of clopidogrel-treated patients. The log-rank score for these patients is 0.0001 and highly statistically significant.

Figure 1: K-M: All Cause Mortality (Adjudicated) in Patients by Actual Treatment after at Least One Dose (source AWCADJ.xpt)
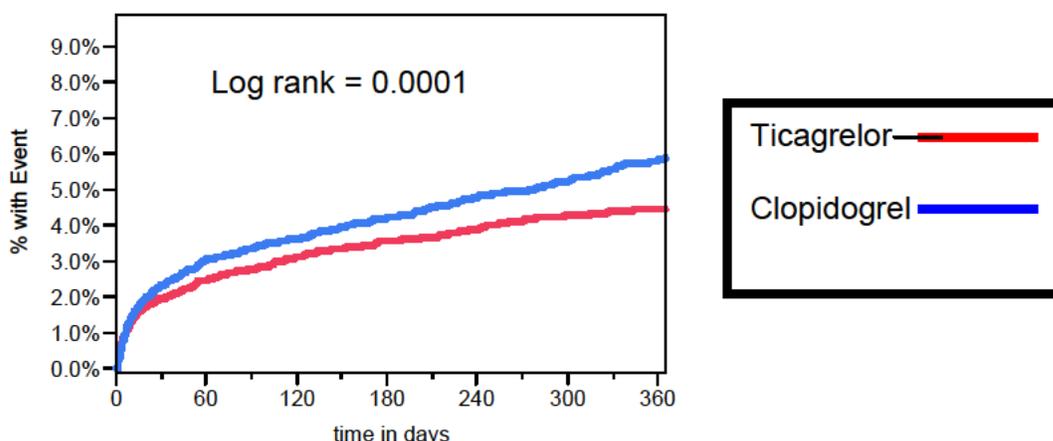
Group	Number failed	Number censored	Percent failed
Ticagrelor 90 mg bd	389	8845	4.21%
Clopidogrel 75 mg od	491	869	5.34%
Combined	880	17581	4.78%

In the all-deaths per patient year analysis of PLATO using the same criterion for defining death (all-cause, adjudicated deaths by actual treatment where the patients took at least one dose of treatment medication), there were 389 total deaths/ 6301 ticagrelor patient years = 62 deaths/ 1000 patient-years vs. 491 deaths/ 6388 clopidogrel patient years = 77 deaths/ 1000 patient-years.

In North America (mostly U.S.), I used the data from the efficacy data set by randomized treatment in patients that received drug. In this important subpopulation, there was a higher frequency of all-cause adjudicated deaths in ticagrelor-treated patients than in clopidogrel –treated patients [35 (3.8%) vs. 29 (3.2%)], respectively. A

Kaplan-Meier curve for deaths in North America by actual treatment after at least one dose is shown in Figure 3. While the overall frequency of death in North America was somewhat lower than in the rest of the world, ticagrelor did not confer a death benefit. Also, in North America there were twice as many deaths attributed to myocardial infarction in the ticagrelor group compared to the clopidogrel group (equal frequency of death from myocardial infarction seen in the rest of the world). In light of the numerical difference in deaths that does not favor ticagrelor, the increased frequency of death from myocardial infarction in the ticagrelor-treated U.S. group and the negative efficacy findings in North America, it appears that there is an unacceptably high risk-benefit ratio in the U.S.

In Appendix A I reviewed the deaths of patients in North America that occurred when the K-M curves began to split until they began to plateau again. There was one case of noncompliance. On further investigation, the U.S. population had more noncompliance than the rest of the world but this difference did not explain the difference in mortality between treatment arms.

Figure 2: K-M: Adjudicated all-cause Mortality, by Actual Treatment (N.A. only), Patients received at Least One Dose of Treatment (source AWCADJ.xpt)

Log-rank = 0.45
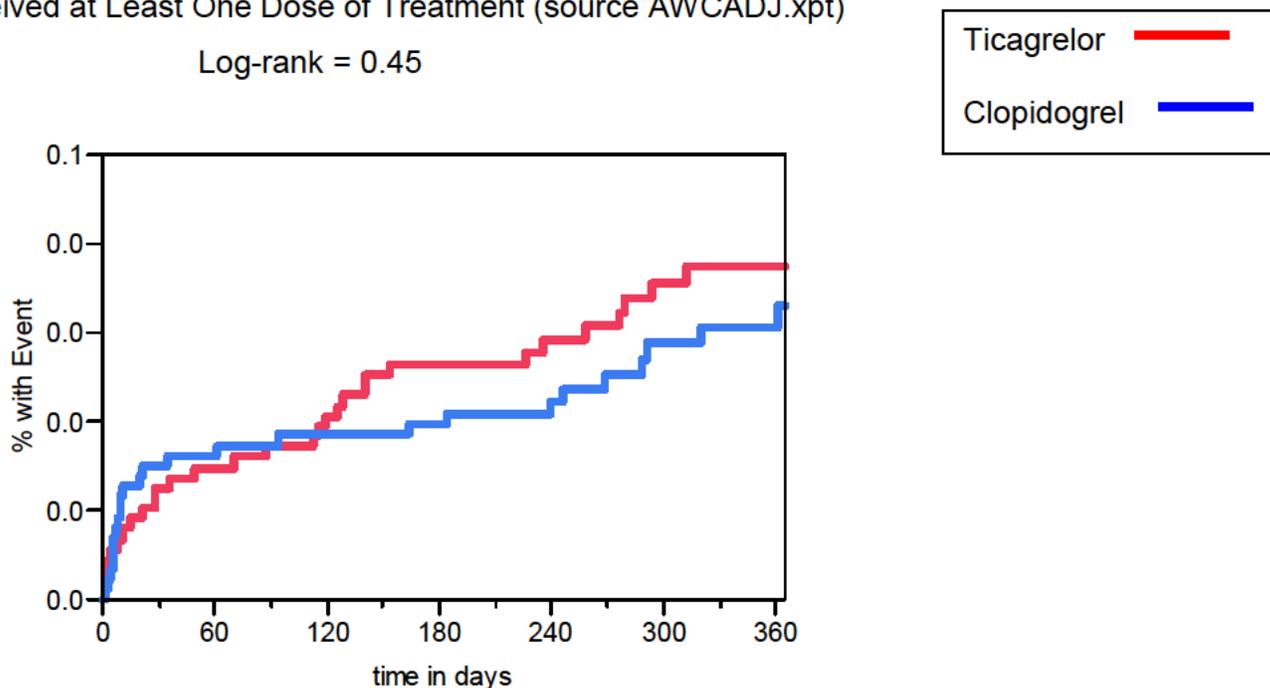
Group	Number failed	Number censored	Percent failed
Ticagrelor 90 mg bd	31	854	3.50%
Clopidogrel 75 mg od	25	852	2.85%
Combined	56	1696	3.30%

Causes of Death

Table 5 provides a categorical breakdown of causes of death. Vascular deaths accounted for most deaths (~ 95% of deaths in both treatment groups) in PLATO. The term "vascular death" includes cardiovascular deaths, cerebrovascular deaths, bleeding deaths and any other death for which there was no clearly documented nonvascular cause. Bleeding deaths were not as common as other causes of death (0.2% of patients) and occurred equally in both groups.

Table 6 is a listing of investigator assignments for cause of death. Causes of death were similar between treatment groups. The most common cause of death was myocardial infarction occurring in about 1% of randomized patients. Sudden death, heart failure, other vascular events and stroke were among the more common causes of death.

Table 5: Sponsor's analysis: Summary of deaths on treatment – safety analysis set

Category	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N=9186
All deaths[a]	283 (3.1%)	339 (3.7%)
Vascular deaths	271 (2.9%)	317 (3.5%)
Bleeding deaths	17 (0.2%)	20 (0.2%)
Trauma	2 (0.0%)	1 (0.0%)
Non-trauma	15 (0.2%)	19 (0.2%)
Non-vascular death	12 (0.1%)	22 (0.2%)

[a] Patients in the full analysis set who did not take any study drug were excluded from the safety analysis set.
Therefore, some deaths that occurred among patients in the full analysis set are excluded from this table.
bd Twice daily dosing; od Once daily dosing.

Source: PLATO study report, p. 251

Table 6: Listed Causes of Death from Efficacy Data Set (by randomized treatment)

```
                                              Randomised Treatment
                                         Ticagrelor       Clopidogrel
                                         90 mg bd         75 mg od
Characteristic                           N - 9333         N - 9291
_____      _____      _____

Aortic dissection                         1 ( 0.0%)        2 ( 0.0%)
Arterial embolism                         0 ( 0.0%)        2 ( 0.0%)
Cancer                                   14 ( 0.2%)       17 ( 0.2%)
Cardiac arrhythmia                       20 ( 0.2%)       28 ( 0.3%)
Death from bleeding (not related to trauma) 13 ( 0.1%)    15 ( 0.2%)
Endocarditis                              0 ( 0.0%)        0 ( 0.0%)
Heart failure                            51 ( 0.5%)       62 ( 0.7%)
Liver failure                             0 ( 0.0%)        1 ( 0.0%)
Multiorgan failure                        9 ( 0.1%)       14 ( 0.2%)
Myocardial infarction                    89 ( 1.0%)       88 ( 0.9%)
Other coronary artery disease             4 ( 0.0%)        4 ( 0.0%)
Other non-vascular cause                  8 ( 0.1%)       11 ( 0.1%)
Other vascular cause                     44 ( 0.5%)       55 ( 0.6%)
Pneumonia                                10 ( 0.1%)        8 ( 0.1%)
Pulmonary embolism                        2 ( 0.0%)        8 ( 0.1%)
Renal failure                             2 ( 0.0%)        5 ( 0.1%)
Respiratory failure                      13 ( 0.1%)       12 ( 0.1%)
Ruptured aortic aneurysm                  1 ( 0.0%)        0 ( 0.0%)
Sepsis                                    7 ( 0.1%)       23 ( 0.2%)
Stroke                                   20 ( 0.2%)       18 ( 0.2%)
Sudden death                             60 ( 0.6%)       77 ( 0.8%)
Suicide                                   1 ( 0.0%)        1 ( 0.0%)
Trauma                                    3 ( 0.0%)        1 ( 0.0%)
Unstable angina                           7 ( 0.1%)        8 ( 0.1%)
Valvular disease                          0 ( 0.0%)        1 ( 0.0%)
Vascular death, sub-classification missing  0 ( 0.0%)      1 ( 0.0%)
Unknown                                  39 ( 0.4%)       58 ( 0.6%)
```

Summary
In PLATO, ticagrelor-treated patients had a lower risk of all-cause mortality compared to clopidogrel- treated patients (4.28% vs. 5.45% when examining deaths by randomized treatment and examining efficacy period). These differences were statistically significant. In North America (mostly U.S.), however, the results were different. There was a higher frequency of all-cause adjudicated deaths in ticagrelor-treated patients than in clopidogrel –treated patients.

Vascular deaths were the most common cause of death. Within the category of vascular death, the most common cause of death for both treatments was myocardial infarction (9.3% of all deaths for both treatment groups). Other common causes of death were sudden death and heart failure. The frequency of dying from stroke was higher in the ticagrelor group (2.2% of all deaths for ticagrelor, 1.9% of all deaths for clopidogrel). In an analysis to be discussed later, for patients with a preexistent history of cerebrovascular, carotid artery or vertebrobasilar disease, 1 of 99 (1%) died after stroke in both groups. Bleeding deaths were not as common as other causes of death (0.2% of patients) and occurred equally in both groups. In the U.S. there were twice as many deaths attributed to myocardial infarction in the ticagrelor group compared to the clopidogrel group.

7.3.2 Nonfatal Serious Adverse Events

According to the sponsor's analysis, as shown in Table 7, there were 6 SAEs that occurred ≥ 0.2% in the ticagrelor treatment group where there were ≥0.2% absolute or 50% relative difference between frequencies in the clopidogrel treatment group. Dyspnea, cerebrovascular accident, post procedural hemorrhage, anemia, abdominal pain and epistaxis are included in the list. By my analysis, in which I combined different PT terms to reveal AEs and SAES that could be obscured by "splitting", I discovered that there were other SAE terms that fell into that category including hematuria, intracranial hemorrhage or hematoma, gastroenteritis, pulmonary embolism, and vertigo/dizziness/giddiness. These are listed in Table 8. These events are further explored in the body of the review.

Table 7: Sponsor's analysis: SAEs (≥0.2% where the difference between groups was ≥0.2% absolute or 50% relative)

Characteristic	Ticagrelor 90 mg bd (N = 9235)	Clopidogrel 75 mg od (N = 9186)
Dyspnea	65 (0.7%)	36 (0.4%)
Cerebrovascular accident	62 (0.7%)	42 (0.5%)
Post procedural hemorrhage	51 (0.6%)	37 (0.4%)
Anemia	29 (0.3%)	22 (0.2%)
Abdominal pain	19 (0.2%)	8 (0.1%)
Epistaxis	15 (0.2%)	9 (0.1%)

Source: Adapted from table from the Summary of Safety, p. 99

Some of the most common and important SAEs were bleeding related: hematuria, intracranial hemorrhage or subdural or other intracranial hematoma, epistaxis, retroperitoneal hemorrhage or hematoma. In the following sections of my review it will become clear that spontaneous bleeding in general occurred with a higher frequency in the ticagrelor group. Since ticagrelor at the doses used in PLATO has a higher percentage of inhibition of platelet aggregation (IPA) than clopidogrel, as well as quicker action because it is not a prodrug, one would rightly expect there to be a higher frequency of spontaneous bleeding events and spontaneous serious bleeding events in the ticagrelor treatment group.

There was a higher frequency of dyspnea SAEs in the ticagrelor treatment group. Dyspnea was a common and important AE in the ticagrelor treatment group in PLATO as will be discussed later in the review.

Interestingly, while there fewer deaths with a preferred term of pulmonary embolism (2 for ticagrelor patients vs. 8 for clopidogrel patients), there was an increased frequency of serious AEs of pulmonary embolism in the ticagrelor treatment group [31 (0.34%)

ticagrelor, 20 (0.22%) clopidogrel]. Pulmonary embolism led to discontinuation more often in the ticagrelor group than in the clopidogrel group in PLATO [15 (0.2%) in the ticagrelor group vs. 7 (0.2%) in the clopidogrel group]. Also in the prasugrel summary of safety, there were 3 cases of pulmonary embolism that led to death, all in the prasugrel treatment group. There were 3 SAE pulmonary embolism cases in the prasugrel group and 2 pulmonary embolism SAEs in the clopidogrel group. 4 prasugrel patients discontinued for pulmonary embolism compared to 2 clopidogrel patients. In both PLATO and TRITON-TIMI 38 (pivotal trial for prasugrel) there were very few cases of peripheral embolism.

In PLATO, there was an increased risk for stroke (usually an embolic event) in the ticagrelor treatment group and a slightly higher number of stroke deaths (13 vs. 10 when counting stroke deaths on or off treatment), one adjudicated as being related to an embolic event. Having a history of cerebrovascular disease greatly increased the risk of a cerebrovascular event during the PLATO trial, with a greater increase in the ticagrelor arm. In PLATO, 8/99 (8.1%) patients who had a history of cerebrovascular disease upon study entry had cerebrovascular events (including TIA) during the trial compared to 4/99 (4.0%) patients in the clopidogrel arm. Of those patients, 2 of the ticagrelor treated patients had hemorrhagic cerebral events compared to 1 of the clopidogrel-treated patients.

It might be reasonable to hypothesize that ticagrelor increases the risk for embolic events from the pulmonary and carotid arteries and deep venous thromboses. Perhaps ticagrelor is more likely to cause forming plaque to break off and embolize but this is just conjecture at this point.

There were slightly more SAEs of sick sinus syndrome, atrial flutter, syncope/presyncope, vertigo/dizziness/giddiness. This will be addressed later in the section on ventricular pauses.

The sponsor's analysis did not differ greatly from mine. The sponsor reported that SAEs of dyspnea, cerebrovascular accident, post procedural hemorrhage, pulmonary embolism, abdominal pain, anemia and epistaxis occurred with a higher frequency (difference ≥0.2% absolute or 50% relative) with ticagrelor compared to clopidogrel. Additionally, by the sponsor's analysis, SAEs of gastrointestinal ulcerations and perforations occurred with twice the frequency in the ticagrelor group [38 (0.4%)] as compared to the clopidogrel group [18 (0.2%)]. There was no difference between treatment groups in "Major Bleeds" (which will be defined later) related to procedures. See Table 8 for a tabular presentation of my SAE analysis using renamed AE terms. This analysis is similar to the sponsor's.

Table 8: Serious AE Table (analysis done using renamed terms)

Serious Adverse Event	ticagrelor 90 mg bd N=9235	clopidogrel 75 mg od N=9186	RR	95% CI
Hematuria	23 (0.25%)	12 (0.13%)	1.91	(0.95, 3.83)
Intracranial hemorrhage or subdural or other hematoma	30 (0.32%)	16 (0.17%)	1.87	(1.02, 3.42)
Subcutaneous hemorrhage, Ecchymosis, Hematoma	23 (0.25%)	14 (0.15%)	1.63	(0.84, 3.17)
Sick sinus syndrome	8 (0.09%)	5 (0.05%)	1.59	(0.52, 4.86)
Atrial Flutter	11 (0.12%)	7 (0.08%)	1.56	(0.61, 4.03)
Pulmonary Embolus	31 (0.34%)	20 (0.22%)	1.54	(0.88, 2.7)
Epistaxis	15 (0.16%)	10 (0.11%)	1.49	(0.67, 3.32)
Retroperiotoneal hematoma or hemorrhage	9 (0.1%)	6 (0.07%)	1.49	(0.53, 4.19)
Diarrhea	15 (0.16%)	10 (0.11%)	1.49	(0.67, 3.32)
Dyspnea	79 (0.86%)	53 (0.58%)	1.48	(1.05, 2.1)
Syncope, Presyncope	51 (0.55%)	35 (0.38%)	1.45	(0.94, 2.23)
Vertigo, Dizziness, Giddiness	23 (0.25%)	16 (0.17%)	1.43	(0.76, 2.7)
PCI -related Bleed or Hematoma	38 (0.41%)	27 (0.29%)	1.4	(0.86, 2.29)
Thromoembolic event	45 (0.49%)	34 (0.37%)	1.32	(0.84, 2.05)
Cyanosis, Apnea, Respiratory Failure, Hypoxia	21 (0.23%)	16 (0.17%)	1.31	(0.68, 2.5)
Gastrointestinal/ Anal bleed	108 (1.17%)	87 (0.95%)	1.23	(0.93, 1.64)
Bleed, Hematoma	295 (3.19%)	243 (2.65%)	1.21	(1.02, 1.43)

7.3.3 Dropouts and/or Discontinuations

Table 9 provides the reasons for premature permanent discontinuation of study drug. The dropout and discontinuation rate for ticagrelor was somewhat higher for ticagrelor-treated patients than for clopidogrel-treated patients (23.7% vs. 21.8%, respectively). Most discontinuations were attributed to patients "not willing to continue treatment" (10.2% vs. 9.4%, respectively) and adverse events (7.5% vs. 6.1%, respectively). The greatest difference in discontinuations between the two treatment groups was in the category of 'discontinuation because of adverse events (DAEs), (7.5% vs. 6.1%, respectively) which was mostly attributed to dyspnea followed by epistaxis. Table 10 provides a tabular listing of the most common DAEs. The reasons that patients were not willing to continue treatment were not elaborated upon in the submission.

Table 9: Disposition

	Ticagrelor	Clopidogrel
	N	N
Randomization	9333	9291
Treated	9235 (98.9)	9186 (98.9)
Permanent Discontinuation	2186 (23.7)	1999 (21.8)
Adverse event	690 (7.5)	556 (6.1)
Index criteria not met	22 (0.2)	16 (0.2)
Unwilling to continue	946 (10.2)	859 (9.4)
Severe noncompliance	41 (0.4)	47 (0.5)
Other	479 (5.2)	518 (5.6)
Unknown	4 (0)	1 (0)
Lost to follow up	4 (0)	4 (0)
Patients Completed	7049 (76.3)	7187 (78.3)

Data derived from sponsor's tables 11.1.1.2.2 and 11.1.1.4.1 in PLATO study report

Table 10: PLATO: Summary by PATIENT of the most common AEs (>0.1% in either group) leading to discontinuation

Characteristic	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N=9186
Patients with at least one event	687 (7.4%)	500 (5.4%)
Dyspnea	77 (0.8%)	10 (0.1%)
Epistaxis	38 (0.4%)	12 (0.1%)
Atrial fibrillation	27 (0.3%)	37 (0.4%)
Intracardiac thrombus	22 (0.3%)	17 (0.2%)
Gastrointestinal hemorrhage	19 (0.2%)	12 (0.1%)
Contusion	17 (0.2%)	7 (0.1%)
Nausea	15 (0.2%)	7 (0.1%)
Pulmonary Embolism	15 (0.2%)	7 (0.1%)
Diarrhea	14 (0.2%)	19 (0.1%)

Source: PLATO study report p. 262

7.3.5 Submission Specific Primary Safety Concerns

Bleeding

Bleeding was the major safety concern when the sponsor was designing PLATO. The primary safety endpoint designated in PLATO was time to first major bleeding event.

Most of the Phase 2 studies did not have adjudication committees for bleeding events, and bleeding was presented by investigator reported categorization. PLATO used an independent committee (ICAC) to adjudicate bleeding events. The ICAC judged each bleeding event against a set of definitions to maintain consistency and quality (Table 11).

The comparison of PLATO and TIMI definitions for different categories of bleeding are listed in Table 11. The PLATO categories consider certain bleeds that are likely to be severe, such as intrapericardial bleed with tamponade and intracranial hemorrhage, to be unconditionally major/ life-threatening while according to the TIMI definition these two types of bleeds are counted as minor, minimal or not at all unless they are symptomatic or are accompanied by a hemoglobin decrease of > 5 gm/dL. Also, when it comes to "major other" and minor and minimal bleeds, the PLATO definitions are concerned more with level of disability or intervention required. The TIMI definitions are more focused on drops in hemoglobin which captures fewer events. When considering bleeds that were most severe, the PLATO criteria may fall short because a patient meets the criteria for a major/life-threatening bleed solely if the patient is transfused with 4 or more units of blood or packed red blood cells. Transfusion may be more a decision of clinical practice as opposed to actual "need". Patients could also meet the criteria of a Major bleed by having 2 or more transfusions. This criterion could have also been more influenced by practice habit than by severity of bleed.   As it turned out, in PLATO, the PLATO-defined "Total Major" (which includes "Major/Life-threatening" and "Major") assigned bleeding events exceeded the TIMI defined Major + Minor bleeding events. This means that it was easier to meet the criteria for a PLATO-defined Major bleed than a TIMI-Major bleed.

As an exploratory analysis, I redefined the PLATO definitions to exclude transfusion. I found that the relative risk of having Major, Life-threatening and Fatal bleeding events between ticagrelor-treated and clopidogrel-treated patients was approximately the same as was found when I analyzed the PLATO definitions.

Table 11: Comparisons of PLATO and TIMI Bleeding Severity Scales

PLATO scale	TIMI scale

PLATO-defined Major Fatal/Life threatening
 	
Any one of the following:
  *Fatal
  *Intracranial
  *Intrapericardial bleed with tamponade
  *Hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery
  *Clinically overt or apparent bleeding associated with a decrease in hemoglobin of more than 5 gm/dL
  *Transfusion of 4 or more units whole blood or PRBCs for bleeding
	TIMI-defined Major
	Intracranial, or Clinically significant overt signs of hemorrhage associated with a drop in hemoglobin of > 5 g/dL (or, when hemoglobin is not available, an absolute drop in hematocrit of > 15%)

PLATO-defined Major Other Any one of the following: * Significantly disabling (eg, intraocular with permanent vision loss) * Clinically overt or apparent bleeding associated with a decrease in hemoglobin of 3 to 5 g/dL * Transfusion of 2-3 units (whole blood or PRBCs) for bleeding.	**TIMI-Life threatening** A subset of TIMI-Major that meets any of the following: is fatal; leads to hypotension requiring treatment with intravenous inotropic agents; requires surgical intervention for ongoing bleeding; necessitates the transfusion of 4 or more units of blood (whole blood or packed red blood cells) over a 48-hour period; is a symptomatic ICH
PLATO-defined Minor Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).	**TIMI-defined Minor** Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin of 3 to <=5 g/dL (or, when hemoglobin is not available, a fall in haematocrit of 9 to<=15%) NOTE: TRITON used 3 to <5 g/dL
PLATO-defined Minimal All others not requiring intervention or treatment	**TIMI-defined Minimal** Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin <3 g/dL (or, when hemoglobin is not available, a fall in hematocrit of <9%)

Source: ISS, p. 50.

The sponsor was successful in meeting their primary safety endpoint (time to first major bleeding event) and this is demonstrated in Table 12. Note that the time to first event is not calculated for 'Life-threatening' and 'Major Other' bleeding because it may have been preceded by a more severe bleed. Also, patients may be counted in >1 bleeding event category.

Table 12: Sponsor's analysis: K-M% of major bleeds and hazard ratios

Characteristic	Ticagrelor 90 mg bd N = 9235		Clopidogrel 75 mg od N = 9186		
	Number of bleeding events	total bleeding events (%), KM % in one year	Number of bleeding events	total bleeding events(%), KM % in one year	Hazard ratio (95%CI)
Primary safety					
Total Major	1031	961 (10.4%),11.6%	997	929 (10.1%), 11.2%	1.04 (0.95, 1.13)
Secondary safety endpoints - Total Major bleeding by severity -					
Major Fatal/ Life-threatening	516	491 (5.3%), 5.8%	505	480 (5.2%), 5.8%	1.03(0.90, 1.16)
Fatal	21	20 (0.2%), 0.3%	24	23 (0.3%), 0.3%	0.87(0.48, 1.59)
Life-threatening	495	471 (5.1%), -	481	459 (5.0%), -	-
Major Other	515	494 (5.3%), -	492	474 (5.2%), -	-

Source: p. 182, PLATO study report

Despite this success, it is important to not downplay a few pieces of important information regarding bleeding:

In Table 13, it can be seen that there were numerically more major bleeds in the ticagrelor group. 619/961 (64.4%) and 654/929 (70.4%) of the patients with major bleeds had CABG major bleeds in the ticagrelor treatment group and clopidogrel treatment group, respectively. Also, most of the patients who had procedural bleeds had CABG-related procedural bleeds [619/756 (81.9%) vs. 654/775 (84.4%)] for ticagrelor and clopidogrel treatment groups, respectively. Nonprocedural (spontaneous) bleeds, accounted for [235/961(24.5%) vs. 180/929 (19.4%)] of the major bleeds, for ticagrelor and clopidogrel, respectively. The greatest difference between treatment groups was in the category of nonprocedural bleeds [HR 1.31 (1.08,1.60)].The reason that the breakdown of patients by type of major bleeds exceeds the total breakdown of patients with different major bleeds is that approximately 30 patients had both procedural and non-procedural major bleeds in each treatment group.

Ticagrelor-treated patients who had low baseline eGFRs (< 30 cc/min) were more likely to have adjudicated "Major" bleeding events than ticagrelor-treated patients with eGFRs≥ 30 cc/min. 19.0% of ticagrelor treated patients with baseline eGFRs < 30 cc/min had major bleeding events whereas 10.3% of ticagrelor-treated patients with ≥ 30cc/min had major bleeds. 11.3% of clopidogrel-treated patients with baseline eGFRs < 30cc/min had major bleeding events whereas 9.9% of clopidogrel-treated patients with baseline eGFRs ≥ 30cc/min had major bleeds. See Table 14.

There were insufficient numbers of patients with mild liver disease to evaluate the risk of bleeding in patients with preexisting liver disease. Patient with moderate to severe liver disease were excluded from the study.

Table 13: Patients with Adjudicated Major Bleeds by type (CABG, procedural, nonprocedural) by Actual Treatment (Patients Received at least One Dose of Treatment)

Characteristic	Ticagrelor 90 mg bd N=9235 (%)	Clopidogrel 75 mg od N=9186 (%)
Major Bleed	961 (10.4)	929 (10.1)
CABG major	619 (6.7)	654 (7.1)
Procedural Major Bleeds	756 (8.2)	775 (8.4)
Nonprocedural Major Bleeds	235 (2.5)	180 (2.0)
Non-CABG Procedural Major Bleeds	143 (1.5)	133 (1.4)

Derived from PLATO dataset AWCADJ.xpt

Table 14: Frequency of Major Bleeds by Degree of Renal Disease and Presence of Liver Disease at Randomization

Characteristic	Category	ticagrelor total patients in category	total patients with major bleed	%	clopidogrel total patients in category	total patients with major bleed	%	RR
	N	9235	961	10.4	9186	929	10.1	1.03
Renal Disease								
	eGFR < 15 cc/min	8	2	25	9	0	0	
	eGFR 15-< 30 cc/min	113	21	18.6	133	16	12	1.54
	eGFR 30-<60 cc/min	1767	220	12.5	1812	233	12.9	0.97
	eGFR 60-<90 cc/min	3862	424	11	3808	396	10.4	1.06
	eGFR >=90 cc/min	3307	272	8.2	3252	262	8.1	1.02
Liver Disease	yes	196	22	11.2	217	19	8.8	1.28
	no	9039	939	10.4	8969	910	10.1	1.02

There was a statistically significant difference in major + minor bleeding events between treatment groups. This is demonstrated in Figure 3.

Figure 3: K-M time to event analysis for major + minor bleeds (requiring any intervention)
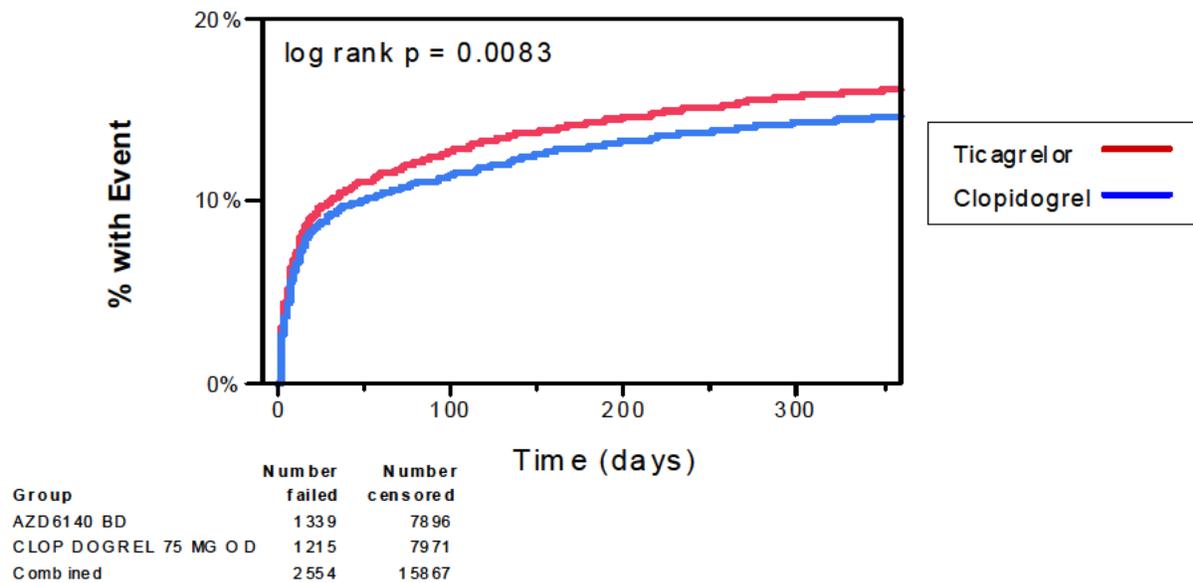
There was no increase in fatal bleeding events in the ticagrelor arm compared to the clopidogrel arm. See Table 15. Two fatal bleeding events were listed more than once because of the decision to subcategorize by bleeding events. Most fatal bleeds were not related to CABG or other procedures.

Table 15: Fatal Bleeding Events and Corresponding Characteristics

Characteristic	Total bleeding events		Patients with > =1 bleeding event	
	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Total Fatal	21	24	20 (0.2%)	23 (0.3%)
Not related to CABG surgery	15	17	15 (0.2%)	16 (0.2%)
Not procedure-related	13	13	13 (0.1%)	12 (0.1%)
Non-CABG procedural	2	4	2 (0.0%)	4 (0.0%)
Procedure-related	8	10	8 (0.1%)	10 (0.1%)
Non-coronary	1	2	1 (0.0%)	2 (0.0%)
Coronary	7	8	7 (0.1%)	8 (0.1%)
CABG-related	6	6	6 (0.1%)	6 (0.1%)
PCI-related	1	2	1 (0.0%)	2 (0.0%)
Coronary angiography related	0	0	0	0

Source: PLATO study report p. 3515

Since effectiveness of ticagrelor was not demonstrated in North America in PLATO, it is important to explore the K-M curve for major + minor bleeding in North America. One might expect that the difference between treatment groups in major + minor bleeds would be absent if the drug was not effective because of low IPA levels. The K-M curves are displayed in the Figure 4. While the log rank score is 0.3 for major + minor bleeds between K-Ms curves for both treatment groups in North America, the trend of increased overall bleeding in the ticagrelor treatment group is still present.

Figure 4: K-M Time to Event Analysis for Major + Minor Bleeds in North America
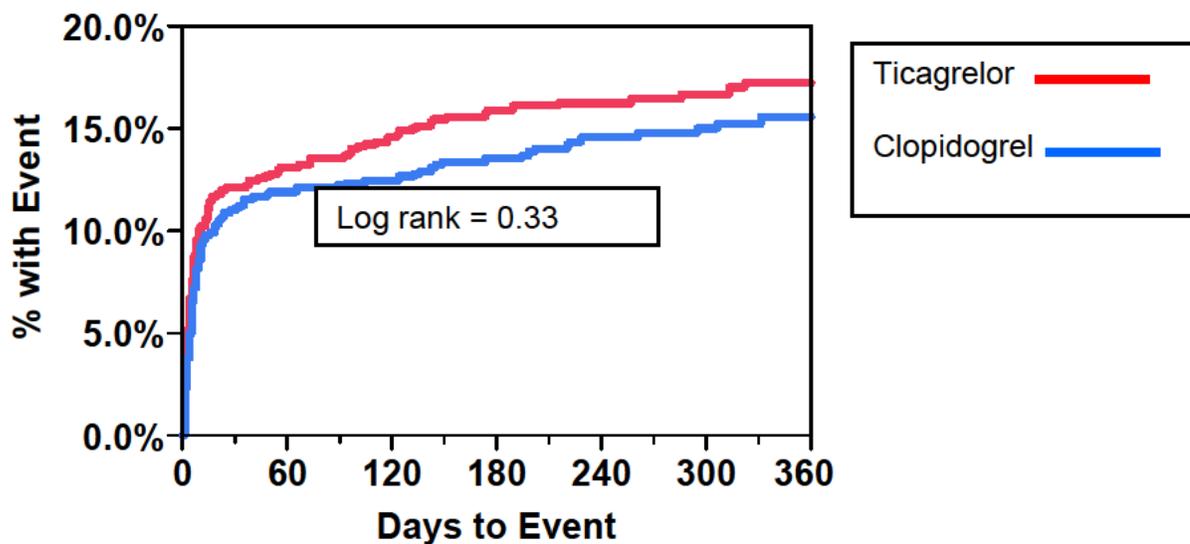
Group	Number failed	Number censored
AZD6140 BD	137	748
CLOPIDOGREL 75 MG OD	122	745
Combined	259	1493

Table 16 shows the bleeding data by region in tabular form.

Table 16: Risk of Bleeding by Region

All Bleeds	Treatment	At Risk N	PLATO Major (K-M%)	PLATO Lifethreatening/ Fatal (K-M%)	PLATO Fatal (K-M%)
Outside N.A.	Ticagrelor	8350	858 (10.3)	441 (5.3)	18 (0.2)
	Clopidogrel	8319	831 (10.0)	438(5.3)	21 (0.3)
N.A.	Ticagrelor	885	103 (11.6)	50 (5.6)	2 (0.2)
	Clopidogrel	867	98 (11.3)	44 (5.1)	2 (0.2)

Since aspirin dose was proposed by the sponsor to account for the decreased effectiveness of ticagrelor in the North America, I constructed Table 17 that shows the numbers of patients who had PLATO-defined Major, Lifethreatening/Fatal, and Fatal bleeding by median aspirin dose. If aspirin diminishes the effect of ticagrelor, one might expect decreased bleeding frequencies in patients on higher dose of aspirin. While there are low numbers of patients that received median high doses of aspirin, there is no discernable pattern of changes in bleeding by median aspirin dose. The absence of aspirin effect on bleeding was also seen when examining the subset of patients with CABG-related bleeding.

Table 17: Risk of Bleeding by Median Aspirin Dose

ASA dose	Major		Lifethreatening/Fatal		Fatal	
	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel
<100 mg	N=7506 n (%) 732 (9.8)	N=7482 n (%) 684 (9.1)	N=7506 n (%) 360 (4.8)	N=7482 n (%) 340 (4.5)	N=7506 n (%) 17 (0.2)	N=7482 n (%) 13 (0.2)
>=100 -< 300 mg	N=497 n (%) 62 (12.5)	N=498 n (%) 60 (12.0)	N=497 n (%) 31 (6.2)	N=498 n (%) 32 (6.4)	N=497 n (%) 0 (0)	N=498 n (%) 0 (0)
>= 300mg	N=422 n (%) 40 (9.5)	N=454 n (%) 39 (8.6)	N=422 n (%) 20 (4.7)	N=454 n (%) 16 (3.5)	N=422 n (%) 0 (0)	N=454 n (%) 1 (0.2)
Unknown	N=810 n (%) 127 (15.7)	N=752 n (%) 146 (19.4)	N=810 n (%) 80 (9.9)	N=752 n (%) 92 (12.2)	N=810 n (%) 3 (0.4)	N=752 n (%) 9 (1.2)

Spontaneous bleeds accounted for ~ ¼ of all major bleeds. There was a significantly higher frequency of spontaneous bleeding in the ticagrelor group in PLATO as compared to the clopidogrel group. This is demonstrated graphically with K-M type to analysis curves in Figure 5. This difference in spontaneous bleeding frequency accounts for the difference in overall bleeding between the treatment groups. This pattern of increased spontaneous bleeding in the ticagrelor group was also evident in the North American population. One could make a conjecture that this increased frequency of spontaneous bleeding in the ticagrelor treatment group was because of the increased platelet aggregation inhibition of ticagrelor. Figure 5 is a K-M time to event analysis of the difference between groups in time to event for first spontaneous bleed. Figure 6 is a whisker plot that shows that the pattern is present at all severities of spontaneous bleeding.

Figure 5: KM: Non-procedural (spontaneous) Major and Minor Bleeds
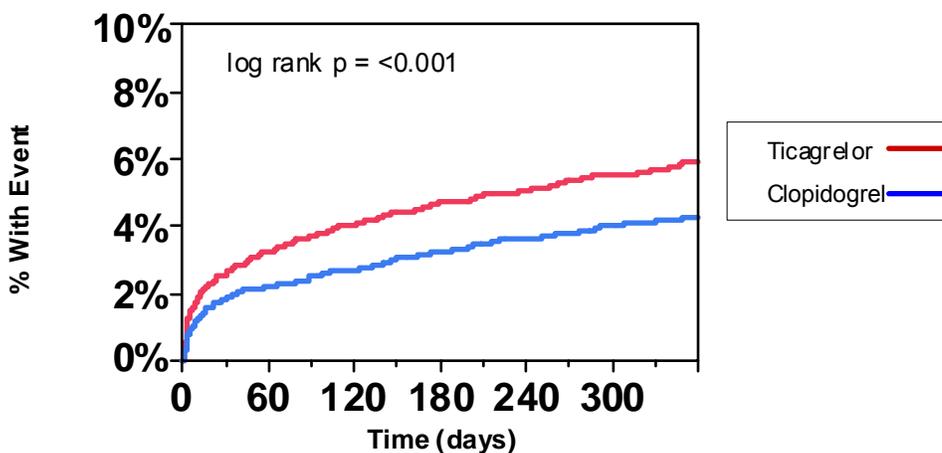
Group	Number faled	Number censored
AZD6140 BD	457	8778
CLOPIDOGREL 75 MG OD	332	8854
Combined	789	17632

Figure 6: Hazard Ratio (95%CI) for non-procedural bleeds by severity
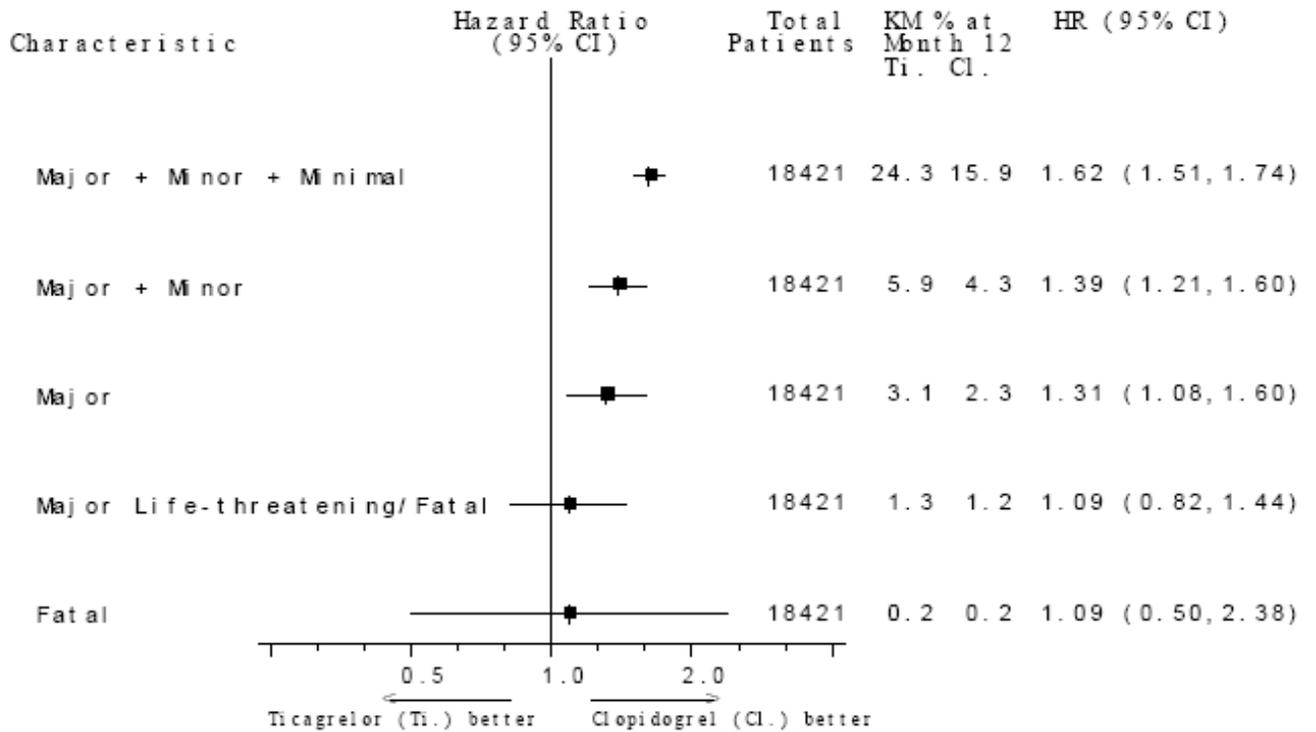
Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti. Cl.	HR (95% CI)
Major + Minor + Minimal		18421	24.3 15.9	1.62 (1.51, 1.74)
Major + Minor		18421	5.9 4.3	1.39 (1.21, 1.60)
Major		18421	3.1 2.3	1.31 (1.08, 1.60)
Major Life-threatening/Fatal		18421	1.3 1.2	1.09 (0.82, 1.44)
Fatal		18421	0.2 0.2	1.09 (0.50, 2.38)

Ticagrelor (Ti.) better ← → Clopidogrel (Cl.) better

Source: PLATO study report, p. 207

The 2 most common spontaneous major bleeds were as follows:

1. Gastrointestinal: [1.3% of ticagrelor-treated and 1.0% of clopidogrel-treated patients had major gastrointestinal bleeds .
2. Intracranial [0.3% of ticagrelor-treated and 0.15% of clopidogrel-treated patients had major intracranial bleeds.

While there was little difference in the frequency of spontaneous bleeds that resulted in death (13 for ticagrelor and 12 for clopidogrel), in the ticagrelor arm, 11 of the 13 (84.6%) deaths were from intracranial hemorrhages and in the ticagrelor arm 1/12 (8.3%) deaths was from an intracranial hemorrhage. All but one of the patients who had an intracranial hemorrhage also had a stroke. One ticagrelor-treated patient died from an intracranial hemorrhage thought to be secondary to head trauma. Of the other ticagrelor patients that died of bleeding, one was from pericardial bleeding and the other was from hemoptysis. Of the spontaneous bleeds that resulted in fatal events in the clopidogrel group, 5/13 were gastrointestinal and only 1 was intracranial. The reason that the total number of fatal bleeds is 12 in the clopidogrel group and the number of reasons for death is 13 in the clopidogrel group is that one clopidogrel-treated patient had 2 bleeds that were considered to be fatal.

Table 18 provides a tabular listing of all major/fatal-lifethreatening and fatal nonprocedural bleeding events by primary anatomic location.

Figure 7 displays a Kaplan Meier time-to-event curve for hemorrhagic stroke. Most events occurred within the first 200 days of enrollment.

Table 18: Sponsor's Analysis: Summary of 'Major Fatal/Life-threatening' and Fatal non-procedure bleeding events by primary anatomic location

Primary location	Total Major		Fatal/Life-threatening		Fatal	
	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Total bleeds	251	190	109	99	13	13
Gastrointestinal	124	94	47	47	0	5
Intracranial	27	14	27	14	11	1
Urinary	13	14	4	4	0	0
Pericardial	11	11	10	10	1	2
Subcutaneous/dermal	11	4	3	1	0	1
Epistaxis	6	8	0	3	0	0
Haemoptysis	2	3	2	0	1	0
Retroperitoneal	0	3	1	3	0	1
Intraocular	0	2	0	0	0	0
Intraarticular	0	0	0	0	0	0
Other	46	37	15	17	0	3

Source: Intracranial hemorrhage report, p. 8

Figure 7: KM: Hemorrhagic stroke time to event curve
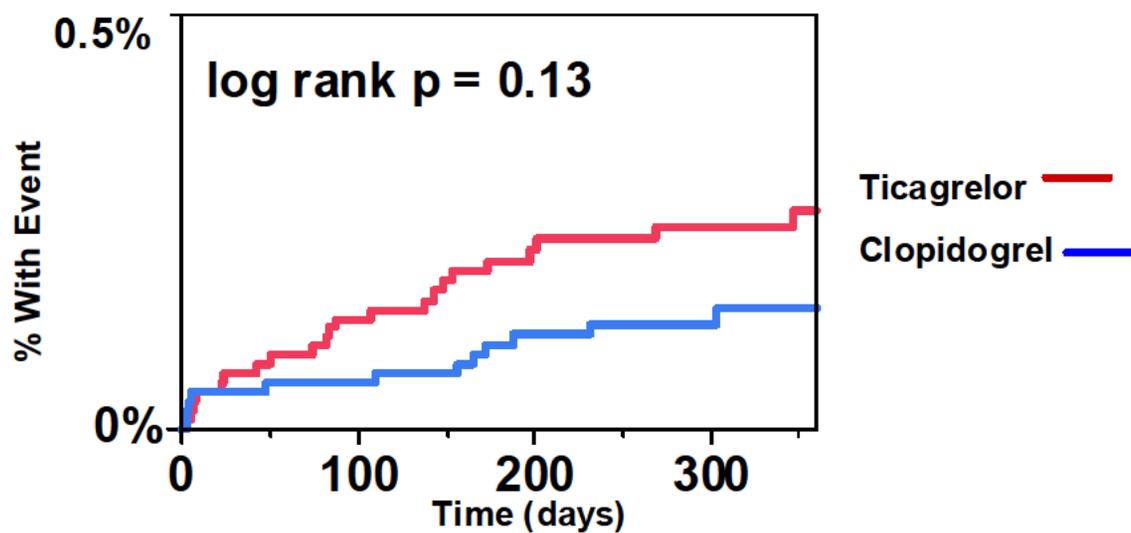
Group	Number failed	Number censored	KM% failed
Ticagrelor	22	9213	0.24%
Clopidogrel	13	9173	0.14%

Spontaneous bleeding is an important safety issue, particularly when it comes to intracranial bleeding. If approved, the ticagrelor label should include a warning about increased risk for intracranial bleeding and specifically, hemorrhagic strokes.

Bleeding Related to CABG Surgery

Of the 18,421 patients in the safety data set, 1584 patients received CABG surgery (~ 12% over the first year). Table 19 shows the bleeding events related to CABG surgery by treatment in the safety analysis set (patient received one or more doses of study treatment). Most patients had CABG related bleeds. There was a slightly lower CABG-related frequency of bleeding in most PLATO-defined categories of bleeding for ticagrelor-treated patients. Since there was a slightly higher risk of minimal bleeding in ticagrelor-treated patients it is attractive to think that because of its reversibility, ticagrelor may have converted some minor bleeds or even major bleeds into minimal bleeds.

Table 19: Summary of Bleeding Events Related to CABG surgery – safety analysis set

Characteristic/Bleed Severity	Ticagrelor 90 mg bd	Clopidogrel 75 mg od
Patients with CABG procedures	770 (100%)	814 (100%)
No bleeding event	33 (4.3%)	31 (3.8%)
Any bleeding event	737 (95.7%)	783 (96.2%)
Major	619 (80.4%)	654 (80.3%)
Major Fatal/Life-threatening	329 (42.7%)	341 (41.9%)
Fatal	6 (0.8%)	6 (0.7%)
Major Other	290 (37.7%)	313 (38.5%)
Minor	47 (6.1%)	58 (7.1%)
Minimal	71 (9.2%)	71 (8.7%)

Source: PLATO study report, p. 199

Table 20 provides data on major, life-threatening/fatal, and fatal CABG-related bleeding. First, it should be noticed that there were more CABG procedures done within 96 hours of discontinuing study drug in the ticagrelor treatment group. This difference between groups is not explained in the submission and it is not clear if there is anything other than chance that could explain this finding. Second, there was a low frequency of CABG-related deaths in both treatment groups. Third, CABG done within the first 24 hours of stopping study drug resulted in a numerically higher frequency of "fatal/life-threatening bleeds" than when CABG was done after longer periods of stopping study drug. Fourth, there were numerical differences between treatment groups in CABG-related bleeding complications depending on when the drug was stopped prior to CABG. CABG done between 24 and 96 hours (4 days) after stopping study drug resulted in a numerically higher frequency of both major and fatal/ life-threatening bleeds in the ticagrelor group than in the clopidogrel group and was accompanied by a larger volume of chest tube drainage and transfusions. When CABG was done after 96 hours of stopping

study drug, the ticagrelor arm had a more favorable bleeding profile. There was a small trend of higher frequencies of major to fatal bleeds in the ticagrelor group when CABG was done within 96 hours after stopping study drug. When CABG was done after 96 hours, the trend was reversed so that there was a higher frequency of bleeds in the clopidogrel arm. This observation brings into question the "quick offset" of the antiplatelet effect in ticagrelor treated patients which would be expected if the drug was indeed "reversible". I agree with the sponsor's suggestion to wait if possible until 5 days after stopping ticagrelor to perform CABG to decrease the frequency and severity of CABG-related bleeding

Table 20: Sponsor Analysis: ICAC-adjudicated PLATO-defined 'Major, Life-threatening/Fatal, Fatal' CABG-related bleeding by time from last dose of study drug to procedure – safety analysis set

| | Patients with CABG | | Major | | Life-threatening/Fatal | | Fatal | |
Hours from last dose to CABG	Tica-grelor 90 mg bd	Clopi-dogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od
0-24	84	88	70 (83.3%)	78 (88.6%)	55 (65.5%)	52 (59.1%)	2 (2.4%)	1 (1.1%)
>24-48	106	86	95 (89.6%)	70 (81.4%)	50 (47.2%)	42 (48.8%)	1 (0.9%)	1 (1.2%)
>48-72	114	73	94 (82.5%)	56 (76.7%)	56 (49.1%))	33 (45.2%)	0	0
>72-96	84	69	72 (85.7%)	54 (78.3%)	39 (46.4%)	29 (42.0%)	1 (1.2%)	3 (4.3%)
>96-120	79	96	59 (74.7%)	76 (79.2%)	22 (27.8%)	27 (28.1%)	1 (1.3%)	0
>120-144	91	110	67 (73.6%)	83 (75.5%)	29 (31.9%)	45 (40.9%)	0	1 (0.9%)
>144-168	74	107	56 (75.7%)	87 (81.3%)	25 (33.8%)	40 (37.4%)	0	0
8-14 days	109	147	86 (78.9%)	123 (83.7%)	43 (39.4%)	65 (44.2%)	1 (0.9%)	0
Total	**741**	**776**	**599 (80.8%)**	**627 (80.8%)**	**319 (43.0%)**	**333 (42.9%)**	**6 (0.8%)**	**6 (0.8%)**

Source: PLATO study report, p. 201

Because many of the ticagrelor-treated patients were also on clopidogrel within 7 days of having their CABG procedure, I did a separate analysis in which only the ticagrelor-treated patients that did not receive clopidogrel within 7 days of CABG were included. In Table 21 it can be seen that most patients in both treatment groups had bleeds. For Fatal/Life-threatening bleeds, there were similar patterns between the 2 treatment groups. It appears that the rates of Fatal or Life-threatening bleeding came down to baseline by 3.5 days*.

*I considered bleeding rates at >7. 5 days after stopping treatment to be the baseline CABG-related bleeding rate.

Table 21: CABG bleeding by day between stopping drug and CABG

Days Between Stopping Drug And CABG	Treatment	N	All Bleeds	Fatal or Life-Threatening Bleeds	Treatment	N	All Bleeds	Fatal or Life-Threatening Bleeds
0-0.49	Ticagrelor	15	11(73%)	7(47%)	Clopidogrel	40	38(95%)	26(65%)
0.5-1.49		61	55(90%)	36(59%)		98	88(90%)	56(57%)
1.50 - 2.49		89	76(85%)	40(45%)		70	63(90%)	30(43%)
2.5-3.49		88	77(88%)	40(45%)		74	64(86%)	33(45%)
3.5-4.49		61	51(84%)	22(36%)		77	66(86%)	25(32%)
4.5-5.49		80	67(84%)	26(33%)		108	92(85%)	36(33%)
5.5-6.49		92	78(85%)	24(26%)		122	72(86%)	44(36%)
6.5-7.49		54	49(91%)	22(41%)		84	72(86%)	36(43%)
>7.5		194	153(79%)	74(38%)		228	194(85%)	74(32%)
unknown		28	28(100%)	12(43%)		31	31(100%)	16(52%)

On a reassuring note, as shown in
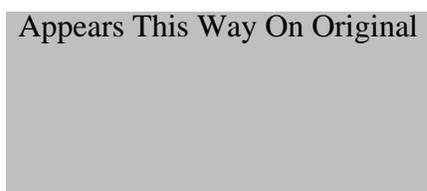
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Figure 8, despite the increased frequency of Major/Life-threatening CABG-related bleeds in the ticagrelor group related to early CABG, the all-cause mortality following CABG was less for ticagrelor than for clopidogrel when considering any time interval between the last dose of study treatment and beginning CABG.

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Figure 8: Sponsor's Analysis: Deaths (all-cause) during or after CABG by Time from Last Dose of Study Drug to Procedure
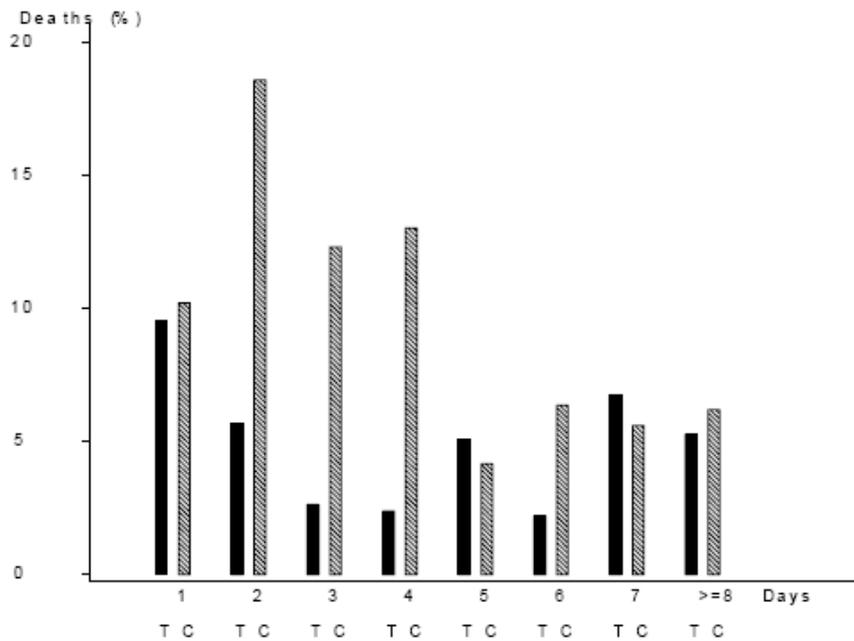
Source: ISS

In a July 16, 2010 communication, the sponsor provided a new analysis on deaths following CABG major bleeds within the first 14 days of first CABG by time from last dose of study drug to CABG. The data were in keeping with the reduced death rate at most time points in patients on ticagrelor that had CABG. See Figure 9.

Figure 9: Death within 14 Days of First CABG by Time from Last Dose of Study Drug to CABG
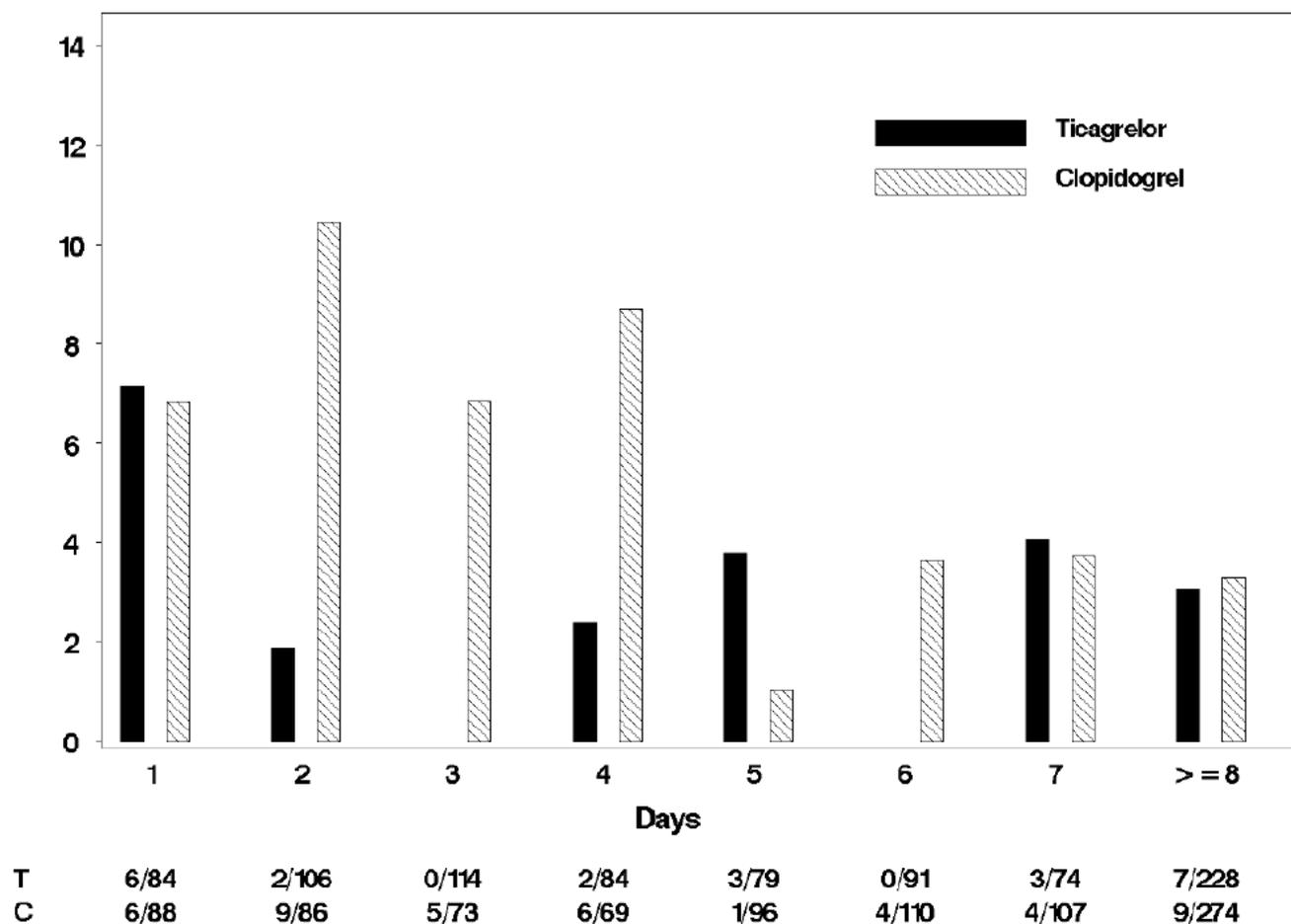
	1	2	3	4	5	6	7	>=8
T	6/84	2/106	0/114	2/84	3/79	0/91	3/74	7/228
C	6/88	9/86	5/73	6/69	1/96	4/110	4/107	9/274

In summary, the most important safety issue for ticagrelor was bleeding. All bleeds were adjudicated according to definitions designed specifically for the ticagrelor development program, a definition system which is broader than TIMI bleeding definitions and could be more subjective because transfusion is a criterion for a PLATO-defined major bleed and not a TIMI major bleed. Ticagrelor was associated with an increase in the frequency of major + minor bleeding. The reason for this increase was primarily due to the increased frequency of spontaneous (non-procedural/ non-CABG) bleeds. There was no increase in overall major/life-threatening or fatal bleeds in the ticagrelor treatment group compared to the clopidogrel treatment group as a whole. However, the pattern of increased non-procedural bleeds in ticagrelor-treated patients was also operative for major/life-threatening/fatal bleeds. When it comes to spontaneous (nonprocedural) bleeds, there were more in the ticagrelor group at all degrees of severity.

Overall, CABG did not cause increased bleeding in the patients that were in the ticagrelor treatment group. However, if one looks at risk of CABG-related bleeding by time after stopping drug, one can see that there are a few more cases of major/ life-threatening bleeding in the ticagrelor group compared to the clopidogrel treatment group until day 5 after stopping drug when the pattern reverses. However, despite the slightly increased frequency of major/life-threatening CABG-related bleeds in the ticagrelor group related to early CABG, the all-cause mortality following CABG was less for ticagrelor than for clopidogrel when considering any time interval between the last dose of study treatment and beginning CABG.

Dyspnea

Dyspnea has been reported with currently available antiplatelet drugs, clopidogrel, prasugrel and aspirin in approximately 4.5% of patients. However, discontinuation for dyspnea occurred in only approximately 0.1% of patients.

Dyspnea associated with ticagrelor administration was first observed in Phase 2 studies (DISPERSE and DISPERSE2) and was confirmed in the large Phase 3 PLATO study. PLATO did not exclude patients with COPD, CHF, or asthma.

i) Deaths after dyspnea AEs

There were 2 dyspnea AEs with an outcome of death (1 in each treatment group) reported during study treatment. Both were reported to have died from pneumonia.

One additional dyspnea AE with an outcome of death occurred after permanent discontinuation of ticagrelor treatment. This patient permanently discontinued study medication on day 4 and died on Day 124 of pneumonia and cardiac decompensation.

It is difficult to ascertain from these narratives what role ticagrelor played in the deaths of these patients.

ii) Dyspnea SAEs

In PLATO, according to my analysis of AEs, 79 (0.86%) of ticagrelor –treated patients had dyspnea SAEs and 53 (0.58%) of clopidogrel-treated patients had dyspnea SAES while on treatment [RR=1.48,(1.05,2.1)].

iii) Discontinuations because of dyspnea

Overall, dyspnea accounted for 79 (0.9%) of discontinuations in ticagrelor-treated patients and 13 (0.1%) of discontinuations in the clopidogrel-treated patients. SAEs of dyspnea accounted for 10 (0.1%) of discontinuations in the ticagrelor-treated patients and only 1 of discontinuations in the clopidogrel-treated patients. Importantly, patients who had any dyspnea AE during treatment were more likely to discontinue study medication due to any AE in both treatment groups, with 9.4% of ticagrelor-treated patients with dyspnea and 5.7% of clopidogrel-treated patients with dyspnea discontinuing as a result of any AE, whereas 4.6% vs. 4.4% of patients without dyspnea in the ticagrelor vs. clopidogrel groups, respectively, discontinued for any AE. This high frequency of discontinuations for AEs in ticagrelor-treated patients who developed dyspnea suggests that dyspnea is troublesome to patients.

iv) All Dyspnea AEs

In PLATO, most cases of dyspnea were in the mild to moderate range of severity. According to my analysis, (1345/9235) 14.6% of the ticagrelor-treated patients had at least one episode of dyspnea (including dyspnea at rest and on exertion, nocturnal and paroxysmal nocturnal dyspnea), while (803/9186) 8.7% of the clopidogrel-treated patients had at least one episode of dyspnea while on treatment. It is important to note that 22.3% of patients in the USA had dyspnea on ticagrelor (10.7% on clopidogrel).

According to the sponsor's analysis, the largest difference in dyspnea prevalence between the two treatment groups was in the subgroup of patients whose etiology for dyspnea was reported as "unexplained/unknown etiology". 4.1% and 1.8% of the ticagrelor-treated and clopidogrel-treated patients fell into that category, respectively. However, there was also a difference in prevalence between the two treatment groups in the subgroup of patients whose etiology for dyspnea was reported as cardiac-related reasons for dyspnea. 7.7% and 5.8% of the ticagrelor-treated and clopidogrel-treated patients fell into that category, respectively. The difference of 1.9% between treatment groups in patients with cardiac-related reasons for dyspnea is not high enough to suggest that ticagrelor could be worsening or causing heart failure. Furthermore, there was no difference between groups in frequency of patients who had reports of heart failure: 4.4% for ticagrelor-treated patients and 4.6% for clopidogrel-treated patients.

Of interest, there were no differences between groups in reports of abnormal breath sounds, tachypnea, bronchospasm or COPD/ COPD exacerbations.

25% of patients on strong CYP3 inhibitors at time of randomization developed dyspnea suggesting that there is a direct dose relationship. Additional support for a direct dose relationship comes from the DISPERSE2 study where ACS patients treated with ticagrelor 90 mg bd and 180 mg bd for 4-12 weeks had a reported incidence of dyspnea of 10% and 16%, respectively.

Also supporting a dose relationship for dyspnea, an exploratory exposure-response analysis evaluating pre-specified safety endpoints was performed with ticagrelor using predictive modeling. The analysis identified a time-dependent exposure-response relationship, which showed that increasing ticagrelor exposure correlated with an increased likelihood of dyspnea.

v) Risk Factors for Developing Dyspnea

Age appeared to be a risk factor for developing dyspnea. 18.3% of patients ≥ 75 years old had dyspnea on ticagrelor (12% on clopidogrel). Patients on an ACE inhibitor, aspirin, and/or a beta blocker at time of randomization did not have a higher likelihood of developing dyspnea on ticagrelor. Being on an ARB, however, was an added risk for developing dyspnea on ticagrelor (176/823, 21.4%), not so for clopidogrel (80/807, 9.9%). The highest weight quintile had a higher incidence of dyspnea events. One would imagine that heavier patients with recent ACS would have a greater tendency to be dyspneic compared to thinner patients. Perhaps ticagrelor may just push heavier people over the threshold and make them more likely to report dyspnea to the investigator. This weight relationship was not seen with clopidogrel.

See Table 22 for a breakdown of frequency of patients with one or more dyspnea AEs (including all descriptions of dyspnea). At all ages, there were more patients with dyspnea in the ticagrelor treatment group. The frequency of patients with dyspnea increased with increased age for both treatments.

Table 22: Patients with dyspnea AE by actual treatment (patients who received at least one dose of treatment before developing dyspnea)

Treatment	< 65 years old Ticagrelor N=5252 Clopidogrel N=5276	>= 65 years old -<75 years old Ticagrelor N=2599 Clopidogrel N=2447	> =75 years old Ticagrelor N=1383 Clopidogrel N=1463
Ticagrelor	653 (12.43%)	439 (16.89%)	253 (18.29%)
Clopidogrel	377 (7.15%)	246 (10.05%)	180 (12.30%)

According to the sponsor's analysis, dyspnea AEs occurred more frequently in patients with UA/NSTEMI (14.6%) compared with STEMI (12.6%) in the ticagrelor treatment group. The number of patients with dyspnea AEs in the clopidogrel group was similar regardless of the final diagnosis of ACS (7.8% for patients with UA/NSTEMI vs. 7.9% for patients with STEMI). The significance of this difference is unclear. As one would expect, patients with baseline COPD, asthma and CHF had a higher prevalence of dyspnea AEs than patients without a history of these underlying cardiopulmonary conditions. However, as shown in Table 23, the relative risk of having at least one dyspnea AE, SAE or stopping drug for dyspnea was not higher for patients with baseline asthma or COPD.

Table 23: Dyspnea AEs, SAEs, AE leading to discontinuation in all patients and in patients who had baseline asthma or COPD

Dyspnea Adverse Event*

	Ticagrelor	Clopidogrel	RR
All subjects			
N	**9235**	**9186**	
adverse event	1344 (14.6%)	803 (8.7%)	1.7
serious adverse event	79 (0.9%)	53 (0.6%)	1.5
adverse event, drug stopped	108 (1.2%)	25 (0.3%)	4.3
Subjects with baseline asthma or COPD			
N	**759**	**718**	
adverse event	177 (23.3%)	102 (14.2%)	1.6
serious adverse event	17 (2.2%)	10 (1.4%)	1.6
adverse event, drug stopped	19 (2.5%)	3 (0.4%)	6.0

*** Preferred Terms:** dyspnea, dyspnea at rest, dyspnea exertional, dyspnea paroxysmal nocturnal, nocturnal dyspnea, orthopnea, and painful respiration.

vi) Onset of Dyspnea

Dyspnea occurred earlier in the ticagrelor group than in the clopidogrel treatment group as shown in Figure 10. The analysis of the time to first event showed a statistically significant difference between ticagrelor and clopidogrel [HR 1.84 (95% CI 1.68, 2.02)]. The median time to onset of dyspnea was a median of 20 days for ticagrelor-treated patients and a median of 33 days for clopidogrel-treated patients.

Figure 10: Kaplan-Meier plot of time to first dyspnea AE
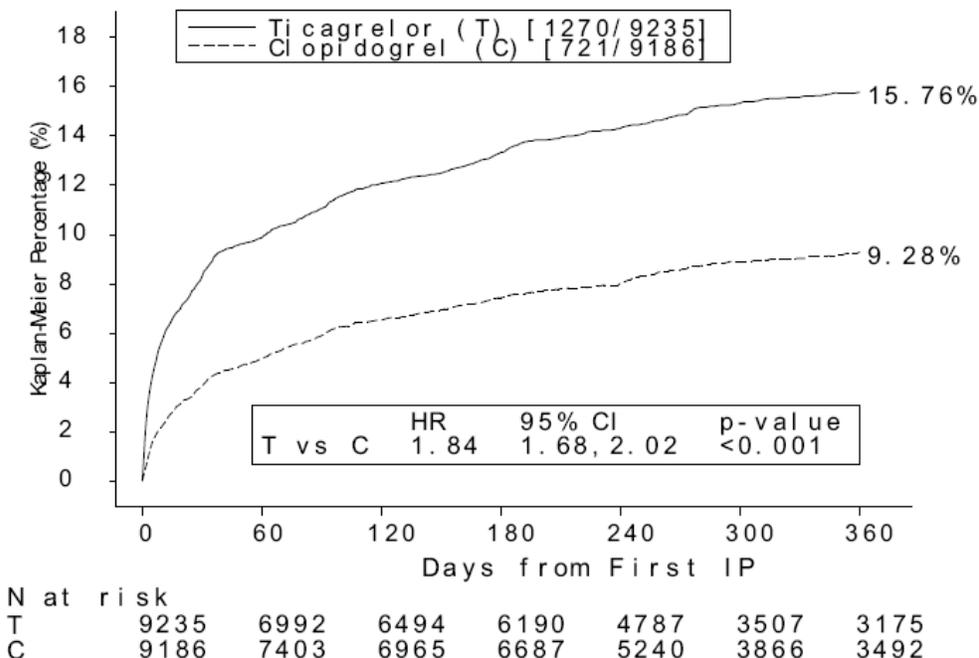
Source: PLATO study report, p. 22959

vii) Length of Dyspnea Episodes

Figure 11 and Figure 12 present my analysis of lengths of dyspnea events during PLATO in a graphic format. The difference between the figures is the scale of the X axis. In Figure 11, I divided the scale so that lengths of 20 days or less were grouped together. In Figure 12 events lasting ≥ 20 days were lumped together. While it might appear from Figure 11 that most of the dyspneic episodes are short lived, it is clear from Figure 12 that more episodes lasted ≥ 20 days. One can conclude from this analysis that most dyspnea episodes lasted more than 20 days. Additionally, for any length of dyspnea episode (from 0-2 days to 440 days), the ticagrelor treatment group had numerically more patients with dyspnea than did the clopidogrel treatment group. On a reassuring note, 2/3 of dyspnea AEs resolved during treatment.

Figure 11: Frequency of Different Lengths of Dyspnea Episodes I
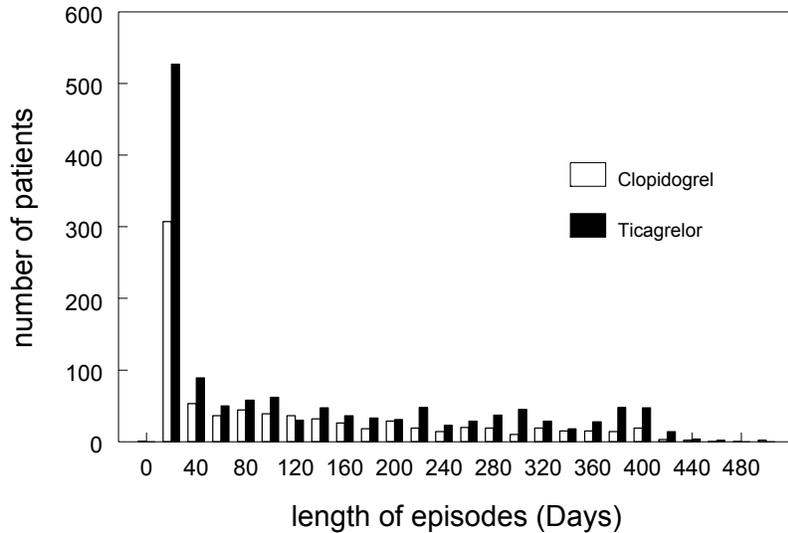
Figure 12: Frequency of Different Lengths of Dyspnea Episodes II

vii) Mechanism of Dyspnea

Dyspnea could be related to adenosine re-uptake inhibition. Adenosine (when given by IV infusion) causes dyspnea and is believed to have a direct effect on receptors in the bronchial tree but the exact effect is not known. Although ticagrelor does not act as an adenosine analogue, it does inhibit reuptake of endogenous adenosine into red blood cells and therefore

could lead to dyspnea by increasing the presence of endogenous adenosine in the circulation and interstitium of the bronchial tree.

ix) Effect of Dyspnea on Outcomes

An exploratory analysis conducted by the sponsor of the primary efficacy endpoint (CV death, MI and stroke) in patients with dyspnea strongly supports that patients who reported dyspnea during PLATO benefited as much from ticagrelor treatment as the entire PLATO population. While done as a retrospective analysis, it is reassuring that the outcome data support the effectiveness of ticagrelor in patients who reported dyspnea.

x) Pulmonary Function Substudy

In Section 7.4.5, there is a summary of the Pulmonary Function Substudy that enrolled a subgroup of randomly chosen patients at the same time that they were enrolled in PLATO. The goal of the study was to determine if patients on ticagrelor had an increased likelihood of having abnormal pulmonary function tests (PFT)s during ticagrelor treatment compared to the clopidogrel-treated patients. The study had several deficiencies that relate to the study design, execution and analysis and make interpretation of the results difficult. These deficiencies were as follows:

1. No baseline values (would be hard to do).
2. Outlier data was eliminated and substituted with averages of other data during the study which could obscure differences.
3. High percentage of patients in both treatment groups with h/o current or past smoking (ticagrelor 62%, clopidogrel 55%) which could obscure differences because of preexisting PFT abnormalities
4. Fewer patients than expected enrolled in this substudy.
5. The exposure was 6 months only in most of these patients.
6. Few of the patients had dyspnea, especially unexplained dyspnea at enrollment.
7. PFTs were not done at time of dyspneic episodes
8. The smaller than expected sample size reduced the power for detecting differences between groups.
9. Using mean values reduced the power for detecting differences.

While the conclusion of the sponsor was that there were no differences in pulmonary function tests between treatment groups, the Pulmonary Function Substudy was not well enough designed to convince this reviewer that ticagrelor has no effect on PFTs.

xi) Dyspnea Summary

In summary, dyspnea occurred frequently in patients treated with ticagrelor in all clinical phase 2 studies and in PLATO (14.6% of ticagrelor-treated patients vs. 8.7% of clopidogrel-treated

patients). Dyspnea SAEs occurred in less than 0.9% of ticagrelor-treated patients and in less than 0.6% of clopidogrel-treated patients. Dyspnea in ticagrelor-treated patients resulted in more discontinuations than dyspnea in clopidogrel-treated patients (0.9% vs. 0.1%, respectively). More impressively, nearly 10% of ticagrelor-treated patients that had dyspnea discontinued treatment for other AEs compared to <6% of clopidogrel-treated patients. Additional concerning observation is that the onset of dyspnea was considerably earlier in the ticagrelor-treated patients compared to the clopidogrel-treated patients, lasted usually >20 days (up to approximately 400 days) and at any length of episode, the ticagrelor treatment group had numerically more patients with dyspnea than did the clopidogrel treatment group. In my opinion, the Pulmonary Function Substudy was not conducted or analyzed in a way that made it interpretable. Therefore, while there is no evidence to support harmful effects of ticagrelor on pulmonary function or on lung parenchyma, the data from PLATO is insufficient to rule these out.

On the reassuring side, dyspnea is a symptom that resolved in 2/3 of the affected patients during the study. This suggests that it is unlikely that ticagrelor is causing chronic pulmonary changes in most patients. While two ticagrelor-treated patients with dyspnea AEs died, it is hard to assign the cause of the deaths in these patients to ticagrelor because of other comorbidities and confounding circumstances. Most reassuringly, patients with dyspnea know it and can discontinue ticagrelor if they are troubled by it. And importantly, despite its exploratory nature, a retrospective analysis of PLATO outcomes data showed that patients with dyspnea at any time during the trial had favorable clinical outcomes.

Being on an ARB was an added risk for developing dyspnea on ticagrelor (176/823, 21.4%). If patients develop dyspnea, consideration should be given to discontinuation of ARBs if possible.

Bradycardia and Arrhythmias

In a hERG study, ticagrelor blocked the hERG encoded potassium channel with a half maximal inhibitory concentration (IC50) value of 1.72 µM. However, the nonclinical data from Purkinje fiber and anesthetized dog showed no cardiac effects.

In phases 1 and 2, sinus pauses, ventricular pauses and adverse events related to bradycardia were observed in ticagrelor-treated patients and healthy volunteers. Additionally, as discussed earlier, in DISPERSE2 (the only phase 2 study where there were deaths) there were 3 deaths that were listed as sudden death, ventricular fibrillation or tachycardia out of 23 deaths in the entire study. None of the clopidogrel treated patients had arrhythmia related deaths. In the phase 2 pooled studies there were 6 arrhythmia AEs in the ticagrelor treatment groups that resulted in discontinuation: 1 cardiac arrest, 1 ventricular tachycardia, 1 ventricular fibrillation, 1 ventricular tachyarrhythmia, 1 bradycardia and 1 atrial tachycardia. None of these events occurred in the clopidogrel arms.

Theoretically, the inhibition of erythrocyte adenosine uptake which is the most potent activity of ticagrelor independent of $P2Y_{12}$ receptor function could result in increased interstitial

adenosine in the myocardium. Adenosine depresses sinoatrial node activity, AV nodal conduction, and ventricular automaticity, attenuates cardiac stimulatory action of catecholamines and the release of norepinephrine from nerve terminals (Belardinelli and Lerman 1991). An obvious concern is that if you have an ACS patient who is already predisposed to arrhythmias and then you expose this patient to a proarrhythmic drug, you might be putting that patient at considerable risk for life-threatening and fatal arrhythmias.

In PLATO there was close tracking of cardiac related AEs. The AE data are shown in my analysis (Table 24).

Contrary to expectations, in PLATO there were few differences in most arrhythmia AEs between treatment groups. Scrutinizing the data more carefully, it appears that there was a higher frequency of patients who had "supraventricular arrhythmias" (a renamed category in which I included atrial fibrillation, atrial flutter, premature atrial contractions and non- specified supraventricular arrhythmias) in ticagrelor-treated patients but a lower frequency of patients who had "ventricular arrhythmias" (in which I included premature ventricular contractions, nonsustained ventricular tachycardia, sustained ventricular tachycardia, and ventricular fibrillation) and a lower frequency of ventricular fibrillation. There were also a lower frequency of patients that fell into the "Sudden Death, Arrest, Electromechanical Dissociation, Cardiogenic Shock" in the ticagrelor-treated patients.

Other adverse events that are potentially symptomatic of arrhythmias did not favor ticagrelor and provokes one to question the reliability of reports of adverse events of ECG diagnosed arrhythmias.

For instance, there was a higher frequency of patients on ticagrelor compared to clopidogrel of the following symptomatic AEs: syncope/ presyncope [ticagrelor: 152(1.7%), clopidogrel 146(1.59%), RR 1.24(1,1.54)] and "vertigo, dizziness, and giddiness" [ticagrelor 603 (6.53%), clopidogrel 536(5.87%), RR 1.12(1,1.25]. While not reported in Table 24, there was a similar frequency of hypotension in both groups (0.3% range).

Table 24: Arrhythmia-Related and Conduction Disturbance AEs

AE Category (renamed)	ticagrelor 90 mg bd N=9235	clopidogrel 75mg od N=9186	RR	95% CI
Arrhythmia	1349 (14.61%)	1330 (14.48%)	1.01	(0.94, 1.08)
Atrial fibrillation	447 (4.84%)	455 (4.95%)	0.98	(0.86, 1.11)
Atrial Flutter	48 (0.52%)	46 (0.5%)	1.04	(0.69, 1.55)
Atrio-ventricular block	104 (1.13%)	104 (1.13%)	0.99	(0.76, 1.3)
Bradycardia	398 (4.31%)	369 (4.02%)	1.07	(0.93, 1.23)
Bundle Branch Blocks and QRS prolongation	20 (0.22%)	25 (0.27%)	0.8	(0.44, 1.43)
Conduction disturbance	145 (1.57%)	142 (1.55%)	1.02	(0.81, 1.28)
Nodal, Junctional or Idioventricular rhythm	13 (0.14%)	13 (0.14%)	0.99	(0.46, 2.14)
Nonsustained ventricular tachycardia, SVT, unspecified Ventricular tachycardia	193 (2.09%)	191 (2.08%)	1.01	(0.82, 1.23)
Premature atrial contraction	41 (0.44%)	35 (0.38%)	1.17	(0.74, 1.83)
Premature ventricular contraction	107 (1.16%)	130 (1.42%)	0.82	(0.63, 1.06)
Serious Atrioventricular Block (type 2b, 3)	64 (0.69%)	61 (0.66%)	1.04	(0.74, 1.48)
Sick sinus syndrome	28 (0.3%)	23 (0.25%)	1.21	(0.7, 2.1)
Sinus Arrest, Pause, Block, Dysfunction	20 (0.22%)	17 (0.19%)	1.17	(0.61, 2.23)
Sudden Death/ arrest, Electromechanical dissociation, cardiogenic shock	160 (1.73%)	199 (2.17%)	0.8	(0.65, 0.98)
Supraventricular arrhythmia	688 (7.45%)	659 (7.17%)	1.04	(0.94, 1.15)
Sustained Ventricular Tachycardia	5 (0.05%)	6 (0.07%)	0.83	(0.25, 2.72)
Syncope, Presyncope	182 (1.97%)	146 (1.59%)	1.24	(1, 1.54)
Tachycardia	357 (3.87%)	358 (3.9%)	0.99	(0.86, 1.15)
Ventricular Arrhythmia	375 (4.06%)	415 (4.52%)	0.9	(0.78, 1.03)
Ventricular Fibrillation	73 (0.79%)	95 (1.03%)	0.76	(0.56, 1.04)
Vertigo, Dizziness, Giddiness	603 (6.53%)	536 (5.83%)	1.12	(1, 1.25)

While there was a slight trend toward more syncope/presyncope adverse events in the ticagrelor-treated patients, the relative risks for these events were approximately 1.3, too low to raise a major concern despite the biological plausibility of a causal effect. In the sponsor's AE table, syncope occurred in 100 (1.1%) and in 76 (0.8%) of the ticagrelor and clopidogrel-treated patients, respectively. As for dizziness, there were 418(4.5%) patients in the ticagrelor arm and 355 (3.9%) in the clopidogrel arm. The sponsor's SAE table included 26 syncope SAEs (0.3%) for ticagrelor and 23(0.3%) syncope SAEs for clopidogrel. The lower numbers in the sponsor's analysis for both treatment groups are likely due to the splitting of arrhythmia-related symptoms.

As for SAEs, there was a slightly higher frequency of ticagrelor- treated patients with SAEs in the "syncope/presyncope" category [51 (0.55%) for ticagrelor and 35 (0.38%) for clopidogrel]. There were no substantial differences in frequency of arrhythmia-related SAEs between treatment groups for the other terms that were listed in Table 24.

Very few syncope events resulted in discontinuation of drug [4(0.04%) for ticagrelor and 3 (0.03%) for clopidogrel].

Additionally, during the full course of the Holter substudy, patients with pauses ≥ 3 seconds during the Holter period were more likely to experience the following symptoms if they were on ticagrelor: dizziness, 6 patients on ticagrelor, compared to none on clopidogrel and syncope (4 patients on ticagrelor compared to 1 patient on clopidogrel).

On the reassuring side, Fatal AEs such as sudden cardiac death (10 patients [0.1%] with ticagrelor vs. 21 patients [0.2%] with clopidogrel) and deaths due to ventricular fibrillation (4 patients [<0.1%] with ticagrelor vs. 8 patients [0.1%] with clopidogrel) occurred in numerically fewer patients in the ticagrelor group compared to clopidogrel. There was no difference overall in AEs resulting in discontinuations (DAEs) in the arrhythmia or arrhythmia-related categories.

A summary of the Holter substudy is included in section 7.4.5.

In brief, the Holter substudy was well designed and demonstrated that ticagrelor causes more arrhythmias and pauses than clopidogrel. However, in the substudy, the frequency of symptomatic events was no greater in the ticagrelor-treated patients. There was a numerically higher occurrence of nocturnal pauses with ticagrelor compared to clopidogrel in patients that had 5 or more ventricular pauses of ≥ 3 seconds during Holter monitoring periods. This observation raised the possibility that ticagrelor could worsen sleep apnea.

One limitation of the PLATO study is that patients with an increased risk of bradycardic events (e.g., no pacemaker and known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker) were excluded from the study so there is limited information of the effect of ticagrelor on patients with these conditions.

In summary, the data from DISPERSE2 is not favorable for ticagrelor vis-à-vis cardiac arrhythmias. In PLATO, the data for ticagrelor is not favorable for atrial arrhythmias and ventricular pauses but it is favorable for sudden death and ventricular arrhythmias. This data in addition to the slightly higher frequency of syncope, presyncope, dizziness, wooziness, and giddiness events in the ticagrelor arm of PLATO, is compelling enough evidence to conclude that the product label should include a warning about the potential for syncope and presyncope and cardiac arrhythmias, particularly ventricular pauses. While it might be attractive to limit ticagrelor's use to patients without histories of sick sinus syndrome, second or third degree AV block, recurrent dizziness, history of loss of consciousness, syncope, advanced COPD or sleep apnea, the reduced frequency of cardiac arrest outweighs these other concerns.

Renal Function Effects

No signals for renal toxicity were identified during non-clinical development and phase 1 clinical studies. In the phase 2 studies, all treatment arms had increases in serum creatinine levels throughout the trial. However, when looking at frequency of categorical changes, i.e., > 30% to ≤ 50% increase, or >100% increase in serum creatinine; there was a trend toward a somewhat greater and earlier categorical increase in serum creatinine in the ticagrelor treatment groups compared to the clopidogrel treatment group. Most patients in the small placebo group also had categorical increases in serum creatinine by week 8. Since renal impairment carries high morbidity and mortality and is an independent predictor of cardiovascular mortality in patients with cardiovascular disease[3], the findings of categorical changes in renal function were explored thoroughly in my analysis of PLATO.

The PLATO protocol specified that laboratory testing (clinical chemistry and hematology) should be tested at visit one (randomization), visit two (one month), visit three (3 months), visit four (6 months) and visit six (end of treatment at 12 months ± 10 days). The protocol allowed for safety laboratory monitoring to be discontinued if the data and safety monitoring board (DSMB) decided that testing was no longer required. As specified in the protocol, the DSMB decided that patients randomized on or before January 31, 2008 would continue to have safety laboratory testing (hematology and chemistry) during the course of the study in accordance with the study plan. Patients who were randomized on or after February 1, 2008 did not have safety laboratory testing (hematology and chemistry) after Visit 1 (Randomization).

For interpreting the results, it is important to know that while the mean baseline creatinine values were normal, the mean eGFR-MDRD values were below 90 cc/min. Therefore, most of the patients enrolled in PLATO had a baseline of chronic renal insufficiency. In Table 25, there are fewer Visit 1 values than Visit 2 values which indicates that ~ 250 patients in each treatment group had missing baseline values. There were fewer measurements at Visit 5 because it was an unscheduled visit. The 30-day follow-up visit was done off-drug. Table 25 shows that mean serum creatinine increased with both drugs, but the magnitude of the increase was slightly higher with ticagrelor (by 0.01 – 0.05 mg/dL, which is a minimal difference. The shift table for mean serum creatinine values did not add cause for concern, and neither did the mean eGFR data or shift tables. The mean serum creatinine values trended toward a greater increase while on treatment with ticagrelor and then stabilized or came down slightly in the recovery period. A substudy looking at absolute changes of urinary cystatin C, a biomarker of renal function, showed that both treatment arms had 20 -25% mean increases from baseline. The mean changes were driven by small changes in the majority of patients as opposed to large changes in a minority of patients. However, as can be seen in Table 26, mean changes in creatinine tend to obscure the effects of ticagrelor on renal function. One can readily see from Table 26 that there is a trend toward higher percentages of ticagrelor-treated patients who developed creatinine increases between 30 and 50% and between 50 and 100%. One must keep in mind that there is a large amount of missing data because patients

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3 Walsh CR, O'Donnell CJ, Camargo CA, Giuliano RP, Lloyd-Jones DM. Elevated serum creatinine is associated with 1-year mortality after acute myocardial infarction. Am Heart J 2002;144:1003-1011.

randomized after February 1, 2008 did not have safety laboratory values collected after Visit 1 (as prespecified in the protocol at the discretion of the DSMB) and because some patients missed a baseline value or the timepoint of the baseline value was not recorded properly. My concern is that the missing data might contribute to an underestimation of the negative effect of ticagrelor on renal function.

Table 25: Sponsor's Analysis Summary statistics for serum creatinine by visit and treatment group – PLATO safety laboratory analysis set

Visit schedulea		Ticagrelor		Clopidogrel	
		N	**Mean creatinine mg/dL Mean (SD)**	**N**	**Mean Creatinine mg/dL Mean (SD)**
Visit 1	Index Event	4641	0.98 (0.31)	4624	0.98 (0.32)
Visit 2	1 mo	4901	1.06 (0.35)	4870	1.04 (0.32)
Visit 3	3 mo	4494	1.05 (0.33)	4496	1.03 (0.33)
Visit 4	6 mo	4022	1.05 (0.33)	3998	1.04 (0.32)
Visit 5	9 mo	229	1.08 (0.33)	222	1.03 0.25)
Visit 6	12 mo	3652	1.07 (0.41)	3643	1.04 (0.31)
	30 day follow-up	3595	1.06 (0.37)	3545	1.05 (0.34)

Source: Modified from Table 87, PLATO study report NDA 22-433, p. 315.

Table 26: Sponsor's Analysis: Greatest change from baseline to maximum serum creatinine value while on-treatment – safety data laboratory set

Criteria	Ticagrelor 90 mg bd N=4031	Clopidogrel 75 mg od N=4035
Change in serum creatinine (baseline to maximum value)		
Creatinine increase >100%	35 (0.9%)	34 (0.9%)
Creatinine increase >50% to 100%	300 (7.4%)	237 (5.9%)
Creatinine increase >30% to 50%	692 (17.2%)	588 (14.6%)
Creatinine increase 0 to <30%	2632 (65.3%)	2750 (68.2%)
Decrease	372 (9.2%)	426 (10.6%)
Missing data	1579	1547

Source: PLATO study report, Table 89, p. 317.

Mechanism of Renal Function Changes

The mechanism of increased serum creatinine with ticagrelor treatment is unknown. Adenosine infusion directly into the renal arteries of dogs that were salt-depleted resulted in a

change in renal hemodynamics (decreased efferent arteriolar resistance but unchanged afferent arteriolar resistance) and led to decreased GFR, filtration fraction, sodium excretion and renal venous renin. It is possible that ticagrelor which indirectly increases serum levels of adenosine may indirectly increase serum creatinine and decrease GFR through this mechanism (H Tagawa and A. Vander, Effects of Adenosine Compounds on Renal Function and Renin Secretion in Dogs, Circulation Research, Vol 26, March 1970, p. 327-338).

Renal Deaths and Adverse Events

Two patients after having received treatment of AKI in the ticagrelor treatment group died vs.four similar patients who had received clopidogrel treatment.

Overall, according to the sponsor's analysis, there were 80 (0.8%) patients receiving treatment with ticagrelor who were reported to have 1 or more renal-related SAEs while on and off treatment. Of the clopidogrel treatment group, there were 67 (0.7%) patients with renal-related SAEs. The frequency of SAEs of renal failure acute, renal failure and renal failure chronic were the same in both treatment groups. Six SAEs related to hematuria accounted for most of the small increase in renal related SAEs on ticagrelor compared to clopidogrel. There were no imbalances in renal transplantation or dialysis between the treatment groups.
In Sponsor's Table 27 , it is shown that 12 (13.6%) of patients with baseline eGFRs <30cc/min/1.73m$_2$ developed renal failure whereas only 5 (5.4%) of clopidogrel treated patients with baseline eGFRs of <30cc/min/1.73m$_2$ were reported to have renal failure. Also, as stated in the section on bleeding risk, there were more major bleeds in patients with eGFR < 30 cc/min/1.73 m$_2$ [23 (19%) vs. 16 (11.3%)]. Because of the small numbers of patients in this subgroup, these observations could be chance findings.

In Table 27, it is also shown that there was a higher frequency of hematuria in the ticagrelor treatment group at all degrees of renal dysfunction which corresponds to the previously noted increase in spontaneous bleeding.

Table 27: Sponsor's Table: Renal AEs by Baseline Renal Function including Hematuria

	Baseline renal function[a]							
	Severe (<30 mL/min/1.73 m²)		Moderate (≥30 to <60 mL/min/1.73 m²)		Mild (≥60 to <90 mL/min/1.73 m²)		Normal (≥90 mL/min/1.73 m²)	
Preferred term[b,c]	Ticagrelor 90 mg bd N=88	Clopidogre l 75 mg od N=93	Ticagrelor 90 mg bd N=1178	Clopidogrel 75 mg od N=1224	Ticagrelor 90 mg bd N=3542	Clopidogrel 75 mg od N=3546	Ticagrelor 90 mg bd N=2807	Clopidogrel 75 mg od N=2775
Patients with at least 1 event	19 (21.6%)	23 (24.7%)	147 (12.5%)	105 (8.6%)	142 (4.0%)	110 (3.1%)	56 (2.0%)	43 (1.5%)
Haematuria	0	1 (1.1%)	36 (3.1%)	31 (2.5%)	62 (1.8%)	64 (1.8%)	42 (1.5%)	28 (1.0%)
Renal failure	12 (13.6%)	5 (5.4%)	39 (3.3%)	25 (2.0%)	20 (0.6%)	15 (0.4%)	2 (0.1%)	1 (0.0%)
Blood creatinine increased[d]	2 (2.3%)	1 (1.1%)	17 (1.4%)	13 (1.1%)	21 (0.6%)	6 (0.2%)	2 (0.1%)	1 (0.0%)
Renal failure acute	1 (1.1%)	3 (3.2%)	15 (1.3%)	18 (1.5%)	13 (0.4%)	10 (0.3%)	6 (0.2%)	3 (0.1%)
Renal impairment	0	3 (3.2%)	15 (1.3%)	8 (0.7%)	13 (0.4%)	2 (0.1%)	0	1 (0.0%)
Renal failure chronic	3 (3.4%)	6 (6.5%)	20 (1.7%)	9 (0.7%)	2 (0.1%)	2 (0.1%)	0	2 (0.1%)
Proteinuria	0	0	1 (0.1%)	3 (0.2%)	7 (0.2%)	7 (0.2%)	3 (0.1%)	3 (0.1%)
Oliguria	0	0	3 (0.3%)	0	4 (0.1%)	2 (0.1%)	0	5 (0.2%)

From my analysis, the frequency of patients >75 years old that had renal AEs (not counting hematuria) was only slightly increased over patients < 65 years old (2.2 vs.1.6% for ticagrelor and 1.8% vs. 1.6% for clopidogrel). The frequency of renal SAEs not counting hematuria was increased in patients >75 years over patients <65 years old (2.0% vs.0.4% for ticagrelor and 1.9% vs. 0.4% for clopidogrel). Nevertheless, there was no difference between treatment groups in this pattern.

While there is a higher risk of dying when patients with renal disease were treated for ACS, there was no substantial difference between treatment groups. See Table 28.

Table 28: Mortality by Baseline GFR

Kidney Disease Category by eGFR	Treatment	N in Kidney Disease Category N=17069	n Survived	n Died	% Died
	All	6559	6434	125	1.91
>= 90 cc/min	Ticagrelor	3307	3257	50	1.51
	Clopidogrel	3252	3177	75	2.31
60<90 cc/min	All	6670	6344	326	4.89
	Ticagrelor	2862	2700	162	5.66
	Clopidogrel	3808	3644	164	4.31
30-<60cc/min	All	3579	3220	359	10.03
	Ticagrelor	1749	1619	148	8.38
	Clopidogrel	1812	1601	211	11.64
15-<30cc/min	All	246	185	61	24.8
	Ticagrelor	113	86	27	23.89
	Clopidogrel	133	99	34	25.56
<15 cc/min	All	15	11	4	26.67
	Ticagrelor	4	0	4	100
	Clopidogrel	11	0	11	0

Interestingly, there were fewer renal-related SAEs that lead to permanent discontinuation from PLATO in the ticagrelor treatment arm compared to the clopidogrel treatment arm, [4(0.0%) compared to 8(0.1%), respectively]. It is reassuring that more than half of the renal-related SAEs in both treatment groups resolved while patients were still on treatment. If the renal-related SAEs had been related solely to the drug, recovery would probably not have occurred.

Overall, more ticagrelor-treated patients developed renal AEs [449 (4.9%) in the ticagrelor treatment group compared to 345 (3.8%) in the clopidogrel-treatment group]. The most frequent preferred terms (occurring in order of descending frequency) for renal-related AEs while on treatment were hematuria, renal failure, increased creatinine and acute renal failure. All other preferred term AEs (renal impairment, renal failure chronic, proteinuria, oliguria or nephropathy) occurred in less than 0.5% of the patients.

Figure 13 shows the KM plot for time to first renal-related AE. Percentages presented in this figure represent the event rate at 12 months. The ticagrelor treatment group showed an increase in the percentage of patients with at least 1 renal-related AE. The analysis of the time to first event was significantly different between treatment groups (HR 1.31 [95% CI 1.14, 1.50]), and the 2 curves appear to separate early and become parallel within 90 to 120 days. The majority of this separation is evident by Day 60.

Figure 13: Kaplan-Meier plot of time to first renal-related AE – safety analysis set
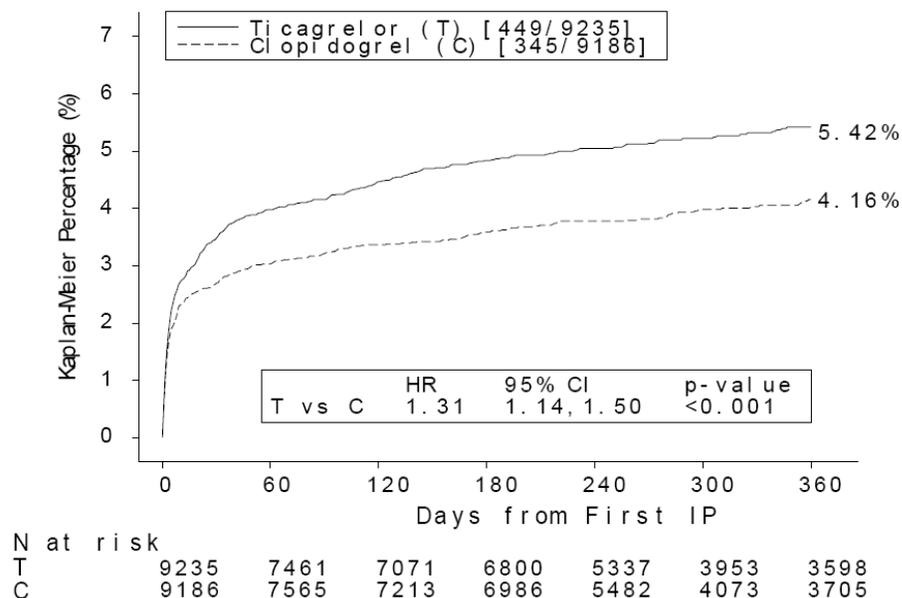
Source: PLATO study report, p. 305

As shown in Table 29, the frequencies of renal related AEs, renal function AEs, and > 50% increases in serum creatinine were higher in ticagrelor-treated patients who were on ARBs > 50% of study days compared to ticagrelor-treated patients who didn't receive ARBs >50% of study days. This was true for the clopidogrel-treated patients but the change in frequency of adverse renal events was not as marked. If the hemodynamic mechanism proposed earlier is accurate, it would stand to reason that ARBs would worsen renal function in ticagrelor-treated patients and it may be prudent to avoid them during treatment. While ACE inhibitor use (not shown) increased the frequency of creatinine increase > 50%, they did not change the frequency of renal AEs for the worse.

Table 29: Sponsor's Analysis: Frequencies of >50% elevation of creatinine, renal-related AEs, renal function AEs by use of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) by treatment

Concomitant ACEI or ARB use >50% of study days	Renal outcome	ticagrelor	clopidogrel	Concomitant ACEI or ARB use >50% of study days	ticagrelor	clopidogrel
ACEI USE: YES	Total at risk for >50% creatinine increase	2721 (100%)	2763 (100%)	ACEI USE: NO	752 (100%)	744 (100%)
	Creatinine increase >50%	228 (8.4%)	187 (6.8%)		51 (6.8%)	37 (5.0%)
	Total at risk for a renal-related AE	6056 (100.0%)	6059 (100.0%)		1874 (100.0%)	1883 (100.0%)
	Renal related AE	249 (4.1%)	206 (3.4%)		95 (5.1%)	58 (3.1%)
	Total at risk for renal function AE	6056 (100%)	6059 (100%)		1874 (100%)	1883 (100%)
	Renal function AE	119 (2.0%)	82 (1.4%)		56 (3.0%)	39 (2.1%)
ARB USE YES	Total at risk for >50% creatinine increase	511 (100%)	508 (100%)	ARB USE: NO	3300 (100%)	3322 (100%)
	Creatinine increase >50%	57 (11.2%)	36 (7.1%)		251 (7.6%)	212 (6.4%)
	Total at risk for a renal-related AE	1127 (100.0%)	1126 (100.0%)		7634 (100.0%)	7585 (100.0%)
	Renal related AE	73 (6.5%)	48 (4.3%)		333 (4.4%)	265 (3.5%)
	Total at risk for renal function AE	1127 (100%)	1126 (100%)		7634 (100%)	7585 (100%)
	Renal function AE	51 (4.5%)	31 (2.8%)		166 (2.2%)	111 (1.5%)

Source: reformatted Table 4, PLATO renal report, p.15. The reason for smaller at risk population for >50% creatinine increase is that patients randomized after February 1, 2008 did not have safety laboratory values collected after Visit 1 (as determine by the DSMB) and because some patients missed a baseline value or the timepoint of the baseline value was not recorded properly.

Because of the renal safety concern, I was interested in knowing if there was any difference in the effectiveness of ticagrelor by baseline eGFR. Ticagrelor seems to be as affective in patients with markedly reduced baseline renal function .See Table 21 (sponsor's table).

Table 30: ICAC-Adjudicated Primary Clinical Efficacy Endpoint by Baseline Renal Function

Group	n	Ticagrelor 90 mg bd N = 9333		n	Clopidogrel 75 mg od N = 9291		HR (95% CI)	p-value
		Patients with events	KM% /year		Patients with events	KM% /year		
Severe	88	22 (25.0%)	27.1%	93	30 (32.3%)	36.6%	0.73 (0.42, 1.27)	0.2727
Moderate	1178	172 (14.6%)	15.8%	1224	241 (19.7%)	21.5%	0.72 (0.59, 0.88)	0.0011
Mild	3542	345 (9.7%)	10.2%	3546	362 (10.2%)	10.9%	0.96 (0.83, 1.11)	0.5676
Normal	2807	172 (6.1%)	6.5%	2775	210 (7.6%)	8.0%	0.81 (0.66, 0.99)	0.0388
Unknown	1718	153 (8.9%)	9.4%	1653	171 (10.3%)	11.0%	0.85 (0.69, 1.06)	0.1570

Data derived from Appendix 2.7.3.6 Tables 3 in CTD Module 5.3.5.3.
Hazard ratio and p-values calculated from Cox proportional hazards model with explanatory variables for study treatment, subgroup and treatment-subgroup interaction.
Kaplan-Meier percentage calculated at 12 months.
p-value (Int.) assesses the interaction between randomised treatment and subgroup.

I was also interested in knowing how the severity of renal dysfunction correlated with increased death in the ticagrelor-treated patients as compared to the clopidogrel-treated patients. . As one would expect, the frequency of death worsened with worsening degrees of baseline renal function in both groups. There were only 15 patients in the study with eGFR < 15 cc/min. 4/4 that were in the ticagrelor treatment group died, whereas none of the 11 in the clopidogrel treatment group died. This is a disturbing observation. However, the numbers are too low to make any conclusion about ticagrelor and risk of dying when there is baseline renal failure. Post-marketing data will be useful to elucidate this issue.

In summary, ticagrelor was associated with increases in serum creatinine probably because of renal hemodynamic changes. Also, while there were very few patients in the subgroup of patients with baseline eGFRs < 30cc/min/1.73m^2, there were numerically more patients with major bleeds and renal failure in the ticagrelor treatment group compared to the clopidogrel treatment group. When patients have poor baseline renal function they rely on hemodynamic changes within the kidney to maintain their GFR. It is possible that ticagrelor is more likely than clopidogrel to lead to the decompensation of renal function in patients who are completely reliant on hemodynamic factors to maintain their GFR. ACS Patients with poor baseline renal

function are at higher risk for renal AEs and death. While there are too few data in this subgroup of patients to make firm conclusions, it is possible that ticagrelor might also contribute to the risk of progression to worsening renal failure in these already high risk patients.

Elevated Uric Acid

Increases in serum uric acid with ticagrelor were first observed in the phase 2 studies DISPERSE and DISPERSE2 and later confirmed in PLATO (approximately 15% mean increase from baseline for ticagrelor-treated patients vs. approximately 7.5% for clopidogrel-treated patients). The degree of uric acid elevation from baseline went from a mean of 15.4 % to 7.3% by the 30-day follow-up after stopping ticagrelor. No mean decrease was seen in the uric acid levels in the clopidogrel-treated patients at the 30-day follow-up visit. Relatively few of all treated patients experienced AEs that were potentially related to uric acid elevation (2.1% of the ticagrelor treated patients and 1.8% of the clopidogrel treated patients. Gout, the most frequently occurring uric acid-related AE, occurred in 0.6% of patients in both treatment groups. There was no difference between groups in incidence of nephrolithiasis. The only difference in AEs between the treatment groups was hyperuricemia (0.5% vs. 0.2%). 2.5% of patients on ticagrelor who crossed the clinically relevant threshold for hyperuricemia (7.0 mg/dL in men and > 6.0 mg/dL in women) developed gout and 2.2% of clopidogrel-treated patients who crossed the threshold developed gout. There were 4 patients in the ticagrelor group that developed a gout/hyperuricemia SAE compared to 2 in the clopidogrel group

The data do not support an association between ticagrelor treatment and gout-related events. Having an elevated serum uric acid level does not reliably predict if the patient has gout or will develop gout, so routine monitoring of serum uric acid levels during ticagrelor treatment should not be indicated[4].

Mechanism of Elevation of Uric Acid

It is known that adenosine blocks uric acid transport channel activity[5]. Since ticagrelor increases adenosine by interfering with erythrocyte reuptake, it is proposed that this is the mechanism by which uric acid levels increase in ticagrelor-treated patients.

Hormonally Mediated Effects

It was observed in preclinical rat studies that there were uterine carcinomas and benign hepatocellular adenomas after high exposure to ticagrelor.

There was no clinical evidence from the phase 1 and 2 clinical studies that treatment with ticagrelor in humans increased the risk of developing cancer, and more specifically gynecological cancer.

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4 Logan et al, Serum uric acid in acute gout, Ann Rheum Dis 1997, p. 696-7
5 M Rafey et al, Uric acid transport, Curr Opin Nephrol Hypertens 12:511-6, 2003 Lippincott Williams & Wilkins.

In Table 31, one can see that vaginal bleeding when counted as an AE was not common and there was little difference between treatment groups. There were very few SAEs or discontinuation from vaginal bleeding event. While there was a ticagrelor-treated patient who was diagnosed with endometrial adenocarcinoma on the 14th day of treatment, a causal relationship in this particular case is not possible.

Table 31: AEs that might be hormonally related

Category of possibly hormonally related AE All patients Females only Males only	Ticagrelor 90 mg bd N= 9235 N= 2634 N= 6601	Clopidogrel 75 mg QD N= 9186 N= 2603 N= 6583	RR
	n(percent)	n(percent)	
Vaginal bleeding (females only)	22 (0.84)	17 (0.65)	1.3
Breast tenderness/ pain (all patients)	8 (0.09)	6 (0.04)	2.3
Gynecomastia (males only)	15 (0.23)	3 (0. 05)	4.6
Breast Cancer (females only)	4 (0.15)	10 (0.38)	1
Prostate enlargement, mass, or disorders (males only)	39 (0.59)	40 (0.61)	1
BPH (males only)	10 (0.15)	8 (0.12)	1.3
Prostate cancer (males only)	13 (0.19)	12 (0.18)	1.1
Cervical/uterine tumor (females only)	5 (0.19)	5 (0.19)	1
Cervical/uterine malignancy (females only)	1 (0)	0 (0)	0
Erectile Dysfunction (males only)	43 (0.65)	50 (0.76)	0.9
Decreased Libido (all patients)	5 (0.05)	1 (0.01)	5
Sexual Dysfunction (males only)	3 (0.05)	11 (0.17)	0.3

Some patients may be listed in more than one category

Of greater concern than the vaginal bleeding was the isolated increased frequency of gynecomastia in the ticagrelor-treated patients. It is well known that gynecomastia is hormonally mediated. Drugs may cause gynecomastia by increasing estrogen effects as is the case with digitalis, by decreasing testosterone effects as is the case with spironolactone or increasing prolactin levels as is the case with some antipsychotic medications. There were 17 patients who developed gynecomastia on ticagrelor and 3 patients who developed gynecomastia on clopidogrel. The RR for developing gynecomastia was 5.3 in PLATO.

A Kaplan-Meier curve was generated from the 17 ticagrelor patients with gynecomastia, breast, mass or swelling of breast and the 3 clopidogrel patients with gynecomastia (Figure 14). This graphically demonstrates that the onset of gynecomastia was early and there was a

steady rate of new cases. The difference in frequency of gynecomastia between groups was statistically significant (log-rank = 0.0016).

Figure 14: K-M: Gynecomastia (17 of men with gynecomastia or breast swelling or breast mass in ticagrelor group), 3 of men with gynecomastia in the clopidogrel group)

Source: Dr. Thomas Marciniak from his secondary clinical review

There was no increase in breast cancer during PLATO and no increase in any other hormonally related adverse event aside from gynecomastia. The mechanism for the development of gynecomastia is unknown. Many patients in this trial were on spironolactone. In fact, most of the narratives of gynecomastia reported that the patients were also taking spironolactone. Since this is a randomized trial, one would expect equal spironolactone exposure in both treatment groups. Perhaps ticagrelor causes gynecomastia in patients that have other predisposing conditions for gynecomastia.

My assessment is that in the absence of a biologically plausible mechanism for the increased frequency of gynecomastia in ticagrelor-treated patients, and in the absence of any other hormonally mediated effect differences between treatment groups, one can not draw any firm conclusions about the increased frequency of gynecomastia observed in the ticagrelor group. Nevertheless, gynecomastia should be a labeled adverse effect.

Hepatic Effects

There was 1 patient in the ticagrelor arm that died of metastatic hepatic cancer. In the clopidogrel arm, 3 died of hepatic related events. One died of metastatic hepatic cancer, one of hepatic failure and one of hepatic neoplasm.

A total of 8 patients in the ticagrelor group and 13 patients in the clopidogrel group met enzymatic criteria for potential Hy's Law (ALT or AST level of >3xULN, a total bilirubin level of >2xULN, and an ALP <2xULN concurrently) with abnormal tests occurring at anytime during the study. Two (<0.1%) patients in the ticagrelor treatment group and 1 (<0.1%) patient in the clopidogrel treatment group met enzymatic laboratory criteria for potential Hy's Law concurrently while on treatment. Both of the Hy's law cases in the ticagrelor arm occurred soon after starting drug and resolved spontaneously. It is not likely that their enzymes increased as a result of ticagrelor exposure. More likely the enzyme abnormalities were secondary to circulatory changes at the onset of their ACS. The descriptions of the two ticagrelor-treated patients that met Hy's law criteria are in Appendix B.

There were no differences between groups in mean levels of liver enzymes throughout the course of the trial. There were initial elevations of aspartate aminotransferase (AST) and alanine transaminase (ALT) followed by normalization in both treatment groups, likely reflecting the underlying index event rather than an effect of the study drug. There were no clinically relevant changes over time in alkaline phosphatase or bilirubin levels.
Similar trends were seen in patients with and without baseline hepatic disorders. For the most part, there were no differences between treatment groups in terms of frequency of liver enzyme elevations above prespecified cut offs such 2 or 3 times the upper limit of normal. However, bilirubin elevation to 1.5 or 2.0 X elevation of normal occurred more frequently in the ticagrelor treatment group. There were 68 (0.74%) patients that were on ticagrelor and 39 (0.1%) patients that were on clopidogrel that met the criterion of a bilirubin elevation of 1.5X normal. There were 25 (0.3%) ticagrelor treated patients and 10 (0.1%) clopidogrel-treated patients, respectively, that had bilirubin elevations that were 2X normal levels. This difference between groups in bilirubin elevations was not reflected by an increase in hepatobiliary AEs or serious AEs.

There was a low frequency of hepatic AEs in PLATO. There were no differences between groups in the frequency of hepatic AEs (1.7% for both treatment groups). For hepatic SAEs, ticagrelor was slightly better than clopidogrel (0.1% for ticagrelor and 0.2% for clopidogrel.

There is no evidence to suggest that ticagrelor is hepatotoxic in humans.

Neurological System Effects

In PLATO, certain neurological events, particularly, intracranial bleeding events were adjudicated by a neurologist. The intracranial bleeding results were reviewed by the ICAC in a blinded fashion. It can be seen in Table 32 that there are a couple of categories of neurologically-related AEs that were more commonly seen in the ticagrelor treatment group, namely, thrombotic and hemorrhage (all) stroke [124 (1.34%) vs. 103 (1.12%) for ticagrelor-

treated and clopidogrel-treated patients, respectively] and focal weakness [17 (0.18%) vs. 11 (0.12%) for ticagrelor-treated and clopidogrel-treated patients, respectively.

Table 32: Neurological AEs

AE Category (renamed)	ticagrelor 90 mg bd N=9235	clopidogrel 75mg od N=9186	RR	95% CI
Dimentia	4 (0.04%)	12 (0.13%)	0.33	(0.11, 1.03)
Encephalopathy	27 (0.29%)	22 (0.24%)	1.22	(0.7, 2.14)
Focal weakness	17 (0.18%)	11 (0.12%)	1.54	(0.72, 3.28)
Gait disturbance, Fall	53 (0.57%)	66 (0.72%)	0.8	(0.56, 1.15)
Headache, migraine	640 (6.93%)	578 (6.29%)	1.1	(0.99, 1.23)
Hypotonia, Hypertonia	22 (0.24%)	24 (0.26%)	0.91	(0.51, 1.62)
Malaise, Fatigue, Weakness, Somnolence	552 (5.98%)	570 (6.21%)	0.96	(0.86, 1.08)
Neuropathy, Paresthesia, Hypoaesthesia, Numbness, Neuralgia	227 (2.46%)	230 (2.5%)	0.98	(0.82, 1.18)
Nonsustained ventricular tachycardia, SVT, unspecified Ventricular tachycardia	193 (2.09%)	191 (2.08%)	1.01	(0.82, 1.23)
Seizures	13 (0.14%)	16 (0.17%)	0.81	(0.39, 1.68)
Stroke/TIA	147 (1.59%)	137 (1.49%)	1.07	(0.85, 1.34)
Thrombotic or Hemorrhagic Stroke	124 (1.34%)	103 (1.12%)	1.2	(0.92, 1.55)
Thromoembolic event	63 (0.68%)	53 (0.58%)	1.18	(0.82, 1.7)
Transient Ischemic Attact	26 (0.28%)	38 (0.41%)	0.68	(0.41, 1.12)
Tremor	28 (0.3%)	21 (0.23%)	1.33	(0.75, 2.33)

As shown earlier in the bleeding analysis, Figure 15 is a K-M time to event analysis that clearly demonstrates the increased frequency and time to event for hemorrhagic stroke events in the ticagrelor-treated patients. In Figure 16, one can see that the ticagrelor group also had a higher frequency of all stroke events.

I analyzed the incidence of stroke/TIA for patients with a history of cerebrovascular disease (cerebrovascular, carotid artery, vertebrobasilar artery disease) to see if the risk would be higher for ticagrelor treated patients compared to clopidogrel treated patients. It is important to note that having a history of cerebrovascular disease greatly increased the risk of a cerebrovascular event during the PLATO trial, and this risk was greater in the ticagrelor arm than in the clopidogrel arm. By my analysis of PLATO, 8/99 (8.1%) patients who had a history of cerebrovascular disease upon study entry had a stroke or TIA event during the trial compared to 1.59% of all patients irrespective of medical history on ticagrelor having a stroke/TIA (RR=5.1). 4/99 (4.0%) patients in the clopidogrel arm with h/o of cerebrovascular disease had a stroke/TIA compared to 1.49% of all clopidogrel treated patients (RR=2.5). Of those patients, 2 of the ticagrelor treated patients had hemorrhagic cerebral events compared to 1 of the clopidogrel-treated patients. This means that for patients that had a history of cerebrovascular events, patients on ticagrelor had a RR of having another cerebrovascular event was 2.0 X higher than similar patients that were treated with clopidogrel. Also, there was 1 patient in each group that died after their events. In Table 33, the patients with a history of

cerebrovascular disease, carotid or vertebrobasilar disease who had an event during the trial are listed.

While I did not check for efficacy outcomes in this subpopulation of patients with a history of cerebrovascular disease, carotid artery disease and vertebrobasilar insufficiency, it is important to note that for every 1000 patients with these conditions before taking ticagrelor, 81 will have a consequent stroke or TIA on ticagrelor and 10 will die. This is an extraordinarily high number and supports the position that preexisting cerebrovascular disease, carotid artery disease and vertebrobasilar insufficiency should be contraindications for use of ticagrelor.

Figure 15: K-M: Hemorrhagic Stroke

K-M: Hemorrhagic Stroke

log rank p = 0.13

Group	Number failed	Number censored
AZD6140 BD	22	9213
CLOPIDOGREL 75 MG OD	13	9173
Combined	35	18386

Figure 16: K-M: Stroke

K-M: Stroke

log rank p = 0.22

Group	Number failed	Number censored
AZD6140 BD	123	9112
CLOPIDOGREL 75 MG OD	104	9082
Combined	227	18194
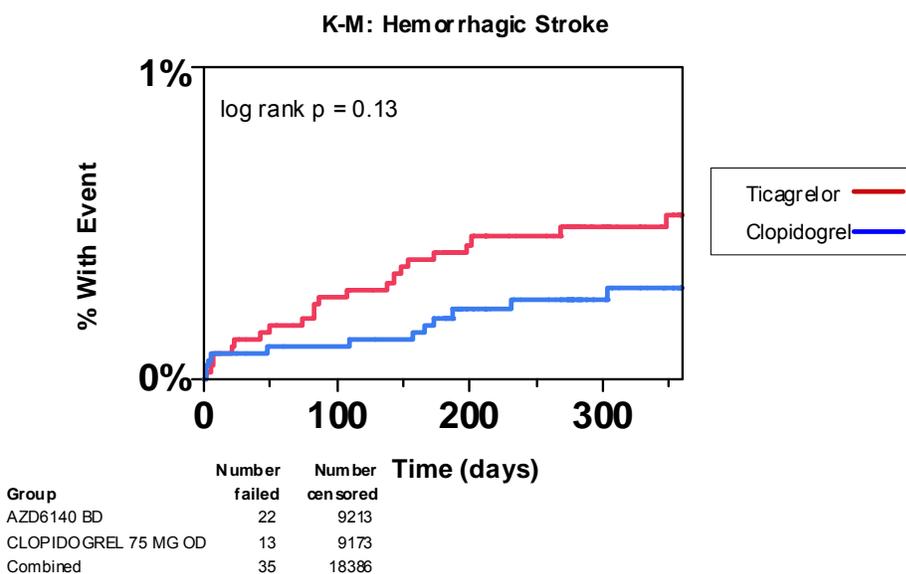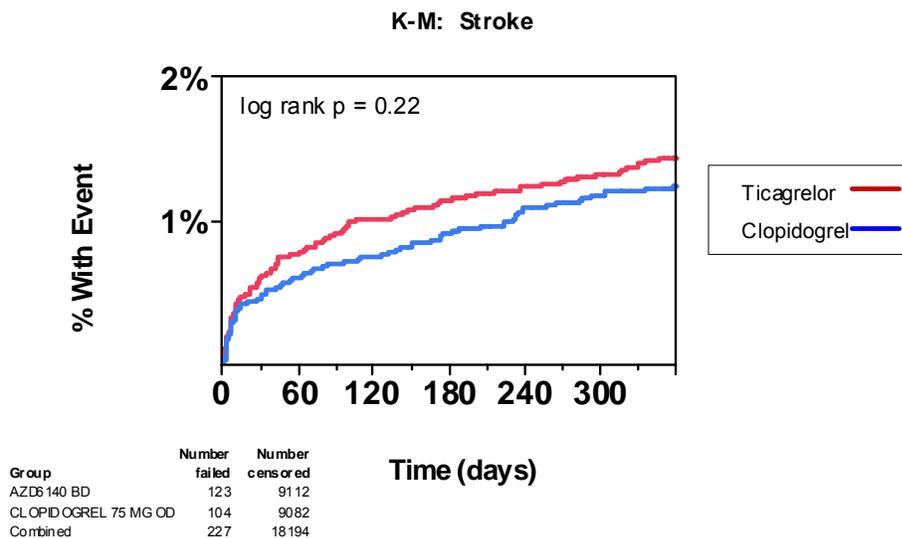
Table 33: Patients with h/o cerebrovascular, vertebrobasilar or carotid disease who had a cerebrovascular event

Treatment Ticagrelor		Treatment Clopidogrel	
History	**Verbatim term**	**History**	**Verbatim term**
Vertebrobasilar insufficiency	Ischemic stroke	Cerebral hemorrhage	Cerebral hemorrhage
Cerebrovascular Disorder	Cerebral hemorrhage	Subarachnoid hemorrhage	TIA during CABG
Cerebral Ischemia	Subarachnoid bleed	Cerebrovascular insufficiency	Ischemic stroke
Cerebral Vascular Accident	Ischemic stroke	Cerebrovascular accident	Acute ischemic cerebral infarct
Cerebral arteriosclerosis	Hemorrhagic stroke		
Vascular encephalopathy	Vascular encephalopathy, decompensated		
Carotid artery stenosis	Stroke		
Cerebrovascular accident	Cerebrovascular accident		

Table 34 shows the higher frequency of major/life-threatening intracranial hemorrhagic bleeds and fatal hemorrhagic bleeds in the ticagrelor group. Most notable is that the ticagrelor treatment group had 11 fatal intracranial bleeds compared to the 1 fatal intracranial bleed in the clopidogrel treatment group. There were no specific factor(s) to differentiate patients with intracranial bleeding events from others in PLATO. Demographic and clinical characteristics were similar between treatments with ticagrelor and clopidogrel.

Table 34: Intracranial Bleeds

Characteristic	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N =9186	RR
Number (percent) of Major Fatal/ Life-threatening Intracranial Bleeds	27 (26 patients) (0.3)	14 (0.15)	2
Fatal Events	11 (0.12)	1 (0.0)	
Out of the Hospital Events	17 (0.19)	10 (0.11)	1.73
Average days to bleed	161	160.9	

Modified from table in PLATO safety report, p.3541

Hemorrhagic stroke, is a concerning safety signal. There will need to be a warning about risk of all stroke and hemorrhagic stroke in the label, particularly if there is a history of prior cerebrovascular event or condition.

Neoplasms

There were no concerning findings with regard to neoplasms. See Section 7.6.1 for a detailed analysis.

7.4   Supportive Safety Results

7.4.1   Common Adverse Events

Table 35 displays the most common AEs by descending frequency of the sponsor's preferred terms that occurred in ≥ 2% of the patients. The most common AE was dyspnea in 12% of patients. While headache, cough, dizziness, nausea, atrial fibrillation and so on down the list were common, the only AEs with standout differences between treatment groups were dyspnea, epistaxis, contusion, and hematoma. This analysis supports the previous sections on the important AEs associated with ticagrelor.

Table 35: Sponsor analysis: PLATO: Common AEs by descending frequency of preferred terms by treatment that occurred in ≥ 2% of the patients

Preferred Term	ticagrelor 90mg bd	clopidogrel 75mg od
Dyspnea	1104 (12.0%)	598 (6.5%)
Headache	600 (6.5%)	535 (5.8%)
Epistaxis	558 (6.0%)	308 (3.4%)
Cough	452 (4.9%)	427 (4.6%)
Dizziness	418 (4.5%)	355 (3.9%)
Nausea	397 (4.3%)	346 (3.8%)
Atrial fibrillation	390 (4.2%)	418 (4.6%)
Contusion	357 (3.9%)	187 (2.0%)
Hypertension	353 (3.8%)	363 (4.0%)
Non-cardiac chest pain	344 (3.7%)	306 (3.3%)
Diarrhea	342 (3.7%)	304 (3.3%
Back pain	329 (3.6%)	301 (3.3%)
Hypotension	300 (3.2%)	306 (3.3%)
Fatigue	295 (3.2%)	296 (3.2%)
Chest pain	288 (3.1%)	323 (3.5%)
Bradycardia	269 (2.9%)	270 (2.9%)
Pyrexia	266 (2.9%)	261 (2.8%)
Vomiting	234 (2.5%)	215 (2.3%)
Cardiac failure	214 (2.3%)	236 (2.6%)
Edema peripheral	211 (2.3%)	228 (2.5%)
Hematoma	203 (2.2%)	122 (1.3%)
Constipation	202 (2.2%)	237 (2.6%)
Anxiety	200 (2.2%)	170 (1.9%)
Pain in extremity	196 (2.1%)	211 (2.3%)
Post procedural hemorrhage	192 (2.1%)	180 (2.0%)
Dyspepsia	185 (2.0%)	168 (1.8%)
Urinary tract infection	184 (2.0%)	161 (1.8%)
Ventricular tachycardia	184 (2.0%)	193 (2.1%)
Asthenia	181 (2.0%)	191 (2.1%)

Source: p. 85 in Clinical Summary of Safety, PLATO

As a sensitivity analysis, I renamed verbatim terms into my own broader group terms. The frequencies of AEs by these broader terms are included in Table 36. A lower rank means a higher relative risk. "Bleed, Hematoma" rose to the top of the list. Nevertheless, there were no

findings that differed substantially from the sponsor's analysis other than what has already been covered in this review.

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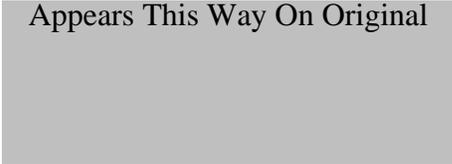
Table 36: Common AEs in order of decreasing frequency by treatment for AEs occurring ≥ 2% of the time

Category	ticagrelor 90 mg bid N=9235	clopidogrel 75 mg od N=9186	RR	95% CI	RANK
Bleed, Hematoma	3312 (35.86%)	2564 (27.91%)	1.28	(1.23, 1.34)	31
Muscle pain, Musculo-skeletal pain, Back pain	1913 (20.71%)	1833 (19.95%)	1.04	(0.98, 1.1)	75
Infection	1488 (16.11%)	1438 (15.65%)	1.03	(0.96, 1.1)	87
Arrhythmia	1349 (14.61%)	1330 (14.48%)	1.01	(0.94, 1.08)	94
Dyspnea	1345 (14.56%)	803 (8.74%)	1.67	(1.53, 1.81)	8
Gastroduodenal Disorder, Helicobactor Pylori	1333 (14.43%)	1230 (13.39%)	1.08	(1, 1.16)	67
Subcutaneous hemorrhage, Ecchymosis, Hematoma	1292 (13.99%)	811 (8.83%)	1.58	(1.46, 1.72)	12
Flu, Cold, Cough, Sore throat, Rhinitis, Hoarseness, Laryngeal disease	947 (10.25%)	882 (9.6%)	1.07	(0.98, 1.17)	70
PCI -related Bleed or Hematoma	924 (10.01%)	711 (7.74%)	1.29	(1.18, 1.42)	29
Noncardiac or unspecified Chest pain,	911 (9.86%)	904 (9.84%)	1	(0.92, 1.09)	99
Surgical, Post-surgical bleed/hematoma	821 (8.89%)	843 (9.18%)	0.97	(0.88, 1.06)	120
Lower Gastrointestinal disorders	806 (8.73%)	786 (8.56%)	1.02	(0.93, 1.12)	90
Coronary Artery Bypass Graft Bleed	748 (8.1%)	748 (8.14%)	0.99	(0.9, 1.1)	101
Supraventricular arrhythmia	688 (7.45%)	659 (7.17%)	1.04	(0.94, 1.15)	75
Headache, migraine	640 (6.93%)	578 (6.29%)	1.1	(0.99, 1.23)	60
Nausea, Vomiting	622 (6.74%)	539 (5.87%)	1.15	(1.03, 1.28)	48
Vertigo, Dizziness, Giddiness	603 (6.53%)	536 (5.83%)	1.12	(1, 1.25)	53
Epistaxis	574 (6.22%)	325 (3.54%)	1.76	(1.54, 2.01)	5
Acute and Chronic Heart failure, Cardiac asthma, Cardio-pulmonary heart failure, Diastolic	555 (6.01%)	576 (6.27%)	0.96	(0.86, 1.07)	122
Malaise, Fatigue, Weakness, Somnolence	552 (5.98%)	570 (6.21%)	0.96	(0.86, 1.08)	122
Bacterial infection	506 (5.48%)	492 (5.36%)	1.02	(0.91, 1.15)	90
Hypertension Increase, Crisis, Unstable Blood Pressure	490 (5.31%)	522 (5.68%)	0.93	(0.83, 1.05)	133
Viral Infection	466 (5.05%)	415 (4.52%)	1.12	(0.98, 1.27)	53

Category	ticagrelor 90 mg bid N=9235	clopidogrel 75 mg od N=9186	RR	95% CI	RANK
Atrial fibrillation	447 (4.84%)	455 (4.95%)	0.98	(0.86, 1.11)	116
Renal dysfunction, Polyuria, Anuria/oliguria, Incontinence	444 (4.81%)	362 (3.94%)	1.22	(1.07, 1.4)	35
Bradycardia	398 (4.31%)	369 (4.02%)	1.07	(0.93, 1.23)	70
Diarrhea	382 (4.14%)	339 (3.69%)	1.12	(0.97, 1.29)	53
Ventricular Arrhythmia	375 (4.06%)	415 (4.52%)	0.9	(0.78, 1.03)	140
Tachycardia	357 (3.87%)	358 (3.9%)	0.99	(0.86, 1.15)	101
Hypotension, Hypovolemic shock, Hypovolemia	353 (3.82%)	350 (3.81%)	1	(0.87, 1.16)	99
Anxiety and Agitation, Abnormal dreams, Stress, Agression	342 (3.7%)	279 (3.04%)	1.22	(1.04, 1.42)	35
Fever	331 (3.58%)	318 (3.46%)	1.04	(0.89, 1.2)	75
Gastrointestinal/ Anal bleed	327 (3.54%)	255 (2.78%)	1.28	(1.09, 1.5)	31
Anemia	315 (3.41%)	291 (3.17%)	1.08	(0.92, 1.26)	67
Edema (non-central, non-facial, non generalized)	306 (3.31%)	320 (3.48%)	0.95	(0.82, 1.11)	128
Accident, non-surgical/ procedural Trauma, Fracture	302 (3.27%)	255 (2.78%)	1.18	(1, 1.39)	42
Rash, Erythema	302 (3.27%)	296 (3.22%)	1.01	(0.87, 1.19)	94
Increased cholesterol, Decreased HDL, Increased lipids	282 (3.05%)	254 (2.77%)	1.1	(0.93, 1.31)	60
Hematuria	242 (2.62%)	195 (2.12%)	1.23	(1.02, 1.49)	34
Bronchopneomonia and Pneumonia, Pneumonitis	233 (2.52%)	245 (2.67%)	0.95	(0.79, 1.13)	128
Neuropathy, Paresthesia, Hypoaesthesia, Numbness, Neuralgia	227 (2.46%)	230 (2.5%)	0.98	(0.82, 1.18)	116
Sleep disorder	226 (2.45%)	230 (2.5%)	0.98	(0.82, 1.17)	116
Dyspnea on Exertion	224 (2.43%)	160 (1.74%)	1.39	(1.14, 1.7)	19
Constipation	220 (2.38%)	250 (2.72%)	0.88	(0.73, 1.05)	146
Electrolyte disorder	207 (2.24%)	220 (2.39%)	0.94	(0.78, 1.13)	131
Nonsustained ventricular tachycardia, SVT, unspecified Ventricular tachycardia	193 (2.09%)	191 (2.08%)	1.01	(0.82, 1.23)	94

When sorting my recategorized AEs by relative risk, there were several differences between treatment groups as shown in Table 37. Most of the AEs that are in this table and not in the common AEs ≥ 2% table include very few numbers of patients and there is little reason to be concerned about a drug related effect. The relatively high frequency of gynecomastia led to the initiation of further analysis which was discussed in a previous section.

Table 37: PLATO: Common AEs in order of descending relative risk by treatment

Category	ticagrelor N=9235	clopidogrel N=9186	RR	95% CI
Gynecomastia	15 (0.16%)	3 (0.03%)	4.97	(1.44, 17.17)
Leukemia	5 (0.05%)	2 (0.02%)	2.49	(0.48, 12.81)
Neutropenia	6 (0.06%)	3 (0.03%)	1.99	(0.5, 7.95)
Intracranial hemorrhage or subdural or other hematoma	32 (0.35%)	18 (0.2%)	1.77	(0.99, 3.15)
Epistaxis	574 (6.22%)	325 (3.54%)	1.76	(1.54, 2.01)
Angioedema	14 (0.15%)	8 (0.09%)	1.74	(0.73, 4.15)
Acidosis	12 (0.13%)	7 (0.08%)	1.71	(0.67, 4.33)
Dyspnea	1345 (14.56%)	803 (8.74%)	1.67	(1.53, 1.81)
Colonic Polyp, mass or cancer	20 (0.22%)	12 (0.13%)	1.66	(0.81, 3.39)
Infectious endocarditis, Myocarditis, Mediastinitis	15 (0.16%)	9 (0.1%)	1.66	(0.73, 3.79)
Acute psychosis, Hallucinations, Delusions	21 (0.23%)	13 (0.14%)	1.61	(0.81, 3.21)
Subcutaneous hemorrhage, Ecchymosis, Hematoma	1292 (13.99%)	811 (8.83%)	1.58	(1.46, 1.72)
Retroperiotoneal hematoma or hemorrhage	14 (0.15%)	9 (0.1%)	1.55	(0.67, 3.57)
Focal weakness	17 (0.18%)	11 (0.12%)	1.54	(0.72, 3.28)

Since there was only one dose of ticagrelor in the study, in order to look for a dose relationship for adverse events, I constructed a table (Table 38) that ordered the AEs (as I renamed them) by frequency by weight quintile. Quintile 1 is the lowest weight quintile and the quintile 5 is the highest weight quintile. The more negative the slope, the higher the likelihood that there is a dose relationship between the dose of drug and the adverse event category. I included in the table the most negative slopes and the most positive slopes to provide an idea about which AEs were or were not "dose related". In this analysis it appeared that gastroduodenal disorder, helicobacter pylori was highly "dose related". It appears that spontaneous bleeding and stroke were "dose related", while CABG bleeds, and arrhythmias were not. Dyspnea appeared to not be dose related by this analysis. However, the other evidence that exists to the contrary is more persuasive.

Table 38: Weight Relationship to AEs

Weight quintile (1 is lowest weight, 5 is highest weight)	1	2	3	4	5	slope (ticagrelor)	slope (clopidogrel)
ADVERSE EVENT							
Gastroduodenal Disorder, Helicobactor Pylori	18.65%	14.91%	13.58%	11.97%	12.62%	-15.00799	-9.857502
Bleed, Hematoma	36.25%	37.99%	36.13%	36.87%	32.14%	-9.347137	-5.753074
Nausea, Vomiting	8.70%	7.05%	6.66%	4.80%	6.14%	-7.361829	-8.858698
Subcutaneous hemorrhage, Ecchymosis, Hematoma	15.61%	14.27%	13.84%	13.44%	12.72%	-6.609833	-2.303132
Lower Gastrointestinal disorders	9.85%	9.45%	8.08%	8.81%	7.45%	-5.437616	-5.097829
PCI -related Bleed or Hematoma	11.34%	9.40%	10.09%	10.84%	8.16%	-4.915925	-2.530668
Anemia	4.97%	3.23%	3.01%	3.05%	2.61%	-4.905543	-4.942243
Hypotension, Hypovolemic shock, Hypovolemia	5.22%	4.17%	3.01%	3.05%	3.59%	-4.38474	-2.47548
Thrombotic or Hemorrhagic Stroke	1.99%	1.82%	1.16%	0.90%	0.71%	-3.481181	-1.396592
Constipation	3.28%	2.35%	2.32%	2.26%	1.63%	-3.391441	-2.96964
Cerebrovascular disease	2.49%	2.35%	1.58%	1.41%	1.31%	-3.299701	-2.445994
Stroke/TIA	2.24%	2.00%	1.27%	1.24%	1.09%	-3.054531	-2.307457
Diarrhea	4.72%	5.11%	3.12%	4.01%	3.75%	-3.043555	-3.459322
Vertigo, Dizziness, Giddiness	7.16%	6.69%	6.71%	5.65%	6.36%	-2.644468	0.608463
pulmonary heart failure, Diastolic dysfunction, Pulmonary	6.61%	5.52%	6.87%	5.76%	5.22%	-2.547007	-5.559518
Gastrointestinal/ Anal bleed	4.13%	3.64%	3.28%	3.90%	2.77%	-2.452637	0.244136
cardiogenic shock	2.44%	1.76%	1.22%	1.92%	1.20%	-2.322371	-3.272686
Valvular and Chordae abnormalities, murmurs	1.69%	1.53%	1.74%	0.85%	0.98%	-2.103555	-0.864023

Weight quintile (1 is lowest weight, 5 is highest weight)	1	2	3	4	5	slope (ticagrelor)	slope (clopidogrel)
ADVERSE EVENT							
Arrhythmia	12.98%	16.44%	13.79%	15.02%	15.17%	2.963531	5.676285
Ventricular Arrhythmia	2.93%	4.46%	4.23%	4.18%	4.62%	3.092144	2.213403
Viral Infection	4.03%	5.05%	4.97%	6.04%	5.33%	3.594145	4.385027
Dyspnea on Exertion	1.24%	2.76%	2.69%	2.20%	3.37%	3.69878	0.249861
Surgical, Post-surgical bleed/hematoma	7.26%	9.98%	8.14%	10.28%	9.08%	3.936201	-0.900987
Gout and Hyperuricemia	0.85%	1.35%	1.27%	1.86%	2.61%	4.042323	3.186416
Coronary Artery Bypass Graft Bleed	6.36%	8.98%	7.55%	9.49%	8.43%	4.629023	-0.02552
Infection	15.76%	14.86%	15.64%	17.00%	17.24%	5.088566	2.720359
Muscle pain, Musculo-skeletal pain, Back pain	18.45%	20.73%	20.18%	21.29%	23.27%	10.20925	9.057196
Dyspnea	12.08%	13.80%	14.58%	15.08%	17.51%	12.129	0.484967

7.4.2 Laboratory Findings

According to the Summary of Clinical Safety, hemoglobin, hematocrit, white blood cells and differentials, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), creatinine, glucose, and uric acid were collected in PLATO and the 4 Phase II studies.

Electrolytes

Because of the nonclinical observation of a possible mineralocorticoid effect for ticagrelor, I was interested in analyzing the changes in serum potassium. No serum electrolytes were measured in PLATO. The sponsor provided data from the Phase 2 study, DISPERSE2 I examined mean changes and outliers for potassium and sodium. For potassium, in all treatment groups the mean values increased by 0.1 to 0.3 meq/L but there were no differences between groups. There were very few outliers, mostly in the hyperkalemia range (> 5.5 meq/L) compared to the hypokalemia range (<3.5 meq/L) but there was no difference in frequency between treatment groups . If using more conservative cut points than what the sponsor chose, such as > 4.8 meq/L, there still were no apparent differences between groups. For sodium, there was a mean change from baseline of 0-2 meq/L and no differences between treatment groups. There were hardly any outliers (> 152 meq/L or < 132 meq/L). Even when using more conservative outlier measures for sodium than what the sponsor chose (>142 meq/L or <135 meq/L), while there was a greater frequency of outliers, there was no apparent difference between treatment groups.

I created an AE term called "electrolyte disorders". There was no difference between treatment groups in prevalence of patients having "electrolyte disorders" in PLATO [207 (2.24%) vs. 220(2.39%) in ticagrelor arm and clopidogrel arm, respectively].

Complete Blood Count

A very small percentage of patients experienced clinically important shifts in hematologic parameters (hemoglobin, white blood cells and platelet counts) and there were no treatment differences in these shifts throughout the study. For hemoglobin, 5% of ticagrelor-treated and 4% of clopidogrel-treated patients had a decrease from normal to low (AstraZeneca threshold of 11.5 g/dL for males or 10.5 g/dL for females). For white blood cells, 0.1% of the ticagrelor-treated and 0.2% of the clopidogrel-treated patients crossed the lower limit of the AstraZeneca threshold of 3×10^9 /L. For platelets, 0.1% of the ticagrelor-treated and 0.4% of the clopidogrel-treated patients crossed the lower limit of the AstraZeneca threshold of 100,000. Mean values for blood cells throughout treatment were also similar. In the phase 2 studies, there was no relationship between dose and changes to any component of the CBC. Thrombocytopenia does not appear to be a safety concern for ticagrelor.

Urinalysis

No urinalysis tests were measured in PLATO. This is disconcerting because the only studies that measured urinalyses were the small phase I studies and DISPERSE, the ticagrelor phase 2 dose-finding study that enrolled 146 male and 54 female patients, aged 34 to 84 years, with documented atherosclerotic disease. The overall mean exposure was only 27.9 days.
The data from the dose finding study, DISPERSE, revealed no worrisome findings. Particularly when one considers the creatinine categorical shifts seen more prominently in the ticagrelor-treatment group and accompanied by more renal AEs, it would have been worthwhile to have a better view of the urinalysis findings in PLATO with its larger target population and longer exposure.

Liver Enzymes

See discussion on hepatic effects in section 7.3.5 Submission Specific Primary Safety Concerns

7.4.3 Vital Signs

Pulse, systolic blood pressure and diastolic blood pressure were measured in PLATO and all Phase 2 studies. Additionally, PLATO measured waist circumference. The OFFSET, RESPOND and other pharmacodynamic studies also included respiratory rate and oral temperature. I evaluated the vital sign data from PLATO and OFFSET.

In PLATO, the changes in heart rate and blood pressure were examined by mean changes, shift tables that used reasonable prespecified thresholds, and absolute increases or decreases. There were some overall changes as described below but the changes were similar between treatment groups. Therefore, there are no changes to vital signs that appear to be related to ticagrelor.

Heart Rate
For heart rate, there was a drop of approximately 8 beats per minute in mean heart rate between Visit 1 and Visit 2. Approximately 5% of patients experienced a decrease in heart rate that crossed the AstraZeneca extended reference range (50 beats/min). Approximately 1.5% of patients experienced an increase that crossed the AstraZeneca extended reference range (100 beats/min). Bradycardia was more likely than tachycardia. This observation may have been related to changes in other medications and also to stabilization after the acute phase.

Blood Pressure
For both diastolic and systolic blood pressure there was a small reduction in mean values between Visit 1 and Visit 2 of approximately 6 mmHg, and no further reduction thereafter. At all visits, 4% and 1% of patients crossed the prespecified upper limit threshold of high systolic blood pressure (160 mmHg) and high diastolic blood pressure (100 mmHg), relative to the previous visit, respectively. There was only a 1% and 1% frequency of decreased systolic (less

than 100 mmHg) and diastolic blood pressure (less than 60 mmHg) relative to the previous visit, respectively. Patients were more likely to develop systolic hypertension (defined by sponsor as > 160 mmHg) than systolic hypotension (defined by sponsor as <100 mmHg) by the sponsor's prespecified standards (4% vs. 1%). Patients had low prevalence of either diastolic hypertension (defined by sponsor as >100 mmHg) or hypotension (defined by sponsor as <60 mmHg), (1% for both).

Waist circumference
There were no changes in mean waist circumference in both treatment groups.

7.4.5   Special Safety Studies/Clinical Trials

APPENDIX B: HOLTER Substudy for exploration of ventricular pauses

A thorough QT study (D5130C00037) was conducted. Ticagrelor was evaluated for effects on QTc interval at a single 900 mg oral dose, compared to placebo, using moxifloxacin as a positive control, in healthy volunteers age 18 to 45 years. The conclusion was reached that there was no cardiac ventricular repolarization effect with ticagrelor and no apparent ticagrelor plasma concentration-related increases in the QTc interval.

In phases 1 and 2, ventricular pauses and adverse events related to bradycardia were observed with ticagrelor, including in a few individual healthy volunteers.   Observations of cardiac arrhythmias from Phase I and II studies include the following examples:

- In a Phase I single ascending dose study (CSR D5130C00049), a healthy volunteer experienced 2 long periods of sinus and ventricular arrest (the longer of these 2episodes was approximately 11 seconds), high-grade AV block, and ventricular escape rhythm associated with syncope as well as nausea and vomiting following ingestion of a 1260 mg single dose of ticagrelor, a 14-fold multiple of the maintenance dose in PLATO.

- In the Phase I Thorough QT study (CSR D5130C00037), during prolonged telemetry, episodes of AV block were observed for 1 healthy volunteer. These were recorded 1 to 1.5 hours post dose, and again approximately 70 hours post dose. The ticagrelor dose given was 900 mg. The ECG changes included first-degree AV block and second-degree AV block with Wenckebach phenomenon, and episodes of 2 to 3 non-conducted P waves superimposed on more pronounced sinus bradycardia and sinus arrhythmia. No pauses >5 seconds occurred, and the QRS complexes were narrow. The volunteer was asymptomatic during these episodes.

- The Phase II study DISPERSE2 examined the safety and tolerability of ticagrelor for up to 12 weeks in patients who had non-ST elevation ACS events. In total, 990 patients were randomized into 3 groups: 1) ticagrelor 90 mg bd; 2) ticagrelor180 mg bd; or 3)

clopidogrel 75 mg od. In DISPERSE2 there was a dose-related association of ticagrelor treatment with an increased occurrence of ventricular pauses ≥2.5 seconds detected on Holter ECG recordings obtained during the first week after the index hospitalization. The incidence was 4.4% for clopidogrel, 5.6% for ticagrelor 90 mg bd, and 9.9% with ticagrelor 180 mg bd. Most of these pauses were asymptomatic and due to sinus node arrest or sinoatrial (SA) block, although a few were due to AV block. In the few cases associated with symptoms, no clear relationship existed between these symptoms and the time of administration of study therapy. A variety of potentially confounding clinical factors prevented a clear assessment of causality.

The sponsors decided to conduct a Holter substudy as part of PLATO to further elucidate the relationship between ticagrelor and ventricular pauses as well as other arrhythmias.

In this section, I will review the Holter substudy (D5130C05262) and observations during the main body of the PLATO trial related to cardiac arrhythmias and arrhythmia related symptoms. The primary variable of interest was the occurrence of ventricular pauses ≥3 seconds. Secondary variables included longer lengths of pauses, other bradycardic episodes, heart rate (HR), atrial (supraventricular) tachyarrhythmias, and ventricular arrhythmias.

Holter monitoring was initiated at or shortly after the administration of first dose of study drug and continued for up to 7 days following randomization. For those patients who had Holter monitoring during the initial hospitalization, repeat monitoring was performed during Visit 2 when possible. These were done on an outpatient basis with recordings of up to 7 days duration. The recording during Visit 1 was performed to capture pauses during the acute phase when patients are at the greatest risk of ischemia-related arrhythmias and because this was the same time frame when increased pauses were observed in DISPERSE2. After unblinding of the data, the sponsor decided not to analyze the Holter monitor reports of patients who were not on treatment at Visit 2. This choice was appropriate because there were very few patients that fell into this category (3.8%) and because presence or lack of findings in this group of patients would tend to obfuscate rather than clarify differences between the two treatment groups. A much larger concern was that approximately 1/3 of the patients in each treatment group had no Visit 2 monitoring, for mostly "unknown" reason or premature discontinuation of study drug. Nevertheless, the results of the Visit 1 Holter monitor readings were captured in these patients and were included in the study report. This was not an ideal choice, but since the data was available, there was no great cause for concern.

Holter recording during procedures (such as PCI) was left to the investigator's discretion, so some recordings may have continued during PCI while others may have been interrupted during the procedure. Therefore, no specific information was collected about arrhythmias that occurred during procedures. For patients with ventricular pauses ≥10 seconds that occurred less than 5 times during Holter monitoring, there was an additional review of data to ensure that those isolated episodes were not recording artifacts.

The Holter recordings were analyzed centrally using an automated arrhythmia detection program followed by cardiologist review at the ECG core laboratory. The following variables were detected:

- Heart rate (mean, minimum, maximum)
- Ventricular pauses including duration and mechanism (such as absence of ventricular electrical activity ≥3 seconds as a result of SA node pause, atrial fibrillation with slow ventricular response, supraventricular rhythm with high degree A-V block or other mechanism)
- Dropped beats
- Bradycardia defined by at least 4 consecutive beats at a rate ≤ 45 beats per minute
- Atrial fibrillation defined as an ECG finding of supraventricular tachyarrhythmia (SVT) characterized by irregular A-V conduction and absence of regular p waves
- Atrial flutter defined as an ECG finding of SVT characterized by a rapid atrial rhythm (≥ 220 bpm), slower ventricular response, and the presence of atrial flutter waves
- Other SVT
- Non-sustained ventricular tachycardia defined as an ECG finding of ventricular tachycardia lasting < 30 seconds
- Sustained ventricular tachycardia defined as an ECG finding of a ventricular tachycardia that lasts > 30 seconds
- Ventricular fibrillation defined as showing irregular and changing ventricular wave patterns of varying contours and amplitude without discernible QRS complexes

Determination of Sample Size

The target sample size of 2500 for the Holter recordings allowed for a 20% non-completion rate for the second recording so that at least 2000 paired recordings were obtained. With 2000 patients receiving Holter monitoring (1000 per treatment group) at both visits and an expected rate of ventricular pauses of about 5% in the clopidogrel group based on DISPERSE2, the 95% CI for an absolute 5% increase in the ticagrelor group was expected to be an absolute increase of 2.7% to 7.3%.During the study, the number of patients with Visit 1 Holter monitoring was increased by about 20% to ensure that there were enough patients that had paired readings during Visit 1and Visit 2 since the attrition rate between Visit 1 and Visit 2 was higher than expected. This was a reasonable approach.

Study Subjects/ Disposition
In total, 2908 patients were included in the Holter analysis set from 41 of the 43 countries that participated in PLATO.

Four hundred sixty-one of the 862 study centers in PLATO conducted Holter monitoring and had patients included in the Holter analysis set. Although it was intended that all patients at sites with monitoring equipment would have Holter monitoring starting at the beginning of the study, there were some patients not monitored for logistical reasons or as a result of their

medical condition. The sponsor stated that there was no deliberate selection of patients for inclusion. This method of patient selection was reasonable.

Demographics

In Table 39, one can see that the distribution of demographic characteristics was similar between the treatment groups. The maximum weight was higher in the clopidogrel group (175 kg vs. 163 kg) whereas the maximum BMI was higher in the Ticagrelor group (68 vs. 56). Because the means and medians were similar for weight and BMI, there is no cause for concern.

Most of the characteristics were similar in this substudy when compared to the characteristics of the PLATO full analysis set.

Table 39: Demographics for Holter Substudy

Characteristic	Statistic or Category	Ticagrelor 90 mg bd N = 1472	Clopidogrel 75 mg od N = 1436	Total N = 2908
Age (years)	N	1472	1436	2908
	Mean	63.1	63	63
	SD	11.49	11.34	11.41
	Median	64	63	63
	Min	26	25	25
	Max	97	91	97
Sex	Total	1472 (100%)	1436 (100%)	2908 (100%)
	Male	1085 (73.7%)	1052 (73.3%)	2137 (73.5%)
	Female	387 (26.3%)	384 (26.7%)	771 (26.5%)
Weight (kg)	N	1471	1435	2906
	Mean	81.4	80.6	81
	SD	16.63	16.74	16.69
	Median	80	80	80
	Min	41	40	40
	Max	163	175	175
BMI (kg/m2)	N	1468	1430	2898
	Mean	27.9	27.7	27.8
	SD	4.96	5	4.98
	Median	27.3	27.1	27.2
	Min	13	13	13
	Max	68	56	68
Smoking Status	Total	1472	1436	2908
	Non-smoker	514 (34.9%)	515 (35.9%)	1029 (35.4%)
	Ex-smoker	439 (29.8%)	405 (28.2%)	844 (29.0%)
	Habitual smoker	519 (35.3%)	516 (35.9%)	1035 (35.6%)

Source: Holter study report, p. 28, 29

There were numerically fewer patients with persistent ST segment elevation (29.4% of patients in the Holter analysis set) than in the PLATO full analysis set (37.6% total) for both treatment groups combined. This was probably because of the greater urgency of treatment of patients with STEMI and the desire to minimize additional steps prior to intervention.

There was similar use of the various concomitant medications that might affect SA and AV nodal function during Holter monitoring between the groups (Beta-blockers, antiarrhythmics, calcium channel blockers, amiodarone, digoxin, adenosine, dipyridamole and ivabradine, and CYP3A inhibitors).

Results

Exposure

The number of patients with at least 1 dose of study drug during the Visit 1 or Visit 2 Holter monitoring period was similar between treatment groups (for Visit 1 there were 1451patients in the ticagrelor group and 1415 patients in the clopidogrel group and for Visit 2 there were 985 patients in the ticagrelor group and 1006 patients in the clopidogrel group). The high attrition rate between Visit 1 and 2 was not explained but it was similarly high in both groups (approximately 1/3). The reason that only 2/3 of the patients were evaluated in the main analysis is that the sponsor chose to analyze only paired readings.

Main Analysis

The findings as shown in Table 40, were that there was a higher frequency of ventricular pauses ≥ 3 seconds in the ticagrelor as compared to the clopidogrel group, mostly at Visit 1, which occurred during the acute phase of their coronary syndrome. There were more ventricular pauses for both treatment groups during Visit 1 compared to Visit 2, presumably because patients with acute coronary syndrome have a greater susceptibility to arrhythmias. Most pauses were SA node pauses. Although there were fewer overall ventricular pauses ≥ 5 seconds, the same pattern persisted. It is unfortunate that only approximately 2/3 of patients were captured in this analysis. However, this was enough to capture differences between the groups. The relative risk for having a ventricular pause ≥ 3 seconds when treated with ticagrelor compared to when treated with clopidogrel at Visit 1 was 1.743 (1.152 -2.637) but only 1.341 (0.704 – 2.554) at Visit 2.

For all patients who had Holter monitors (including the 487 patients in the ticagrelor group and 430 patients in the clopidogrel group who had Visit 1 but not Visit 2 recordings), ticagrelor-treated patients had a higher risk of having a ventricular pause ≥ 3 seconds during Visit 1 than clopidogrel-treated patients (RR=1.61 [95% CI 1.14, 2.26]). This corroborative finding made the sponsor's choice to not include patients without paired Holters in the main analysis less objectionable.

Table 40: Arrhythmias at Visit 1 and Visit 2 for patients with paired readings

Characteristic	Statistic or Category	Visit 1		Visit 2	
		Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od
Total Patients	N	964	985	964	985
Duration of Holter Monitoring (Days)	Mean (SD)	6.1 (1.27)	6.0 (1.50)	6.0 (1.59)	5.9 (1.66)
Heart rate (bpm)	Mean (SD)	68.0 (10.52)	67.9 (10.09)	68.1 (10.21)	67.9 (10.22)
Patients with at least 1 bradyarrhythmia		571 (59.2%)	531 (53.9%)	556 (57.7%)	498 (50.6%)
Ventricular pauses ≥ 3 secs		58 (6.0%)	34 (3.5%)	21 (2.2%)	16 (1.6%)
AV node pause ≥3 secs		15 (1.6%)	11 (1.1%)	6 (0.6%)	7 (0.7%)
SA node pause ≥3 secs		43 (4.5%)	22 (2.2%)	17 (1.8%)	11 (1.1%)
Other pause ≥3 secs		4 (0.4%)	4 (0.4%)	0	0
Ventricular pauses ≥5 secs		20 (2.1%)	10 (1.0%)	8 (0.8%)	5 (0.5%)
AV node pause ≥5 secs		6 (0.6%)	5 (0.5%)	2 (0.2%)	1 (0.1%)
SA node pause ≥5 secs		15 (1.6%)	4 (0.4%)	7 (0.7%)	4 (0.4%)
Other pause ≥5 secs		0	2 (0.2%)	0	0
Dropped Beats		321 (33.3%)	298 (30.3%)	288 (29.9%)	262 (26.6%)
Bradycardia		400 (41.5%)	385 (39.1%)	401 (41.6%)	372 (37.8%)
Patients with at least 1 tachyarrhythmia		690 (71.6%)	687 (69.7%)	592 (61.4%)	614 (62.3%)
Supraventricular Tachyarrhythmia		571 (59.2%)	567 (57.6%)	517 (53.6%)	543 (55.1%)
Ventricular Tachyarrhythmia		361 (37.4%)	347 (35.2%)	207 (21.5%)	214 (21.7%)

Source: Holter study report p.37

Risk Factors for Developing Arrhythmias and Pauses

Apparent risk factors for developing ventricular pauses were higher mean weight and BMI if one was in the ticagrelor treatment group only, having a medical history of diabetes for both treatment groups and being on concomitant medications for both treatment groups.

Patients with ventricular pauses ≥3 seconds had a higher mean weight, especially in the ticagrelor group, compared to patients without pauses; the mean weight was 86.1 kg for patients with pauses compared to 81.1 kg for patients without pauses in the ticagrelor-treated group. This pattern was not evident in the clopidogrel-treated group. Mean BMI and BMI groups followed the same patterns in the ticagrelor group only.

Patients with ventricular pauses ≥3 seconds were also more likely to have diabetes in both treatment groups; in the ticagrelor group 28.1% of patients with vs. 23.2% of patients without pauses had diabetes and in the clopidogrel group. 33.9% of patients with pauses vs. 25.7% of patients without pauses had diabetes. A numerically higher percentage of patients with ventricular pauses ≥3 seconds in the ticagrelor group compared to clopidogrel, were taking selected concomitant medications such as CYP3A moderate inhibitors, calcium channel blockers, and >1 medication known to predispose patients to arrhythmias. The absolute difference in the number of patients taking these medications was relatively small and unlikely to account for any differences in arrhythmic episodes between treatment groups. These patterns were also observed in patients with ventricular pauses ≥5 seconds.

Ventricular Pauses by Time of Day

There was a numerically higher occurrence of nocturnal pauses with ticagrelor compared to clopidogrel in patients that had 5 or more ventricular pauses of ≥ 3 seconds during Holter monitoring periods. Only 23 and 10 patients tell into this category in the ticagrelor-treatment group and clopidogrel-treatment group, respectively. See Figure 17. If there were fewer than 5 ventricular pauses during the Holter monitoring period, the pattern was not as pronounced. Most of the ventricular pauses were asymptomatic. Increased ventricular pauses at night may be attributable to increased vagal tone during sleep or possibly because of sleep apnea which causes hypoxia. Hypoxia was shown in another AstraZeneca study to increase ticagrelor-induced inhibition of adenosine reuptake in cardiomyocytes, leading to increased interstitial levels of adenosine. One might postulate that hypoxia might cause patients to have more ventricular pauses and therefore, ticagrelor might be best avoided in patients with sleep apnea and advanced COPD.

Figure 17: Patients with 5 or more non-agonal ventricular pauses ≥ 3 seconds by hour of the day
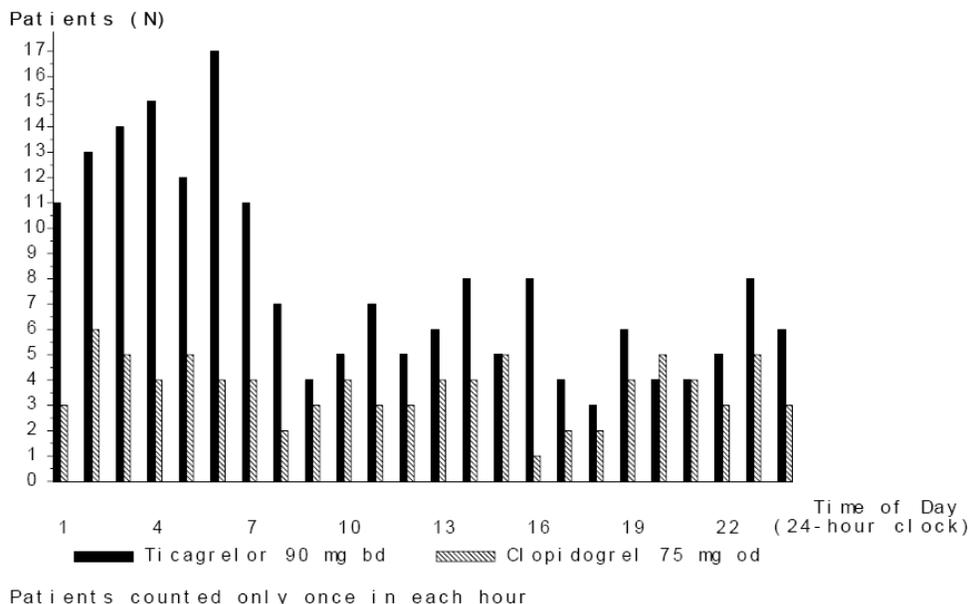
Source: Holter study report p. 46

Proposed Mechanism for Ventricular Pauses

The pathophysiological mechanism for the increase in ventricular pauses with ticagrelor is not known, but the sponsor's hypothesis is that ticagrelor-induced adenosine reuptake inhibition may be playing a role, especially in the setting of ACS, where there may be increased release of adenosine due to ischemia. Adenosine depresses sinoatrial node activity, AV nodal conduction, and ventricular automaticity, and attenuates cardiac stimulatory action of catecholamines and the release of norepinephrine from nerve terminals[6.] The sponsor added that other mechanisms may also be involved in addition to an adenosine-mediated effect, e.g., increased vagal tone.

Tachyarrhythmias

Tacharrhythmias were more common during Visit 1 Holters compared to visit 2 Holters (70.7% vs. 61.9%). Additionally there were some numerical differences between the treatment groups that generally trended to worse results for patients treated with ticagrelor. For instance, for Visit 1 Holter, there were 37.4% vs. 35.2% of patients who had ventricular arrhythmias, for ticagrelor and clopidogrel respectively. There were 37.3% vs. 34.9% of patients treated with ticagrelor vs. clopidogrel, respectively, who had non-sustained ventricular tachycardia (NSVT)

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6 Belardinelli L, Lerman BB. Adenosine: Cardiac Electrophysiology. Pacing Clin Electrophysiol 1991;14:1672-80.

≥ 4 seconds and < 30 seconds. There were 59.2% vs. 57.6% of patients treated with ticagrelor vs. clopidogrel, respectively, in Visit 1 Holter who had supraventricular tachyarrhythmia. Contrary to these results, fewer patients treated with ticagrelor had sustained ventricular tachycardia in the Visit 1 Holter period (0.9% vs. 1.4%) but the numbers were extremely small (9 vs. 14).

Symptoms

As shown in Table 41, the sponsor found no glaring differences in the frequency of the preferred terms (PTs) bradycardia, symptomatic or asymptomatic events between treatment groups when looking at the full safety data set. In my analysis of SAEs, there were no substantial differences between treatment groups for the SAE PT of bradycardia.

Table 41: Sponsor's Analysis: Bradycardia in PLATO Safety Analysis Set

Characteristic	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N=9186
Total patients with ≥1 event	435 (4.7%)	400 (4.4%)
Symptomatic event	172 (1.9%)	183 (2.0%)
Bradyarrhythmia	122 (1.3%)	97 (1.1%)
SA node dysfunction[a]	33 (0.4%)	32 (0.3%)
AV block II and III	38 (0.4%)	29 (0.3%)
Vasovagal reaction	38 (0.4%)	36 (0.4%)
Other cardiac cause	48 (0.5%)	61 (0.7%)
Other known cause	141 (1.5%)	129 (1.4%)
Unknown/uncertain cause	80 (0.9%)	67 (0.7%)

Source: PLATO study report, p. 283

When looking at the small group of patients in the Holter substudy with pauses ≥ 3 seconds (89 in the ticagrelor group and 62 in the clopidogrel group), there was 1 case of syncope in each treatment group that occurred during the Holter period. Also during the Holter period, 1 patient in the ticagrelor group had dizziness while 2 patients in the clopidogrel group had dizziness.

During the full course of the Holter substudy, patients with pauses ≥ 3 seconds during the Holter period were more likely to experience the following symptoms if they were on ticagrelor: Dizziness, 6 patients on ticagrelor, and syncope (4 patients on ticagrelor:1 patient on clopidogrel). No patients with long pauses had loss of consciousness during the study.

Pacemaker insertion in patients with ventricular pauses ≥5 seconds was generally similar between treatment groups (3 patients [9.4%] in the ticagrelor group and 2 [10.0%] in the clopidogrel group), as were temporary and permanent pacemaker placement. Among all patients in the Holter analysis set, numerically fewer patients in the ticagrelor group had pacemaker placement compared to patients in the clopidogrel group.

Conclusions

This was a well designed study that demonstrated that ticagrelor causes more arrhythmias and pauses than clopidogrel. Since there were more cases of dizziness and syncope in the ticagrelor treatment group, ventricular pauses may be a real safety issue. Nevertheless, in view of the decreased prevalence of cardiac arrest in ticagrelor-treated patients, it is probably best to accept these increases in arrhythmia-related symptoms as part of an acceptable risk-benefit tradeoff.

One limitation of PLATO study is that patients with an increased risk of bradycardic events (e.g., no pacemaker and known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker) were excluded from the study so there is limited information of the effect of ticagrelor on patients with these conditions.

PULMONARY FUNCTION Substudy exploration of dyspnea

In PLATO, a pulmonary function substudy was designed to examine the effect of ticagrelor, 90 mg bd, in comparison to clopidogrel, 75 mg od on pulmonary function in a subset of ACS patients.

The purpose of this substudy was to determine the impact of chronic dosing with ticagrelor, lasting at least 6 months and up to 12 months, on pulmonary function in patients with ACS.

Primary Objective
The primary objective of this pulmonary function substudy was to evaluate the effects of ticagrelor in comparison with clopidogrel on forced expiratory volume in 1 second (FEV_1) after completion of study treatment.

Schema

Figure 18 shows the design of the substudy within the whole PLATO study and the sequence of measurement periods. Pulmonary function tests (PFT) were performed in conjunction with study visits for the PLATO study within the allowable visit windows.

Figure 18: Schema of Pulmonary Function Test Study

PFT (Pulmonary function test)

The following measurements were done in order of measurement:
1. Blood oxygen saturation (SpO_2) using pulse oximetry
2. Lung volumes: functional residual capacity (FRC); total lung capacity (TLC); and residual volume (RV) by plethysmography (mean of 3 values that had values within 5%)
3. Single-breath diffusion capacity for the lungs, measured using carbon monoxide ($DLCO_{SB}$).
4. The hemoglobin was measured within 10 days of the PFT. (average of 2 similar values)
5. Spirometry: forced expiratory volume in 1 second (FEV_1); forced vital capacity (FVC); mean forced expiratory flow between 25% and 75% of the FVC (FEF_{25-75}) before and 20 minutes after a short-acting β_2 agonist e.g. albuterol. (mean of at least 3 values that considered good studies and were free of artifact)

The sponsor's rationale for conducting the PFT studies at the prespecified intervals was because most dyspnea episodes began within the first 30 days of treatment. While this method may capture some patients while they were complaining of dyspnea, it would have been better, in order to increase capture of PFT abnormalities, to also conduct the PFTs at the time of dyspnea episode.

The sponsor eliminated tests that were way out of the norm for that patient and/or had artifactual data. While it is never good to eliminate data, in this case it is reasonable to decrease the erroneous effect that outliers would have on the results. The sponsor also averaged the remaining results as an imputed data point. A concern is that the effect of elimination of data and instead using an average the remaining values as a substitute may have obscured abnormalities and differences between the treatment groups.

Patient Selection

Patients were selected from a subset of centers in a subset of countries participating in the PLATO study (fifteen centers in 5 countries (Czech Republic, Hungary, India, Poland and US)

The sites were required to have access to a pulmonary function test laboratory and to an adequate pool of PLATO participants. These requirements could have introduced a selection bias. The sponsor stated that it was not possible for all sites to participate given "timing and logistical restraints." These constraints were not elaborated upon. All PLATO participants who were eligible at the selected sites were invited to join the substudy to decrease further selection bias.

Inclusion criteria

1. Patients must have provided written informed consent for the substudy
2. Patients must have been able to perform all the necessary lung function tests

Exclusion criteria

The exclusion criteria were designed to provide a patient population in which PFTs could be used to identify meaningful changes in pulmonary function as a result of treatment with ticagrelor versus clopidogrel.

1. Patients who have discontinued study medication prior to the first Pulmonary Function assessment
2. Patients with advanced lung disease such as chronic obstructive pulmonary disease (to avoid confounding results)
3. Patients with symptomatic Heart Failure
4. Participants whose index event resulted in a coronary artery bypass graft (CABG)

These inclusion and exclusion criteria are reasonable in theory because confounding and excess "noise" will be limited. However, if a patient discontinued for any AE, particularly dyspnea, it would have been very informative to capture that patient's PFT data at time of dyspnea. In fact, the choice to not capture patients with AEs of dyspnea at the time of dyspnea may have obscured an effect of ticagrelor on PFTs.

Disposition

The pulmonary function substudy protocol specified that up to 450 patients would be enrolled in the pulmonary function substudy with the expectation that 250 would complete (125 in each treatment group). As displayed in Table 42, only 199 patients enrolled in the pulmonary function substudy. More than 80% (166 patients in total) completed Visit 102 and more than 70% (147 patients in total) completed Visit 103. Within each visit, the number of patients who remained in the substudy was somewhat better for the clopidogrel group. The difference was mostly accounted for by withdrawal of informed consent. The sponsor provided no information about why patients withdrew consent.

The sponsor stated that the reason for the low enrollment was that the substudy started enrollment late relative to the overall PLATO study. Clearly, this low enrollment would have the impact of obscuring any differences between the treatment groups if they existed.

Table 42: Disposition

Characteristic	Ticagrelor 90 mg bd N = 101	Clopidogrel 75 mg od N = 98
Patients who had Visit 101	101 (100%)	98 (100%)
Patients who had Visit 102	80 (79.2%)	86 (87.8%)
Patients missing Visit 102 (no substudy withdrawal)	4 (4.0%)	1 (1.0%)
Patients with substudy withdrawal after Visit 101 and prior to Visit 102	17 (16.8%)	11 (11.2%)
Adverse Event	2 (2.0%)	1 (1.0%)
Subject Withdrawal of Informed Consent	13 (12.9%)	9 (9.2%)
Safety Concerns	1 (1.0%)	1 (1.0%)
Severe noncompliance	1 (1.0%)	0
Patients who had Visit 103	71 (70.3%)	76 (77.6%)
Patients missing Visit 103 (no substudy withdrawal)	2 (2.0%)	1 (1.0%)
Patients with substudy withdrawal after Visit 102 and prior to Visit 103	12 (11.9%)	10 (10.2%)
Adverse Event	2 (2.0%)	0
Subject Withdrawal of Informed Consent	9 (8.9%)	10 (10.2%
Severe noncompliance	1 (1.0%)	0

Source: PFT substudy report

Demographics

The most significant demographic difference between the PFT Substudy patients and the patient enrolled in PLATO as a whole was the higher percentage of current or x-smokers (62% ticagrelor and 55% clopidogrel). The effect of increased numbers of patients with a history of smoking on the study cannot be known. It may have magnified or obscured a differences in PFTs between the treatment groups.

Results

The sponsor reported that there were no differences observed in any of the measured pulmonary function variables in ticagrelor-treated patients as compared with clopidogrel-treated patients at any time point of assessment. The sponsor also concluded that there was no evidence of changes in lung function over time in patients taking ticagrelor compared to

those taking clopidogrel. The statistical tests, however, were done using mean measurements which may have obscured differences.

There were a few limitations of the study that relate to the study design, execution and analysis.
1. No baseline values (would be hard to do).
2. Outlier data was eliminated and substituted with averages of other data during the study which could obscure differences.
3. High percentage of patients in both treatment groups with h/o current or past smoking (ticagrelor 62%, clopidogrel 55%) which could obscure differences because of preexisting PFT abnormalities
4. Fewer patients than expected enrolled in this substudy.
5. The exposure was 6 months only in most of these patients.
6. Few of the patients had dyspnea, especially unexplained dyspnea at enrollment.
7. PFTs were not done at time of dyspneic episodes
8. The smaller than expected sample size reduced the power for detecting differences between groups.
9. Using mean values reduced the power for detecting differences.

Conclusions
The numerous limitations of this study make it difficult to interpret its results. A higher powered study with more dyspneic patients would be necessary to convince this reviewer that ticagrelor has no effect on PFTs. Additionally, it would be important to have some idea of how patients in the midst of a dyspneic episode perform on their PFTs.

7.4.6   Immunogenicity

There was an increase in angioedema in the ticagrelor arm in the all AE data but this evened out when looking at angioedema SAEs. The numbers are small and there were no other disturbing signs for excessive immunogenicity for ticagrelor. In fact, the term "allergy and hypersensitivity" AEs and SAEs which includes the other categories listed in these tables favors ticagrelor. The AEs and the SAEs for immunologically mediated disorders are listed in a tabular form in Table 43 and in Table 44, respectively.

Table 43: Immunologically mediated AEs from PLATO dataset

AE Category	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N=9186	RR	CI
Anaphylaxis, Anaphylactoid reaction	8 (0.09%)	9 (0.1%)	0.88	(0.34, 2.29)
Allergy, Hypersensitivity	148 (1.6%)	158 (1.72%)	0.93	(0.75, 1.16)
Angioedema	14 (0.15%)	8 (0.09%)	1.74	(0.73, 4.15)
Laryngeal Edema	70 (0.76%)	67 (0.73%)	1.04	(0.74, 1.45)

Table 44: Immunologically mediated SAEs from PLATO dataset

SAE Category	ticagrelor 90 mg bd N= 9235	clopidogrel 75 mg bd N=9186	RR	95% CI
Anaphylaxis, Anaphylactoid reaction	3 (0.03%)	4 (0.04%)	0.75	(0.17, 3.33)
Allergy, Hypersensitivity	7 (0.08%)	18 (0.2%)	0.39	(0.16, 0.93)
Angioedema	3 (0.03%)	4 (0.04%)	0.75	(0.17, 3.33)
Laryngeal Edema	0 (0%)	2 (0.02%)	0	

7.5   Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Exposure-response relationships were established for major and for major + minor bleeding, however the response curve is very shallow.

7.5.2 Time Dependency for Adverse Events

For dyspnea, a time-dependent exposure-response relationship, which was most pronounced at the start of the treatment period, was identified. At visit 1, slightly over 5% of patients had dyspnea (mild to severe), which decreased to <5% at visit 2, > 3% but < 5% by visit 3, approximately 3% by visit 4 and less than 2% by visit 6. Approximately 10% of patients that had dyspnea dropped out during the study for AEs. For most patients the dyspnea went away during the study while on study drug.

7.5.3   Drug-Demographic Interactions

The sponsor evaluated safety by different demographic features using data from PLATO. The following demographic categories were evaluated: age, gender, racial origin, BMI, baseline hepatic impairment, baseline renal impairment, or baseline diabetes (all intrinsic factors) and geographic distribution, smoking status, and concomitant medication use (extrinsic factor).

Age
The frequency of AEs, SAEs, and DAEs increased with age regardless of treatment group. The percentage of patients reporting AEs increased with increasing age in both treatment groups.

Gender
In PLATO, women on ticagrelor tended to have more AEs, including SAEs, DAEs and deaths than men. Only for overall adverse events during treatment was there a difference between the treatment groups. For overall AEs, women did not have more events than men when they were treated with clopidogrel. This observed difference is probably has no clinical significance.

Race
There were few patients that were not Caucasian. There were only 222 patients that were Black, 1081 that were "Oriental" (which does not include those of Indian and southwest Asian descent, only Chinese and Japanese) and 219 that were "Other". While there were some numerical differences among racial groups, the small patient counts make it more likely that these findings were the result of chance.

Of note, there was 40% greater exposure to ticagrelor in Japanese compared to Caucasians shown in an 8 day phase 1 study (for both Cmax and AUC). The maximum dose of ticagrelor was 300 mg bd. Despite these differences, the 36 healthy male Japanese volunteers that enrolled in this study generally tolerated ticagrelor well. No healthy volunteers died during their participation in this study or experienced an SAE. In PLATO, there were only 6 patients of Japanese descent (from Brazil) enrolled. Only two of these were in the ticagrelor treatment group. They were not in the Holter or PFT substudies. Neither of these two patients had a recorded AE.

Renal Insufficiency
As previously stated in section 7.3.5, patients with baseline eGFRs of < 30 cc/min may be at a somewhat increased renal failure probably because of hemodynamic factors. There were insufficient data in this subgroup of patients to make any firm conclusions about the risks of ticagrelor in patients with baseline eGFRs of < 30 cc/min.

Hepatic Impairment
Moderate to severe hepatic impairment was an exclusion criterion for PLATO. However, 196 and 217 patients in the ticagrelor treatment group and the clopidogrel treatment group,

respectively, had a history of mild baseline hepatic disorder. From a phase 1 study (D5130C000016), Cmax and AUC of ticagrelor for patients with mild hepatic impairment were found to be 12% and 35% higher than matched healthy subjects, respectively. While there were no differences in IPA and no significant difference in plasma binding protein, in PLATO, there was an increase in deaths (3.1% vs. 0.9%), SAEs (20.4% vs. 16.6%) and AEs (84.2% vs. 81.1%) for the ticagrelor-treated patients with baseline hepatic disorder compared to the clopidogrel-treated with baseline hepatic disorder. This imbalance in deaths, SAEs and AEs is cause for concern. Nevertheless, there are favorable clinical outcomes data in this subgroup. See sponsor's Table 45. Patients with anything more than a mild baseline hepatic disorder were excluded from the study. Therefore, the risk of adverse effects in a patient population that has moderate to severe liver disease is unknown.

Table 45: ICAC-Adjudicated Clinical Hierarchy for Patients with Baseline Hepatic Disorder (new analysis)

| | Randomised Treatment | | | | |
| | Ticagrelor 90 mg bd N = 197 | | Clopidogrel 75 mg od N = 218 | | |
Characteristic	Patients with Events	KM %	Patients with Events	KM %	Hazard Ratio (95% CI)
Composite of CV Death/MI (excl. silent MI) /Stroke	17 (8.6%)	9.2%	24 (11.0%)	11.5%	0.79 (0.42, 1.47)
Composite of CV Death/MI (excl. silent MI) /Stroke - Intent to Invasively Manage *	10 (6.9%)	7.4%	17 (10.9%)	11.7%	0.63 (0.29, 1.38)
Composite of All Cause Mortality/MI (excl. silent MI)/Stroke	17 (8.6%)	9.2%	24 (11.0%)	11.5%	0.79 (0.42, 1.47)
Composite of CV Death/Total MI/Stroke/ Severe Recurrent Cardiac Ischemia/ Recurrent Cardiac Ischemia/Transient Ischemic Attack/Other Arterial Thrombotic Events	27 (13.7%)	14.5%	31 (14.2%)	15.6%	0.98 (0.59, 1.64)
MI (excl. silent MI)	7 (3.6%)	3.7%	20 (9.2%)	9.7%	0.39 (0.16, 0.92)
CV Death	8 (4.1%)	4.4%	6 (2.8%)	2.8%	1.52 (0.53, 4.37)
Stroke	3 (1.5%)	1.7%	2 (0.9%)	0.9%	1.71 (0.29, 10.21
All Cause Mortality	8 (4.1%)	4.4%	6 (2.8%)	2.8%	1.52 (0.53, 4.37)

Diabetes
Diabetes resulted in more deaths for both treatment groups. Also, there were more urinary tract infections in diabetics in both treatment groups. There were no concerning differences between treatment groups.

BMI
Interestingly there was a lower frequency of death in patients with BMI $\geq$ 30 for both treatment groups despite an increased risk for dyspnea. There were no concerning differences between treatment groups.

Smoking

An unexpected finding was that for both treatment groups the number of patients with DAEs and SAEs was lower among habitual smokers compared to those patients who were not habitual smokers. The number of deaths was lower in ticagrelor-treated habitual smokers (1.3%) compared to ticagrelor treated patients who were not habitual smokers (2.9%). Regardless of smoking habits, fewer ticagrelor-treated patients died, compared to clopidogrel-treated patients (habitual smokers [1.3% vs. 2.6%, respectively]; not habitual smokers [2.9% vs. 3.4%, respectively]).

7.5.4 Drug-Disease Interactions

As discussed in section 7.3.5, patients with preexistent stage 4 and 5 renal insufficiency were more vulnerable to developing worsening renal insufficiency and more vulnerable to bleeding.

Patients with baseline hepatic dysfunction are at a higher risk for death, SAEs and AEs.

7.5.5 Drug-Drug Interactions

Coadministration of ticagrelor with CYP3A inducers results in increasing its clearance by 110%. Examples of CYP3A inducers are rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital. For this reason, ticagrelor may be less effective in patients on these medications.

Ticagrelor appears to be a weak activator of CYP3A5 which means that the bioavailability of drugs that are metabolized by CYP3A5 may be decreased when the drugs are coadministered. Examples of drugs metabolized by ticagrelor are midazolam, cyclosporine, nifedipine, testosterone, progesterone and androstenedione.

Ticagrelor is also a weak CYP3A4 inhibitor and causes decreased metabolism of simvastatin, atorvastatin, and estradiol. A study was done (D5130C00042) that evaluated the potential interaction between ticagrelor 90mg bd and Nordette®, a monophasic oral contraceptive (0.03 mg ethinyl estradiol plus 0.15 mg levonorgestrel) in 20 healthy female subjects of childbearing potential. Coadministration of ticagrelor and ethinyl estradiol/levonorgestrel resulted in increases in ethinyl estradiol exposure (30% in Cmax and 20% in AUC), but had no effect on levonorgestrel plasma levels. Low progesterone concentrations were seen throughout the luteal phase, suggesting that ovulation did not occur and that ticagrelor should not interfere with the effects of oral contraceptives.

Ticagrelor is also a weak inhibitor of P-gp, making it important to monitor digoxin levels in clinical practice.

Concomitant medications with an identified potential for interaction were simvastatin, atorvastatin, digoxin and diltiazem. Drug classes selected as they are commonly co-prescribed in ACS patients were statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), proton-pump inhibitors (PPI) and beta blockers. Ticagrelor-treated

patients were divided into those who received the drug (or class of drug) for >20% of their time on ticagrelor treatment compared with those who received them ≤20% of their time on ticagrelor treatment (including those for whom the data are missing). Astra-Zeneca did an analysis where they looked at patients by whether or not they had been on these individual drugs by the prespecified criteria. According to the sponsor, none of these drugs when administered concomitantly with ticagrelor caused increased or decreased frequencies of any particular AEs by PT. By my analysis I saw numerical increases in relative risk for certain AEs in the ticagrelor arm for patients on CYP3A4 inhibitors at time of admission when compared to the patients not on CYP3A4 inhibitors at time of admission but the numbers were too small to draw any conclusions. Since there were so few patients on digoxin and diltiazem, the analysis may have made the chances of finding a difference between groups very small. Conversely, the same thing holds true for statins and beta blockers because most of the patients were on these medications during the study and so few did not take the medications. Additionally, when tested, there were no pharmacodynamic interactions between ticagrelor and heparin, enoxaparin, aspirin and desmopressin.

In vitro, ticagrelor and/or AR-C124910XX were shown to moderately inhibit CYP2C9 activities. In a clinical pharmacology study, however, concomitant administration of ticagrelor with tolbutamide, a representative CYP2C9 substrate did not affect the PK parameters of tolbutamide and its primary metabolite, 4-hydroxytolbutamide (Study D5130C00051), which suggest that ticagrelor is not a CYP2C9 inhibitor *in vivo* and unlikely to alter the metabolism of drugs such as warfarin and tolbutamide whose metabolism is mediated via CYP2C9

7.6.1 Human Carcinogenicity

The lifetime carcinogenicity study in rats with ticagrelor showed an increased incidence in uterine adenocarcinoma, a slight increase in hepatic adenomas, and one case of hepatocellular carcinoma. To provide perspective, the effected rats received 180 mg/kg/day of ticagrelor. Daily AUC exposures to ticagrelor in rats given 180 mg/kg/day are 29-fold higher than human AUC exposures following 90 mg bd and exposure to the main active metabolite AR-C124910 following exposure of 180 mg/kg/day are 24-fold higher than the clinical AUC exposures to the metabolite. No increases in tumor incidences were observed in the mouse carcinogenicity study where exposures to ticagrelor and the metabolite were comparable to those seen in rats. Toxicity studies up to a year in duration in marmosets have not shown any uterine proliferative changes.   Ticagrelor and the active metabolite ARC124910 are not mutagenic in the Ames test and mouse lymphoma assay, and ticagrelor was not active in the rat micronucleus test (the metabolite was not tested in the rat micronucleus test).

In PLATO, deaths due to cancer overall were similar between treatment groups, (ticagrelor 15, 0.2%; clopidogrel 17, 0.2%) regardless of the presence or absence of a neoplasm at baseline. The frequency of patients with solid malignant tumors was 72(0.78%) for ticagrelor and 79 (0.86%) for clopidogrel. When examining frequencies of specific types of malignancies separately (hematologic, lymphoma, gastrointestinal, ovarian, prostate, testicular,

hepatobiliary, respiratory system, skin, breast or CNS neoplasms), I found no concerning differences between the treatment groups.

In PLATO, the overall occurrence and patterns of benign and non-benign neoplasms were similar in both treatment groups for the extent of patient follow-up. Patients with histories of non-benign neoplasms had numerically fewer cases of reported neoplasm at any time during follow-up [23 (5.7%) for ticagrelor and 31 (7.8%) for clopidogrel].

7.6.2 Human Reproduction and Pregnancy Data

Animal studies did not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition, or postnatal development. Ticagrelor had no effect on male or female fertility.

The safety of ticagrelor in Humans during pregnancy or lactation has not been established. Limited clinical data on exposure to ticagrelor during pregnancy are available and none on lactation.

Despite enrollment criteria to prevent fetal exposure to ticagrelor, there was 1 documented exposure during pregnancy. A 38-year-old woman became pregnant during the study. The pregnancy continued post-study period, at which time she delivered a healthy female full-term baby.

While it is not known whether ticagrelor is excreted in human milk, studies in rats have shown that ticagrelor and its active metabolite are excreted in mammary milk.

Ticagrelor should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the fetus.

The use of ticagrelor during breastfeeding is not recommended.

7.6.3 Pediatrics and Assessment of Effects on Growth

There were no pediatric patients enrolled.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

A total of 27 cases of overdose (16 in the ticagrelor group and 11 in the clopidogrel group) with study drug, defined as a patient who received more than the dose at once per the clinical study protocol, were reported to the AstraZeneca Patient Safety group. None of these overdose cases were reported with any apparent associated AEs. All except one of these overdoses were related to accidental medication errors.

In addition, there were 7 cases of overdose (5 in the ticagrelor group and 2 in the clopidogrel group) with concomitant medications during the study treatment period. There were 2 SAEs of

overdose in patients in the ticagrelor group (one with chlordiazepoxide as an attempted suicide and one with a narcotic overdose with oxycodone) and none in the clopidogrel group. The 2 SAEs in the ticagrelor group were attempted suicide with chlordiazpoxide and narcotic overdose with oxycodone.

There is currently no known antidote to reverse the effects of ticagrelor, and it is likely because of its high level of protein binding that it is not dialyzable. The main concern with a ticagrelor overdose would be a bleeding event. The label should alert the physician and patients of this potential concern.

9 Appendices

ADVISORY COMMITTEE

On July 28, 2010, the Cardiovascular and Renal Drugs Advisory Committee recommended the FDA approve AstraZeneca's investigational drug ticagrelor for the reduction of thrombotic events in patients with Acute Coronary Syndromes (ACS).

The Advisory Committee voted as follows:
Questions to the Advisory Committee
1. Should ticagrelor be approved for reduction of thrombotic events in patients with nonST-elevation (NSTEMI) and ST-elevation (STEMI) ACS intended to be managed by PCI?
Yes: 7 No: 1 Abstain: 0
2. Should ticagrelor be approved for reduction of thrombotic events in patients with nonST-elevation (NSTEMI) and ST-elevation (STEMI) ACS intended to be managed medically?
Yes: 7 No: 1 Abstain: 0

The Committee chair, Sanjay Kaul, MD, said that the regional differences were hard to reconcile and could be due to practice differences. It seemed that most of the members of the committee chose to ignore the U.S. data when voting in favor of approval.

LABELING RECOMMENDATIONS

This aspect of the review is still under review and will be filed under separate cover.

Appendix A: Deaths in N.A. in Ticagrelor group from day 119 – 180.

E5490005: 56 y/o Caucasian man with h/o habitual alcohol and tobacco use presented to hospital on [redacted] (b) (6) with new-onset cardiac ischemic symptoms, including dyspnea and angina, and with persistent ST elevation ≥ 1 mm) ≥ 20 min on ECG, h/o carotid stenosis (≥ 50%), S/P h/o cerebrovascular revascularization 1997, family h/o coronary heart disease. Physical examination on admission was unremarkable with normal vital signs. Diagnosis: STEMI. Procedure during hospitalization: urgent percutaneous coronary revascularization with stent. Discharged from hospital [redacted] (b) (6) [redacted]. AEs during hospitalization: non-sustained ventricular tachycardia, vasospasm, headache. No bleeding was reported at Visit 2 on March 2, 2007, and at Visit 3, on May 17, 2007, Date of death was [redacted] (b) (6) Cause of death: myocardial infarction. Patient was **non-compliant with medication following discharge.**

Medications during hospitalization:
Nitrogylcerin, Maalox, Lidocaine, Donnatol, Lopressor, Morphine, Aspirin, Benadryl, Darvocet, Lipitor, Enalpril, Dilaudid, Protonix, Lisinopril, Heparin
Aggrastat

E1602058: 71 y/o Caucasian woman with prior h/o MI, presented on [redacted] (b) (6) with cardiac ischemic symptoms at rest ≥ 10 minutes, new bundle branch block and T wave inversion. Patient reported that she was a nonsmoker, had h/o chronic obstructive pulmonary disease (COPD) and experienced dyspnea at baseline. Diagnosis: NSTEMI. The patient had a coronary angiography on [redacted] (b) (6) Ejection fraction was 30 - 39%. EF was measured as 50% 9 days later. Treatment with ticagrelor was interrupted on [redacted] (b) (6) for a non-bleeding adverse event (COPD exacerbation which required hospitalization). Date restarted was May 15, 2008. The patient also missed one dose of ticagrelor on June 20, 2008 and then refused to take it from June 21, 2008 until June 25, 2008. The patient's last visit was on July 3, 2008. According to the case report form, she was compliant with her medications after June 26, 2008. On [redacted] (b) (6), the patient died at home of cardio-pulmonary arrest (secondary to COPD according to the sponsor). Autopsy was not performed. This death was counted as non-vascular.

Concomitant medications: raberpazole, temazepam, advair, tylenol with codeine #3, atrovent, ventolin, lipitor, synthroid, Spireva, alendronate, altace, nitroglycerin, metoporolol, atacand, lasix, B12, gravol, milk of magnesia, solumedrol, avelox, pentaspan, amoxil, diamox, aspirin 81 mg, enoxaparin, .

E1601008: 76 y/o obese Caucasian man with h/o hypercholesterolemia, DM type II, peripheral artery disease and peripheral neuropathy, presented to the hospital on [redacted] (b) (6) [redacted] with ischemic symptoms and elevated cardiac enzymes. Diagnosis: NSTEMI. He had a PCI with stent. One bare metal stent was placed. On his follow up visits the patient was reported to be compliant with his medication. On March 14 the patient developed dyspnea and a respiratory infection. [redacted] (b) (6) the patient was in the ICU for

12 days for a malignant left pleural hemorrhagic effusion and a major bleed with dyspnea. On April 1, 2008, the patient discontinued drug. On ⬛⬛⬛ (b) (6) the patient died.

E1621011: 72 y/o non-smoking Causasian woman with h/o hypertension and schizophrenia presented on ⬛⬛⬛ (b) (6) with cardiac ischemic symptoms and elevated cardiac enzymes. Diagnosis: NSTEMI. The investigational product was prematurely and permanently stopped on ⬛⬛⬛ (b) (6) after a non-urgent CABG of her left main and LAD which resulted in a peri-operative STEMI. No antiplatelet therapy was given post surgery in the hospital where she was operated. The patient was hospitalized on ⬛⬛⬛ (b) (6) for congestive heart failure. The patient died on ⬛⬛⬛ (b) (6), cause unknown.

E5250001: 59 y/o Caucasian man with h/o prior PCI, smoking and hypercholesterolemia presented on ⬛⬛⬛ (b) (6) with ischemic symptoms, persistent ST elevation ≥ 1 mm and elevated cardiac enzymes. Diagnosis: STEMI. On presentation he had diastolic hypertension (135/101 mmHg), obesity (137 kg), and rales and S3 heart sound. On coronary angiography, his EF was <30%. He had a drug eluting stent placed. The patient was compliant with treatment. The patient died of sudden death on ⬛⬛⬛ (b) (6), presumably of a vascular event.

Appendix B: Hy's Laws Cases

One was a 67-year old man who was diagnosed with STEMI and who had no known history of liver disease had liver enzymes on day 1 of the study that were abnormal [(ALT 68 IU/L, AST 182 IU/L, ALP 42 IU/L, total bilirubin 2.7 mg/dL], drawn 20 minutes after administration of investigational product (ticagrelor). These values were consistent with the enzymatic laboratory criteria of Hy's Law at Visit 1 only, and normal the remainder of the study duration (392 days) while on study medication. It is likely that this elevation in liver enzymes was not related to ticagrelor because of the normal follow-up laboratory values and the short interval between drug administration and enzyme elevation.

One was a 67 year old woman who was diagnosed with unstable angina pectoris without ECG changes, but with elevated CK-MB. She developed elevated liver enzymes (ALT 770 IU/L, AST 800 IU/L, ALP 185 IU/L, Total bilirubin 2.7 mg/dL) 10 minutes after administration of ticagrelor. The enzymes were normal with the exception of one abnormal ALT value (177) 96 days later, for the remainder of the study. It is also likely in this case that the elevation in liver enzymes was not related to ticagrelor because of the normal follow-up laboratory values and the short interval between drug administration and enzyme elevation.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MELANIE J BLANK
08/25/2010

DIVISION OF CARDIOVASCULAR AND RENAL DRUG PRODUCTS
MEDIAL OFFICER REVIEW OF NDA SUBMISSION

NDA Number: **22-433**
Document type: **List of Addenda, Clinical Review**
Name of Drug: **Ticagrelor (Brilinta)**
Formulation: **Oral Tablets**
Sponsor: **Astra Zeneca**
Date: **July 16, 2010**
Reviewer: **Melanie Blank, MD**

Addenda to Clinical Review, pages 12, 13, 22, 23, 24, 28, 30, 35, 36, 47, 50, 59, 61, 62 and 95.

Section 7.1.1, p. 12, lines 7 – 10.

"Additional concerning observation is that the onset of dyspnea was considerably earlier in the ticagrelor-treated patients compared to the clopidogrel-treated patients, lasted usually >20 days (up to approximately 400 days) and at any length of episode, the ticagrelor treatment group had numerically"

Change to:

"An additional concerning observation is that the onset of dyspnea was considerably earlier in the ticagrelor-treated patients compared to the clopidogrel-treated patients, lasted usually >20 days (up to approximately 400 days) and at any length of episode, there were numerically more patients in the ticagrelor treatment group than in the clopidogrel treatment group.
.

.Section 7.1.1, p. 13, 1st paragraph.

"Renal effects were a concern because of observations of increased serum creatinine levels during treatment with ticagrelor in the phase 1 and 2 studies. In PLATO, there was an increased frequency of patients that had extreme decreases in eGFR (>30% - 100%) in the ticagrelor group as compared to the clopidogrel group. There was no difference between the treatment groups in frequency of deaths or discontinuations for renal AEs. However, there were more renal AEs and renal SAES in the ticagrelor-treated patients compared to the clopidogrel-treated patients that was greatly magnified in patients with preexisting stage 4 renal insufficiency. Additionally, ticagrelor-treated patients with eGFR less than 30 are at higher risk for endpoint events, renal failure, all-cause death and major bleeds. It may be wise to limit the use of ticagrelor in this patient population."

Change to:

"Renal effects were a concern because of observations of increased serum creatinine levels during treatment with ticagrelor in the phase 1 and 2 studies. In PLATO, there was an increased frequency of patients that had extreme decreases in eGFR (>30% - 100%) in the ticagrelor group as compared to the clopidogrel group. It is possible that ticagrelor, because of its negative effects on adenosine uptake could alter renal hemodynamics by decreasing tension in the afferent arteriole thereby lowering the glomerular filtration pressure.

While there were no discernable differences between treatment groups for renal AEs, discontinuations for renal AEs or deaths from renal AEs, patients on ticagrelor with baseline eGFRs of < 30 cc/min had numerically more major bleeds than clopoidogrel-treated patients [23 (19%) vs. 16 (11.3%), respectively], and renal failure [12 (13.6%) vs. 5 (5.4%), respectively]. Because of the small numbers of patients in this subgroup, these observations could be chance findings.

 However, when patients have poor baseline renal function they rely on hemodynamic changes within the kidney to maintain their GFR. It is possible that ticagrelor is more likely than clopidogrel to lead to the decompensation of renal function in patients who are completely reliant on hemodynamic factors to maintain their GFR. ACS Patients with poor baseline renal function are at higher risk for renal AEs and death. While there are too few data in this subgroup of patients to make firm conclusions, it is possible that ticagrelor might also contribute to the risk of progression to worsening renal failure in these already high risk patients."

Section 7.1.1, p. 13, entire 3rd paragraph, (lines 20-26).

"Only ~ 400 patients with baseline mild hepatic impairment were enrolled. Nevertheless, such patients were more likely to have major bleeds if on ticagrelor (11.2%) vs. 8.7% if on clopidogrel. There were also more deaths (3.2% vs. 0.9%) in ticagrelor vs. clopidogrel-treated hepatically impaired patients, respectively. There were also more SAEs and AEs in the mildly hepatically impaired patient who was treated with ticagrelor. Consideration should be given to contraindicating ticagrelor in hepatically impaired patients"

Change to:

"Only ~ 400 patients with "history of baseline hepatic disorder" were enrolled. While there were no differences in IPA and no significant difference in plasma binding protein, in PLATO, there was an increase in deaths (3.1% vs. 0.9%), SAEs (20.4% vs. 16.6%) and AEs (84.2% vs. 81.1%) for the ticagrelor-treated patients with a baseline of hepatic disorder compared to similar clopidogrel-treated patients. These patients were more likely to have major bleeds if on ticagrelor (11.2%) vs. 8.7% if on clopidogrel. Clinical outcomes data, however, were favorable in this subgroup."

Section 7.3.1, p. 22, lines 1-6.

"I have chosen to take the example of the unadjudicated all-cause deaths by actual treatment group after one dose of treatment to highlight the ticagrelor death benefit.

The Kaplan-Meier curve in Figure 1 demonstrates that 389 (4.21% of ticagrelor-treated patients died compared to 491 (5.65%) of clopidogrel-treated patients. The log-rank score for these patients is 0.0001 and highly statistically significant"

Change to:

"I have chosen to take the example of the adjudicated all-cause deaths by actual treatment group after one dose of treatment to highlight the ticagrelor death benefit.

The Kaplan-Meier curve in
Figure 1 demonstrates that 389 (4.21% of ticagrelor-treated patients died compared to 491 (5.34%) of clopidogrel-treated patients. The log-rank score for these patients is 0.0001 and highly statistically significant.

Section 7.3.1, p. 22, lines 7-13.

Figure 1: All-cause mortality, Unadjudicated and by Actual Group in Patients After at Least One Dose
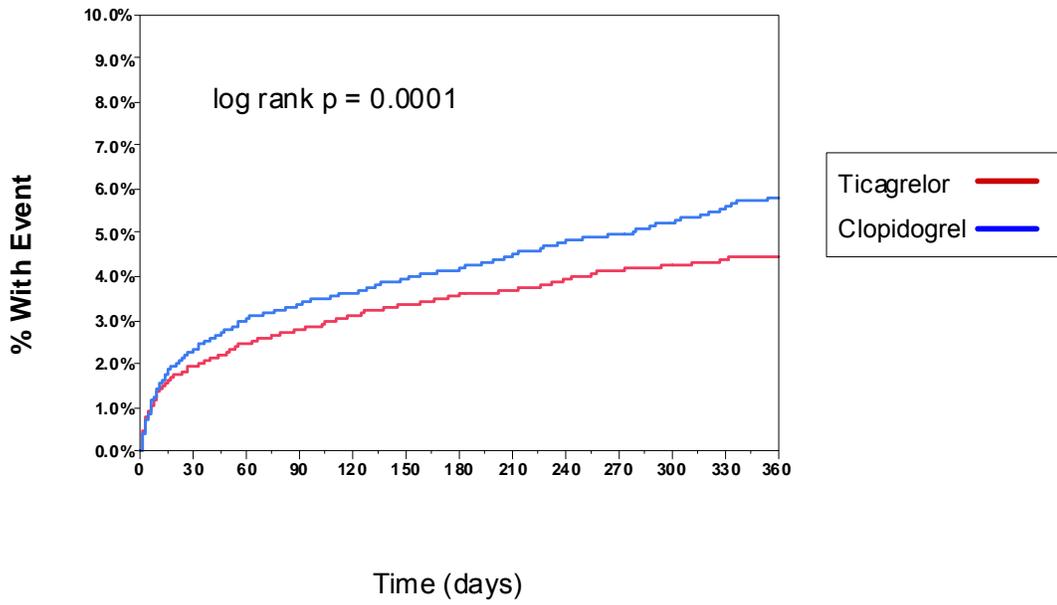
Group	Number failed	Number censored	Percent failed
Ticagrelor 90 mg bd	389	8846	4.21%
Clopidogrel 75 mg od	491	8695	5.65%
Combined	880	17541	5.02%

Change to:

Figure 1: All Cause Mortality (Adjudicated) in Patients by Actual Treatment after at Least One Dose **(source AWCADJ.xpt)**
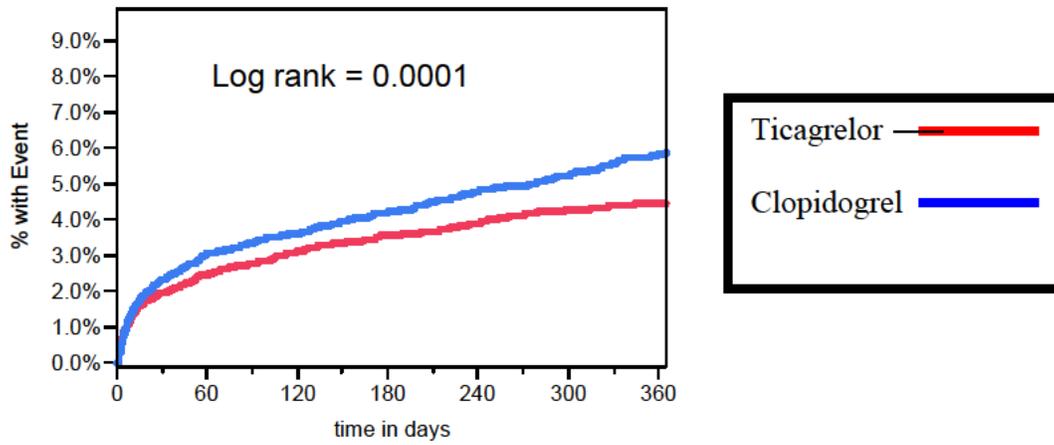
Group	Number failed	Number censored	Percent failed
Ticagrelor 90 mg bd	389	8845	4.21%
Clopidogrel 75 mg od	491	8695	5.34.%
Combined	880	17581	4.78%

Section 7.3.1, p. 23, lines 1-5.

"In the all-deaths per patient year analysis using the same criterion for defining death (all-cause, unadjudicated deaths by actual treatment where the patients took at least one dose of treatment medication), there were 389 total deaths/ 6301 ticagrelor patient years = 62 deaths/ 1000 patient-years vs. 491 deaths/ 6388 clopidogrel patient years = 77 deaths/ 1000 patient-years,"

Change to:

"In the all-deaths per patient year analysis using the same criterion for defining death (all-cause, adjudicated deaths by actual treatment where the patients took at least one dose of treatment medication), there were 389 total deaths/ 6301 ticagrelor patient years = 62 deaths/ 1000 patient-years vs. 491 deaths/ 6388 clopidogrel patient years = 77 deaths/ 1000 patient-years. (PLATO exposure only)."

Section 7.3.1, p. 23, 4th and 5th line of paragraph 2.

"A Kaplan-Meier curve for deaths in North America by randomized treatment is shown in Figure 2,"

Change to:

A Kaplan-Meier curve for deaths in North America by actual treatment after at least one dose is shown in Figure 2"

Section 7.3.1, p. 24, lines 1-6.

Figure 2: KM: All-cause Mortality, by randomized treatment (North America only), adjudicated deaths
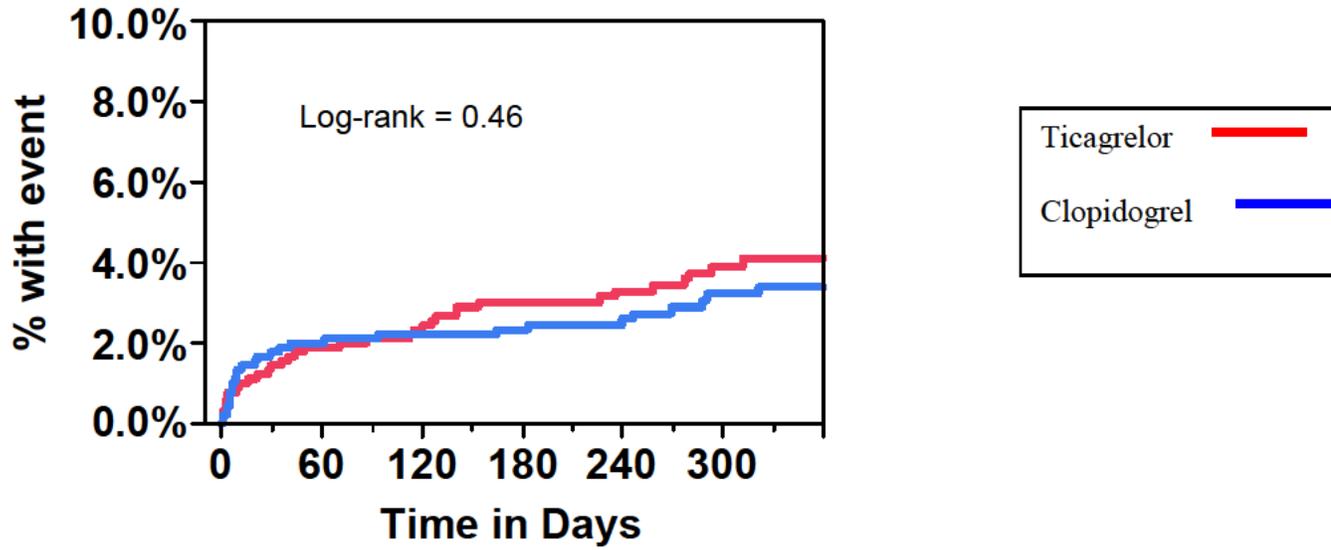
Group	Number failed	Number censored	Percent failed
Ticagrelor 90 mg bd	35	877	3.84%
Clopidogrel 75 mg od	29	873	3.22%
Combined	64	1750	3.53%

Change to:

Figure 2: KM: Adjudicated all-cause Mortality, by Actual Treatment (N.A. only), Patients received at Least One Dose of Treatment (source AWCADJ.xpt)
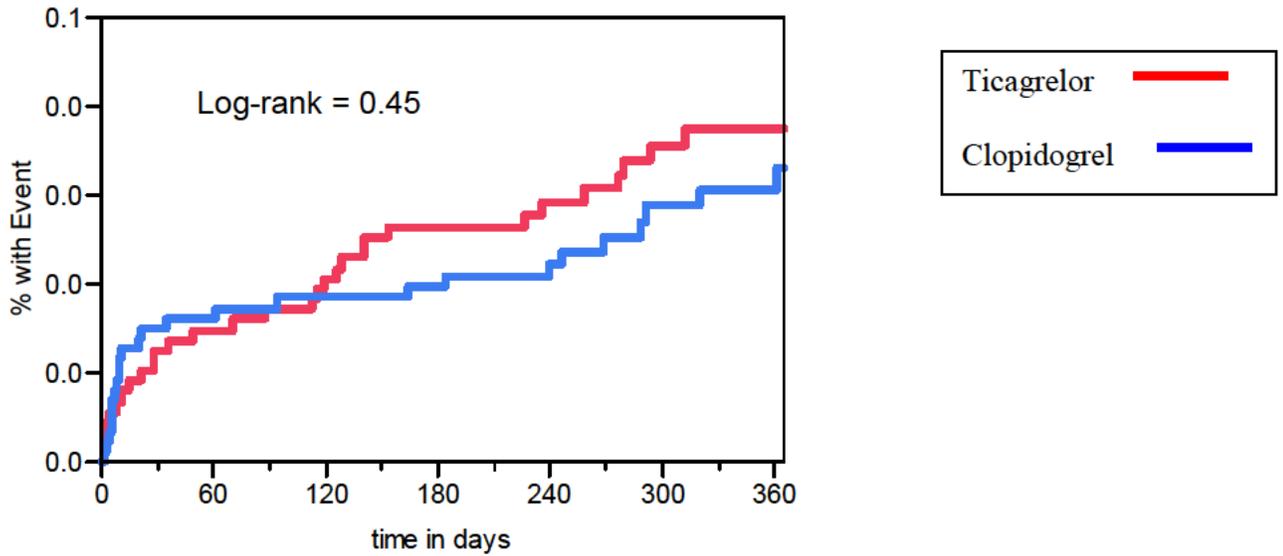
Group Percent failed	Number failed	Number censored	
Ticagrelor 90 mg bd	31	854	3.50%
Clopidogrel 75 mg od	25	852	2.85%
Combined	56	1696	3.30%

Section 7.3.2, p. 28, 9th and 10th lines of paragraph 5.

*"*See **Error! Reference source not found.** for a tabular presentation of my SAE analysis using renamed AE terms. This analysis is similar to the sponsor','"

Change to:

*"*See Table 7 for a tabular presentation of my SAE analysis using renamed AE terms. This analysis is similar to the sponsor's."

Section 7.3.3, p. 30, lines 13-14.

Figure 3: Reasons for Premature Permanent discontinuation of Study Drug
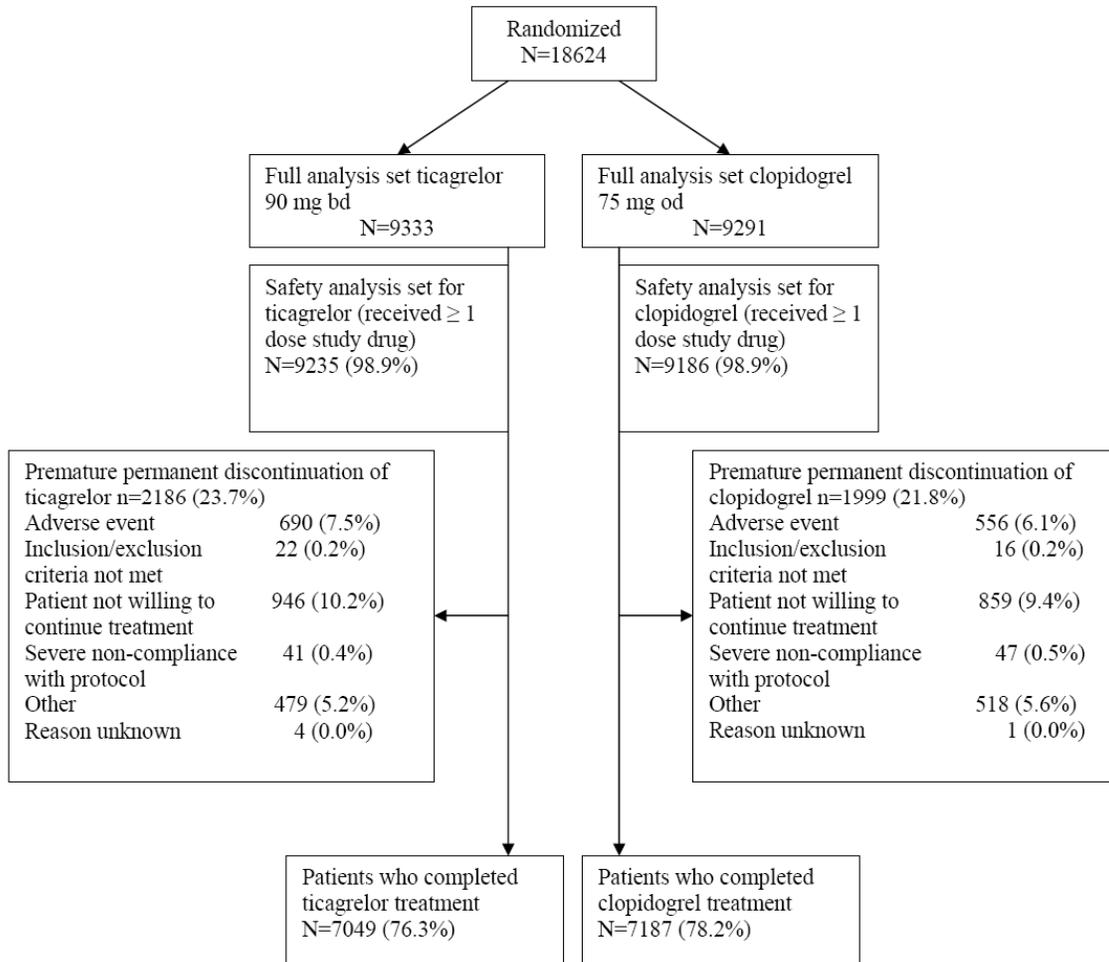
Change to:

Table 7A: Disposition

	Ticagrelor	Clopidogrel
	N	N
Randomization	9333	9291
Treated	9235 (98.9)	9186 (98.9)
Permanent Discontinuation	2186 (23.7)	1999 (21.8)
Adverse event	690 (7.5)	556 (6.1)
Index criteria not met	22 (0.2)	16 (0.2)
Unwilling to continue	946 (10.2)	859 (9.4)
Severe noncompliance	41 (0.4)	47 (0.5)
Other	479 (5.2)	518 (5.6)
Unknown	4 (0)	1 (0)
Lost to follow up	4 (0)	4 (0)
Patients Completed	7049 (76.3)	7187 (78.3)

Source: Data derived from sponsor's tables 11.1.1.2.2 and 11.1.1.4.1 in PLATO study report

Section 7.3.5, p. 35, paragraphs 2-5.

"Most major bleeds were CABG-related (~ 60%) (See Table 11) and most CABG bleeds were major (~85%). (see Table 15). As I will discuss later, the risk of CABG-bleeding is increased in ticagrelor patients who do not wait until day 5 after stopping treatment to have CABG. In other words, it is only because most of the CABG procedures occurred on day 5 or later of treatment cessation that the major bleeding risk was favorable for ticagrelor.

There was a statistically significant increased frequency of major + minor bleeds (overall bleeds that required any intervention) in the ticagrelor-treated group.

There was also an increase in spontaneous (non-procedure related) bleeds in the ticagrelor-treated group as compared to the clopidogrel group, (4.9% for ticagrelor vs. 3.6% for clopidogrel). Intracranial bleeds (to be discussed in the Spontaneous-Bleed section) fell within this category.

There was a somewhat higher frequency of all major bleeds that were not procedure-related [(3.1% for ticagrelor vs. 2.3% for clopidogrel,"

Change to:

"Most major bleeds were CABG-related (~ 67%) (See Table 11) and most CABG bleeds were major (~80%). (see Table 15). As I will discuss later, the risk of CABG-bleeding is increased in ticagrelor patients who do not wait until day 5 after stopping treatment to have CABG. In other words, it is only because most of the CABG procedures occurred on day 5 or later of treatment cessation that the major bleeding risk was favorable for ticagrelor.

There was a statistically significant increased frequency of major + minor bleeds (overall bleeds that required any intervention) in the ticagrelor-treated group.

There was also an increase in spontaneous (non-procedure related) bleeds in the ticagrelor-treated group as compared to the clopidogrel group, (2.5% for ticagrelor vs. 2.0% for clopidogrel). Intracranial bleeds (to be discussed in the Spontaneous-Bleed section) fell within this category."

Section 7.3.5, p. 35, paragraph 7, to p. 36.

Table 11: Type of Major Bleed (CABG, other procedure, spontaneous) by treatment

Major Bleeds	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N= 9186
CABG-related	623 (6.7%)	659 (7.2%)
non-CABG procedure related	30 (0.3%)	46 (0.5%)
Spontaneous	251 (4.5%)	190 (0.21%)
Total	**1031 (11.2%)**	**997 (10.9%)**

Change to:

"In Table 11, it can be seen that there were numerically more major bleeds in the ticagrelor group. 619/961 (64.4%) and 654/929 (70.4%) of the patients with major bleeds had CABG major bleeds in the ticagrelor treatment group and clopidogrel treatment group, respectively. Also, most of the patients who had procedural bleeds had CABG-related procedural bleeds [619/756 (81.9%) vs. 654/775 (84.4%)] for ticagrelor and clopidogrel treatment groups, respectively. Nonprocedural (spontaneous) bleeds, accounted for [235/961(24.5%) vs. 180/929 (19.4%)] of the major bleeds, for ticagrelor and clopidogrel, respectively. The greatest difference between treatment groups was in the category of nonprocedural bleeds [HR 1.31 (1.08,1.60)].The reason that the breakdown of patients by type of major bleeds exceeds the total breakdown of patients with different major bleeds is that approximately 30 patients had both procedural and non-procedural major bleeds in each treatment group."

Table 11: Patients with Adjudicated Major Bleeds by type (CABG, procedural, nonprocedural) by Actual Treatment (Patients Received at least One Dose of Treatment)

Characteristic	Ticagrelor 90 mg bd N=9235 (%)	Clopidogrel 75 mg od N=9186 (%)
Major Bleed	961 (10.4)	929 (10.1)
CABG major	619 (6.7)	654 (7.1)
Procedural Major Bleeds	756 (8.2)	775 (8.4)
Nonprocedural Major Bleeds	235 (2.5)	180 (2.0)
Non-CABG Procedural Major Bleeds	143 (1.5)	133 (1.4)

Derived from PLATO dataset AWCADJ.xpt

Section 7.3.5, p. 47 after Figure 8, line 8.

Add:

"In a July 16, 2010 communication, the sponsor provided a new analysis on deaths following CABG major bleeds within the first 14 days of first CABG by time from last dose of study drug to CABG. The data is in keeping with the reduced death rate at most time points in patients on ticagrelor that had CABG. See Figure 6.16.1."

Figure 6.16.1 Death within 14 Days of First CABG by Time from Last dose of study drug to CA SAFE

T	6/84	2/106	0/114	2/84	3/79	0/91	3/74	7/228
C	6/88	9/86	5/73	6/69	1/96	4/110	4/107	9/274

16
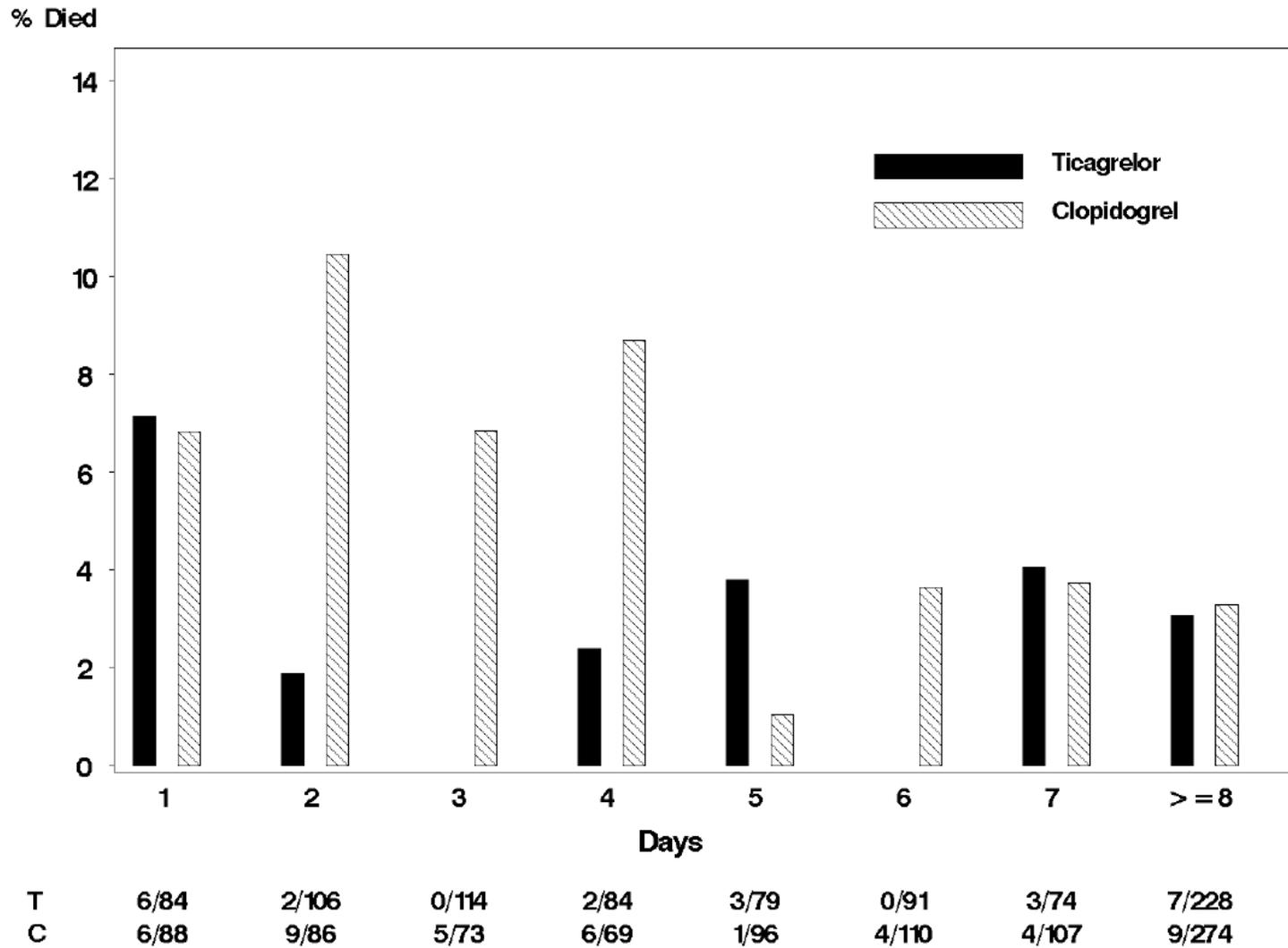
Section 7.3.5, p. 50, after paragraph 1.

Add:

"See Table 16 A for a breakdown of frequency of patients with one or more dyspnea AEs (including all descriptions of dyspnea). At all ages, there were more patients with dyspnea in the ticagrelor treatment group. The frequency of patients with dyspnea increased with increased age for both treatments."

Table 16A: Patients with dyspnea AE by actual treatment (patients who received at least one dose of treatment before developing dyspnea)

Treatment	< 65 years old Ticagrelor N=5252 Clopidogrel N=5276	>= 65 years old -<75 years old Ticagrelor N=2599 Clopidogrel N=2447	> =75 years old Ticagrelor N=1383 Clopidogrel N=1463
Ticagrelor	653 (12.43%)	439 (16.89%)	253 (18.29%)
Clopidogrel	377 (7.15%)	246 (10.05%)	180 (12.30%)

Section 7.3.5, p. 59, lines 13-14.

"Four patients randomized to ticagrelor died from renal-related AEs. Six patients randomized to clopidogrel died from renal-related AEs,"

Change to:

"Two patients after having received treatment of AKI in the ticagrelor treatment group died vs.four similar patients who had received clopidogrel treatment."

Section 7.3.5, p. 59, 1st and 2nd line of paragraph 4.

"However, in the subgroup of patients with baseline eGFRs of <30cc/min/1.73m$_2$ one can see a large differences in the frequency of renal failure depending on treatment arm".

Change to:

"In Sponsor's Table 19A, it is shown that 12 (13.6%) of patients with baseline eGFRs <30cc/min/1.73m$_2$ developed renal failure whereas only 5 (5.4%) of clopidogrel treated patients with baseline eGFRs of <30cc/min/1.73m$_2$ were reported to develop renal failure. Also, there were more major bleeds in patients with eGFR < 30 cc/min/1.73 m$_2$ [23 (19%) vs. 16 (11.3%)]. Because of the small numbers of patients in this subgroup, these observations could be chance findings.

Add Table 19A.

Table 19A: Sponsor's table: Renal AEs by baseline renal function including hematuria

Preferred term[b,c]	Severe (<30 mL/min/1.73 m²)		Moderate (≥30 to <60 mL/min/1.73 m²)		Mild (≥60 to <90 mL/min/1.73 m²)		Normal (≥90 mL/min/1.73 m²)	
	Ticagrelor 90 mg bd N=88	Clopidogre l 75 mg od N=93	Ticagrelor 90 mg bd N=1178	Clopidogrel 75 mg od N=1224	Ticagrelor 90 mg bd N=3542	Clopidogrel 75 mg od N=3546	Ticagrelor 90 mg bd N=2807	Clopidogrel 75 mg od N=2775
Patients with at least 1 event	19 (21.6%)	23 (24.7%)	147 (12.5%)	105 (8.6%)	142 (4.0%)	110 (3.1%)	56 (2.0%)	43 (1.5%)
Haematuria	0	1 (1.1%)	36 (3.1%)	31 (2.5%)	62 (1.8%)	64 (1.8%)	42 (1.5%)	28 (1.0%)
Renal failure	12 (13.6%)	5 (5.4%)	39 (3.3%)	25 (2.0%)	20 (0.6%)	15 (0.4%)	2 (0.1%)	1 (0.0%)
Blood creatinine increased[d]	2 (2.3%)	1 (1.1%)	17 (1.4%)	13 (1.1%)	21 (0.6%)	6 (0.2%)	2 (0.1%)	1 (0.0%)
Renal failure acute	1 (1.1%)	3 (3.2%)	15 (1.3%)	18 (1.5%)	13 (0.4%)	10 (0.3%)	6 (0.2%)	3 (0.1%)
Renal impairment	0	3 (3.2%)	15 (1.3%)	8 (0.7%)	13 (0.4%)	2 (0.1%)	0	1 (0.0%)
Renal failure chronic	3 (3.4%)	6 (6.5%)	20 (1.7%)	9 (0.7%)	2 (0.1%)	2 (0.1%)	0	2 (0.1%)
Proteinuria	0	0	1 (0.1%)	3 (0.2%)	7 (0.2%)	7 (0.2%)	3 (0.1%)	3 (0.1%)
Oliguria	0	0	3 (0.3%)	0	4 (0.1%)	2 (0.1%)	0	5 (0.2%)

Section 7.3.5, p. 59, 8th and 9th line of paragraph 4.

"It is also important to note that irrespective of treatment group, patients over 75 years of age had an increased incidence of renal failure (18-19% compared to patients under 65 years of age (0.3 -0.4%)."

Change to:

From my analysis, the frequency of patients >75 years old that had renal AEs (not counting hematuria) was only slightly increased over patients < 65 years old (2.2 vs.1.6% for ticagrelor and 1.8% vs. 1.6% for clopidogrel). The frequency of renal SAEs not counting hematuria was increased in patients >75 years over patients <65 years old (2.0% vs.0.4% for ticagrelor and 1.9% vs. 0.4% for clopidogrel). Nevertheless, there was no difference between treatment groups in this pattern.

Add:

"In the sponsor's table 19A, it appears there was a higher frequency of hematuria in the ticagrelor treatment group which corresponds to the previously noted increase in spontaneous bleeding.

While there is a higher risk of dying when patients with renal disease are treated for ACS, there was no substantial difference between treatment groups. See Table 19B."

Table19B: Mortality by baseline eGFR

Kidney Disease Category by eGFR	Treatment	N in Kidney Disease Category N=17069	n Survived	n Died	% Died
	All	**6559**	**6434**	**125**	**1.91**
>= 90 cc/min	Ticagrelor	3307	3257	50	1.51
	Clopidogrel	3252	3177	75	2.31
60<90 cc/min	**All**	**6670**	**6344**	**326**	**4.89**
	Ticagrelor	2862	2700	162	5.66
	Clopidogrel	3808	3644	164	4.31
30-<60cc/min	**All**	**3579**	**3220**	**359**	**10.03**
	Ticagrelor	1749	1619	148	8.38
	Clopidogrel	1812	1601	211	11.64
15-<30cc/min	**All**	**246**	**185**	**61**	**24.8**
	Ticagrelor	113	86	27	23.89
	Clopidogrel	133	99	34	25.56
<15 cc/min	**All**	**15**	**11**	**4**	**26.67**
	Ticagrelor	4	0	4	100
	Clopidogrel	11	0	11	0

Section 7.3.5, p. 61, Table 20, <u>half-way down the table on left</u>.

"ARB USE: NO"

Change to:

"ARB USE: YES."

Section 7.3.5, p. 62, lines 2-9

"While the numbers are very small, ticagrelor may not be more effective or possibly worse than clopidogrel in patients with markedly reduced renal function at beginning of treatment. See Table 21."

"Table 21: # events (from composite efficacy endpoint) by stage of chronic kidney disease by treatment

eGFR (CG)	N	Ticagrelor # events/n	Clopidogrel # events/n	HR	95%CI
<15	16	6/8 (75%)	1/8 (20%)	12	1.38, 104
<30	262	39/119 (36%)	50/143 (40%)	0.97	0.64, 1.47
<60	3,847	308/1887 (18%)	390/1960 (22%)	0.8	0.69, 0.93
<90	11,558	650/5770 (12%)	757/5788 (14%)	0.86	0.77, 0.95

*365 day KM%
Source: R. Fiorentino, Clinical Reviewer"

Change to:

"Ticagrelor seems to be as affective in patients with markedly reduced baseline renal function .See Table 21 (sponsor's table)."

"Table 21:   ICAC-adjudicated primary clinical efficacy endpoint by baseline renal function – PLATO full analysis set

Group	n	Ticagrelor 90 mg bd N = 9333 Patients with events	KM% /year	n	Clopidogrel 75 mg od N = 9291 Patients with events	KM% /year	HR (95% CI)	p-value
Severe	88	22 (25.0%)	27.1%	93	30 (32.3%)	36.6%	0.73 (0.42, 1.27)	0.2727
Moderate	1178	172 (14.6%)	15.8%	1224	241 (19.7%)	21.5%	0.72 (0.59, 0.88)	0.0011
Mild	3542	345 (9.7%)	10.2%	3546	362 (10.2%)	10.9%	0.96 (0.83, 1.11)	0.5676
Normal	2807	172 (6.1%)	6.5%	2775	210 (7.6%)	8.0%	0.81 (0.66, 0.99)	0.0388
Unknown	1718	153 (8.9%)	9.4%	1653	171 (10.3%)	11.0%	0.85 (0.69, 1.06)	0.1570

Data derived from Appendix 2.7.3.6 Tables 3 in CTD Module 5.3.5.3.
Hazard ratio and p-values calculated from Cox proportional hazards model with explanatory variables for study treatment, subgroup and treatment-subgroup interaction.
Kaplan-Meier percentage calculated at 12 months.
p-value (Int.) assesses the interaction between randomised treatment and subgroup.

Section 7.3.5, p. 62, paragraph 4.

"In summary, there was an increased frequency of patients that had extreme decreases in eGFR (>30% -100%) in the ticagrelor group as compared to the clopidogrel group. There was no difference between the treatment groups in frequency of deaths or discontinuations for renal AEs. However, there were more renal AEs and renal SAES in the ticagrelor-treated patients compared to the clopidogrel-treated patients that was greatly magnified in patients with preexisting stage 4 renal insufficiency.

Ticagrelor-treated patients with eGFR less than 30 are at higher risk for endpoint events, renal failure, all-cause death and major bleeds. It may be wise to limit the use of ticagrelor in this patient population."

Change to:

"In summary, ticagrelor was associated with increases in serum creatinine probably because of renal hemodynamic changes. Also, while there were very few patients in the subgroup of patients with baseline eGFRs < 30cc/min/1.73m^2, there were numerically more patients with major bleeds and renal failure in the ticagrelor treatment group compared to the clopidogrel treatment group. When patients have poor baseline renal function they rely on hemodynamic changes within the kidney to maintain their GFR. It is possible that ticagrelor is more likely than clopidogrel to lead to the decompensation of renal function in patients who are completely reliant on hemodynamic factors to maintain their GFR. ACS Patients with poor baseline renal function are at higher risk for renal AEs and death. While there are too few data in this subgroup of patients to make firm conclusions, it is possible that ticagrelor might also contribute to the risk of progression to worsening renal failure in these already high risk patients."

Section 7.3.5, p. 62, Table 22.

Table 22: AEs that might be hormonally related

Category of possibly hormonally related AE	Ticagrelor 90 mg bd N= 9235	Clopidogrel 75 mg QD N= 9186	RR
	n(percent)	n(percent)	
Vaginal bleeding	22 (0.24)	17 (0.19)	1.3
Breast tenderness/ pain	8 (0.09)	6 (0.04)	2.3
Gynecomastia	15 (0.16)	3 (0.03)	5.3
Breast Cancer	4 (0.03)	10 (0.03)	1
Prostate enlargement, mass, or disorders	39(0.12)	40 (0.12)	1.2
BPH	10 (0.11)	8 (0.09)	1.2
Prostate cancer	13 (0.13)	12 (0.12)	1.1
Cervical/uterine tumor	5 (0.05)	5 (0.05)	1
Cervical/uterine malignancy	0 (0)	0 (0)	
Erectile Dysfunction	43 (0.5%)	50 (0.8%)	0.625
Decreased Libido	5 (0.1%)	1 (0.1%)	1
Sexual Dysfunction	3 (0.0%)	11 (0.2%)	0

Some patients may be listed in more than one category

Change to:

Table 22: Evidence of Sex Hormone Related Toxicity

Category of possibly hormonally related AE	Ticagrelor 90 mg bd	Clopidogrel 75 mg QD
All patients	N= 9235	N= 9186
Females only	N= 2634	N= 2603
Males only	N= 6601	N= 6583
	n(percent)	n(percent)
Vaginal bleeding (females only)	22 (0.84)	17 (0.65)
Breast tenderness/ pain (all patients)	8 (0.09)	6 (0.04)
Gynecomastia (males only)	15 (0.23)	3 (0. 05)
Breast Cancer (females only)	4 (0.15)	10 (0.38)
Prostate enlargement, mass, or disorders (males only)	39 (0.59)	40 (0.61)
BPH (males only)	10 (0.15)	8 (0.12)
Prostate cancer (males only)	13 (0.19)	12 (0.18)
Cervical/uterine tumor (females only)	5 (0.19)	5 (0.19)
Cervical/uterine malignancy (females only)	1 (0)	0 (0)
Erectile Dysfunction (males only)	43 (0.65)	50 (0.76)
Decreased Libido (all patients)	5 (0.05)	1 (0.01)
Sexual Dysfunction (males only)	3 (0.05)	11 (0.17)

Section 7.5.3, p. 95, paragraph 6

Renal Insufficiency
As previously stated in section 7.3.5, renal deaths and adverse events, patients with preexisting renal disease with an eGFR of < 30 cc/min are at greater risk for death and major bleeding and do not appear to receive benefit from ticagrelor. Consideration should be given to contraindicating ticagrelor in this population.

Change to:

Renal Insufficiency
As previously stated in section 7.3.5, patients with baseline eGFRs of < 30 cc/min may be at a somewhat increased renal failure probably because of hemodynamic factors. There were insufficient data in this subgroup of patients to make any firm conclusions about the risks of ticagrelor in patients with baseline eGFRs of < 30 cc/min.
.

Section 7.5.3, p. 95, paragraph 7, p. 96, lines 1 -9.

Hepatic Impairment
"Moderate to severe hepatic impairment were exclusion criteria for PLATO. However, 196 and 217 patients in the ticagrelor treatment group and the clopidogrel treatment group, respectively, had mild hepatic impairment. From a phase 1 study (D5130C000016), Cmax and AUC of ticagrelor for patients with mild hepatic impairment were found to be12 and 35% higher than matched healthy subjects, respectively. While there were no differences in IPA and no significant difference in plasma binding protein, there was an increase in deaths (3.1% vs. 0.9%); SAEs (20.4% vs. 16.6%) and AEs (84.2% vs. 81.1%) for the ticagrelor-treated hepatically impaired patients compared to the clopidogrel-treated hepatically impaired patients.   There were approximately 400 patients with hepatic impairment enrolled. This imbalance in deaths, SAEs and AEs is cause for concern. Ticagrelor should not be administered to patients with hepatic impairment."

Change to:

Hepatic Impairment
"Moderate to severe hepatic impairment was an exclusion criterion for PLATO. However, 196 and 217 patients in the ticagrelor treatment group and the clopidogrel treatment group, respectively, had a history of baseline hepatic disorder. From a phase 1 study (D5130C000016), Cmax and AUC of ticagrelor for patients with mild hepatic impairment were found to be 12% and 35% higher than matched healthy subjects, respectively. While there were no differences in IPA and no significant difference in plasma binding protein, in PLATO, there was an increase in deaths (3.1% vs. 0.9%), SAEs (20.4% vs. 16.6%) and AEs (84.2%

vs. 81.1%) for the ticagrelor-treated patients with baseline hepatic disorder compared to the clopidogrel-treated with baseline hepatic disorder. This imbalance in deaths, SAEs and AEs is cause for concern. Nevertheless, there are favorable clinical outcomes data in this subgroup. See sponsor's table: 6.24.21."

Add:

Table 6.24.2 ICAC-Adjudicated Clinical Hierarchy for Patients with Baseline Hepatic Disorder (new analysis)

| | Randomised Treatment | | | | |
| | Ticagrelor 90 mg bd N = 197 | | Clopidogrel 75 mg od N = 218 | | |
Characteristic	Patients with Events	KM %	Patients with Events	KM %	Hazard Ratio (95% CI)
Composite of CV Death/MI (excl. silent MI) /Stroke	17 (8.6%)	9.2%	24 (11.0%)	11.5%	0.79 (0.42, 1.47)
Composite of CV Death/MI (excl. silent MI) /Stroke - Intent to Invasively Manage *	10 (6.9%)	7.4%	17 (10.9%)	11.7%	0.63 (0.29, 1.38)
Composite of All Cause Mortality/MI (excl. silent MI)/Stroke	17 (8.6%)	9.2%	24 (11.0%)	11.5%	0.79 (0.42, 1.47)
Composite of CV Death/Total MI/Stroke/ Severe Recurrent Cardiac Ischemia/ Recurrent Cardiac Ischemia/Transient Ischemic Attack/Other Arterial Thrombotic Events	27 (13.7%)	14.5%	31 (14.2%)	15.6%	0.98 (0.59, 1.64)
MI (excl. silent MI)	7 (3.6%)	3.7%	20 (9.2%)	9.7%	0.39 (0.16, 0.92)
CV Death	8 (4.1%)	4.4%	6 (2.8%)	2.8%	1.52 (0.53, 4.37)
Stroke	3 (1.5%)	1.7%	2 (0.9%)	0.9%	1.71 (0.29, 10.21
All Cause Mortality	8 (4.1%)	4.4%	6 (2.8%)	2.8%	1.52 (0.53, 4.37)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

MELANIE J BLANK
07/20/2010

Date: July 19, 2010

From: Thomas A. Marciniak, M.D.
Medical Team Leader

Subject: Ticagrelor for acute coronary syndromes, NDA 22-433, changes from original version to amended version

To: Advisory Committee Members

This memo details the changes from the original, June 29, 2010, version of my memo to the amended, July 16, 2010, version. I have provided the page numbers of the changes with a leading "O" for original version page numbers and leading "A" for amended version page numbers, e.g., "O1 A1" below. I have provided, when needed, paragraph numbers following the page numbers and preceded by a hyphen.

O1-2 A1-2. Added sentence: "This amended version provides alternative estimates of follow-up that are more consistent with the study conduct, adds a discussion of efficacy complexity, and corrects slightly some safety statistics quoted from the primary safety review."

O3. Replaced: "For PLATO the maximum targeted follow-up was one year. Patients randomized less than one year prior to study termination were to have their final study visit at the time of a planned quarterly visit based on their quarter of randomization to insure a 6-month minimum follow-up. The sponsor's short summary of this rolling termination is the following: "In effect, patients were phased out uniformly over a 3-month period starting on 18 October 2008." A communication to the sites recommended a -10 day window. Hence I counted patients as having good CV follow-up if they had an adjudicated death or they had a CV event or study visit on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria about 15% of patients had incomplete CV follow-up, with slightly but significant more ticagrelor than clopidogrel patients having incomplete follow-up (15.9% vs. 14.7%). The distributions of days of missing follow-up were similar in both arms, with the overall distribution shown in Figure 1.

Figure 1: Distribution of Days of CV Follow-up Missing in PLATO

The peaks at 180, 270, and 360 days are due to patients withdrawing shortly after randomization, allowing for the rolling phase-out. The median days of CV follow-up missing were 241 days.

I analyzed vital status follow-up similarly, counting vital status follow-up as good if the patient died or had a last visit or contact on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria 6.5% of ticagrelor and 5.2% of clopidogrel patients had incomplete vital status follow-up. The median days of vital status follow-up missing were 179 days in both arms."

A3. Replaced with: "For PLATO the maximum targeted follow-up was one year. Patients randomized less than one year prior to study termination were to have their final study visit at the time of a planned quarterly visit based on their quarter of randomization to insure a 6-month minimum follow-up. The sponsor's short summary of this rolling termination is the following: "In effect, patients were phased out uniformly over a 3-month period starting on 18 October 2008." A communication to the sites recommended a -10 day window. Hence I initially counted patients as having good CV follow-up if they had an adjudicated death or they had a CV event or study visit (with vital signs measured) on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria about 15% of patients had incomplete CV follow-up, with slightly but significant more ticagrelor than clopidogrel patients having incomplete follow-up (15.9% vs. 14.7%). However, in PLATO patients did not always come in for a visit but may have had follow-up by another route such as a hospital visit or an adverse event report. Trying to account for all possible follow-up in PLATO is complex as shown by Figure 1, the program I used.

Figure 1: Program for Determining CV Follow-up in PLATO

(b) (4)

Figure 1 is frightening. It should not be this difficult to determine what the last date of follow-up is in a one year study. Preferably patients come in for a last study visit unless they are dead, the simpler approach I initially used. By the complex determinations in Figure 1 incomplete CV follow-up is better but still concerning, about 8.6% in each arm. For the primary endpoint (counting any primary endpoint event as good follow-up) the incomplete PEP follow-up is slightly better, 7.8%. The distributions of days of missing CV follow-up were similar in both arms, with the overall distribution shown in Figure 2.

Figure 2: Distribution of Days of CV Follow-up Missing in PLATO

3

The peaks at 180, 270, and 360 days are due to patients withdrawing shortly after randomization, allowing for the rolling phase-out. The median days of CV follow-up missing were 241 days.

I analyzed vital status follow-up similarly, counting vital status follow-up as good if the patient died or had a last visit or contact on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria 3.1% of ticagrelor and 2.6% of clopidogrel patients had incomplete vital status follow-up. The median days of vital status follow-up missing were 262 days for ticagrelor and 255 days for clopidogrel."

NOTE: Because I added one additional, initial figure to my amended review, all subsequent figure numbers are increased by one.

O10-1 A11-1. Added: "Attempting to analyze timing of study drug administration is complicated by the usual problems of inaccuracies with dates and times in clinical trials, e.g., I count 725 cases for which the study drug was administered prior to randomization. It is also confounded by another factor: 48% of the ticagrelor patients were on clopidogrel or received clopidogrel within the first 24 hours and the timing of administration of the clopidogrel was not captured."

O12 A13. Added before *Safety*: "*Efficacy Evaluation Complexity*
The previous sections should be convincing that efficacy evaluation in PLATO is extremely complex. I could argue that PLATO tried to do too much: *A priori* it attempted to evaluate three different conditions (i.e., STEMI, NSTEMI, and UA), two different management approaches (invasive and non-invasive), and two different pre-treatments (prior antiplatelet and no prior antiplatelet use). The complexity, e.g., 3 x 2 x 2 x 2 (study drug) = 24 different treatment cells was then increased 4 to 8-fold by the US vs. OUS discrepancies, with the issues of aspirin dosage and study drug timing, and the short term vs. long term effects. The evaluation is complicated further at least qualitatively by the issues of statin exposure and completeness of follow-up. As of the date of this review we have not successfully identified clear patterns among this complexity."

O12-4 A14-1. Replaced "The FDA primary clinical safety reviewer commented that most major bleeds were CABG-related (~ 75%) and most CABG bleeds were major (~85%)" with "The FDA primary clinical safety reviewer commented that most patients with major bleeds had major CABG-related bleeds (~ 67%) and most CABG bleeds were major (~80%)."

O13-1 A14-2. Replaced "While the stroke rate is slightly higher with ticagrelor, the lower MACE rate (including the strokes) minimize any concerns that I have about strokes" with "While the stroke rate is slightly higher with ticagrelor, the lower MACE rate (including the strokes) mitigate any concerns that I have about strokes."

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

THOMAS A MARCINIAK
07/19/2010

Memorandum

Date: July 16, 2010

From: Thomas A. Marciniak, M.D.
            Medical Team Leader

Subject: Ticagrelor for acute coronary syndromes, NDA 22-433 (Amended)

To: Advisory Committee Members

Ticagrelor (Brilinta™) is a novel P2Y$_{12}$ platelet receptor inhibitor submitted for approval for the indication of reducing the rate of thrombotic events in patients with acute coronary syndromes (ACS, including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI)). Two other drugs (clopidogrel, prasugrel) are approved for similar indications and a third (ticlopidine) is approved for related indications. All three have both common and individual limitations: The common limitations are that the approved drugs are all members of the thienopyridine structural class administered as pro-drugs requiring metabolic activation for effect and binding irreversibly to the P2Y$_{12}$ receptor. Ticagrelor does not require metabolic activation and binds reversibly. The individual limitations are that ticlopidine is rarely used because of a higher rate of neutropenia, clopidogrel may be less effective in some patients because of reduced activation due to genetic or drug-interaction factors, and prasugrel is associated with higher rates of bleeding and a question of cancer promotion. A novel drug without these limitations would be a therapeutic advance.

We have provided detailed primary reviews of clinical efficacy and of clinical safety in the FDA briefing package. In this memo I will highlight the significant clinical efficacy and safety questions that we have identified, referencing the preclinical and clinical pharmacological findings when relevant. This amended version provides alternative estimates of follow-up that are more consistent with the study conduct, adds a discussion of efficacy complexity, and corrects slightly some safety statistics quoted from the primary safety review.

PLATO Study Design
The substantial evidence submitted to support the approval of ticagrelor comes from PLATO, a large, international, multi-center, randomized, double-blind, active-controlled trial. The primary reviews summarize well the details of protocol and study design. In general the trial was well-designed. In retrospect I have identified the following issues:

- Ticagrelor is a moderate inhibitor of cytochrome P450 CYP3A. Because several statins are metabolized by CYP3A and statins are commonly administered to ACS patients, the sponsor proposed at the end-of-phase 2 meeting in December 2005 that concomitant therapy with either simvastatin or lovastatin at doses higher than 40-mg should be avoided. We accepted this proposal as reasonable. The protocol states that "As simvastatin has recommended restrictions for concomitant therapy with inhibitors of CYP3A due to increased reporting of myopathy, concomitant study therapy with simvastatin or lovastatin (which is very similar pharmacokinetically to simvastatin) at doses higher than 40mg should be avoided." In hindsight this restriction on a class of drugs with a mortality benefit appears inappropriate. There is no reason to restrict statin dosage in the clopidogrel arm.

  Simvastatin was the most frequently used statin in PLATO—about 54% of patients took it at some time. Atorvastatin usage was very similar. Rosuvastatin usage was a distant third at about 9%. Note that ticagrelor also affects atorvastatin pharmacokinetics, increasing its AUC by a mean of 36%. These changes in statin exposure may be relevant to the time course of the presumed ticagrelor benefit that I discuss below.

  Because of the restriction of simvastatin dosage the protocol should have specified collecting the dosages of statins used in the trial. Unfortunately the protocol failed to do so. The protocol did specify measuring blood lipid levels.

- PLATO was double-blinded but it was trivial to break the blind at the sites. The clopidogrel formulation used was a clopidogrel tablet cut into two and stuffed into a capsule. The dummy was identical in appearance. However, the sites could unblind any patient by breaking one of the patient's clopidogrel/dummy capsules and examining its contents. The protocol submitted in August 2006 described this clopidogrel formulation but the reviewing FDA medical officer did not identify the formulation as problematic. The sponsor did not submit the protocol for a Special Protocol Assessment. In 2006 we might have complained about but accepted the clopidogrel formulation even if we had identified it as problematic. Because of bad experiences with open label trials since 2006, we should be more cautious about such formulations today.

PLATO Study Conduct

Most aspects of the PLATO study conduct also appear to be good. The structure and processes of the trial, e.g., randomization by interactive voice or web response system, unblinded DSMB, blinded event adjudication committee, etc., are ones that we favor. The trial documentation submitted appears to be well-prepared and complete. The CRFs submitted are computer printouts from a data capture computer system. They are highly legible and appear complete but are difficult to read because of the computer formatting. However, we requested and the sponsor provided quickly the audit trail of all changes to the CRF data base—a 16.5GB file. We could analyze this file with standard statistical packages; I found it helpful in understanding changes in CRF data. The sponsor also submitted adjudication packages that were predominantly in an easier to read document format. These adjudication packages included investigator notes, hospital discharge summaries, ECG tracings, etc., that were helpful in understanding the adjudications.

There was one aspect of PLATO study conduct that was not good: the follow-up rate. By the sponsor's statistics, about 5% of the patients died while about 82% had a final study visit ("completers" per the sponsor's terminology). Hence about 13% of the patients (100% - 5% - 82%) had incomplete follow-up for determining the primary endpoint of CV death, myocardial infarction (MI), or stroke by the sponsor's tallying.

For PLATO the maximum targeted follow-up was one year. Patients randomized less than one year prior to study termination were to have their final study visit at the time of a planned quarterly visit based on their quarter of randomization to insure a 6-month minimum follow-up. The sponsor's short summary of this rolling termination is the following: "In effect, patients were phased out uniformly over a 3-month period starting on 18 October 2008." A communication to the sites recommended a -10 day window. Hence I initially counted patients as having good CV follow-up if they had an adjudicated death or they had a CV event or study visit (with vital signs measured) on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria about 15% of patients had incomplete CV follow-up, with slightly but significant more ticagrelor than clopidogrel patients having incomplete follow-up (15.9% vs. 14.7%). However, in PLATO patients did not always come in for a visit but may have had follow-up by another route such as a hospital visit or an adverse event report. Trying to account for all possible follow-up in PLATO is complex as shown by Figure 1, the program I used.

Figure 1: Program for Determining CV Follow-up in PLATO

(b) (4)

Figure 1 is frightening. It should not be this difficult to determine what the last date of follow-up is in a one year study. Preferably patients come in for a last study visit unless they are dead, the simpler approach I initially used. By the complex determinations in Figure 1 incomplete CV follow-up is better but still concerning, about 8.6% in each arm. For the primary endpoint (counting any primary endpoint event as good follow-up) the incomplete PEP follow-up is slightly better, 7.8%. The distributions of days of missing CV follow-up were similar in both arms, with the overall distribution shown in Figure 2.

Figure 2: Distribution of Days of CV Follow-up Missing in PLATO

The peaks at 180, 270, and 360 days are due to patients withdrawing shortly after randomization, allowing for the rolling phase-out. The median days of CV follow-up missing were 241 days.

I analyzed vital status follow-up similarly, counting vital status follow-up as good if the patient died or had a last visit or contact on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria 3.1% of ticagrelor and 2.6% of clopidogrel patients had incomplete vital status follow-up. The median days of vital status follow-up missing were 262 days for ticagrelor and 255 days for clopidogrel.

These rates of incomplete follow-up are concerning. They greatly exceed the differences between arms in rates for any of the endpoints. If the endpoint results were consistent, then we would be less concerned about the follow-up rates. However, the efficacy results are inconsistent by region and the time course of the effects are inconsistent with those from the thienopyridine ACS trials.

This problem with incomplete follow-up rates has been an issue for other recent CV outcome trials. While we are sympathetic to the difficulties of performing outcome trials in the modern era of increased patient awareness of medical treatments and mounting privacy concerns, if this trend continues we will not be able to interpret CV outcome trial results. This problem is the number one study conduct problem today threatening the integrity of CV outcome trials.

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Efficacy

The PLATO efficacy analyses are time-to-first-event analyses. Before presenting my analyses, I have one analytic issue to discuss. The sponsor, for its time-to-event analyses, used censoring dates for patients without the event of interest based on the last study visit date for the **"completers" but projected based on either** a future planned visit date plus 30 days for withdrawals or upon the last dispense date plus 90 days for patients who continued on study **medication after a "last" visit. While the use** of these strange censoring rules does not change the statistics greatly, I can not see the validity of projecting follow-up. I censored patients at the time of an event or the time of the last study visit (for CV events) or the last vital status follow-up (for all-cause mortality).

Sponsor's Primary Adjudicated Results

The sponsor contracted with an academic center to perform blinded adjudications of CV and bleeding events. The sponsor named this adjudication group the Independent Central Adjudication Committee (ICAC). While the use of a blinded adjudication process is good, it does not guarantee that the adjudications are unbiased. Someone still has to decide what events to refer and what documents to include in the adjudication packages. All of these processes are subject to surreptitious unblinding. For example, besides the DSMB the sponsor reported in Serial 008 that four groups within its organization had treatment codes as well as two **contractors, i.e.,** (b) (4) had access to a password protected list of the randomization code which was known to only named personnel. This was used for the identification of PK samples . . ." **and a second contractor had treatment codes** for the IVRS system. With so many groups having access to treatment codes I am not reassured that the blind was properly maintained.

I show the Kaplan-Meier (K-M) **plot for the sponsor's first primary** endpoint event (CV death, MI, or stroke - MACE) in Figure 3 and for death in Figure 4.

Figure 3: Time to Sponsor's First Primary Endpoint Event (MACE)

Number at risk							
rx = clopidogrel	9306	7941	7609	7352	5879	5042	3962
rx = ticagrelor	9336	8021	7634	7395	5927	5035	3999

——— rx = clopidogrel   – ·– ·– · rx = ticagrelor

Figure 4: Time to Death from Any Cause
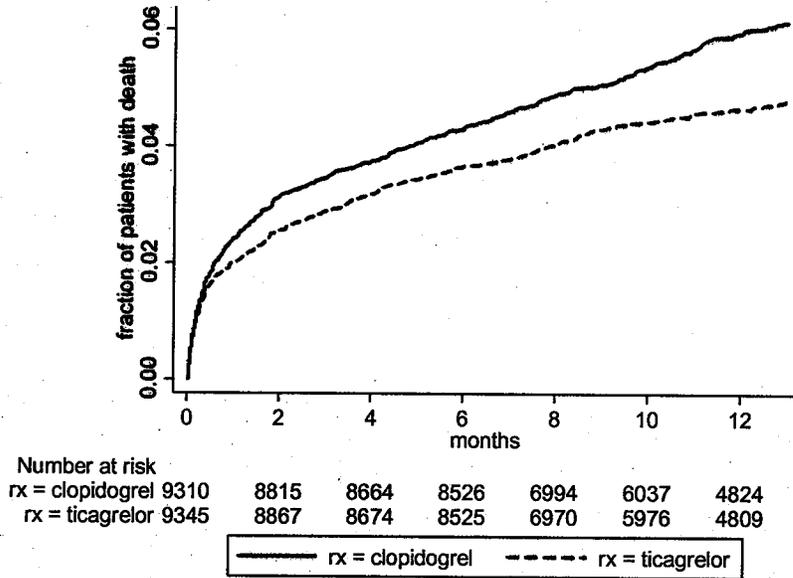
Number at risk							
rx = clopidogrel	9310	8815	8664	8526	6994	6037	4824
rx = ticagrelor	9345	8867	8674	8525	6970	5976	4809

——— rx = clopidogrel　　– – – – rx = ticagrelor

Both time-to-first event analyses are highly statistically significant by the log rank test. One relevant question is that, given the incompleteness of follow-up, are the results real?

Site-Reported MACE

As a check I counted CV death, MI, and stroke events (MACE) as reported by the sites without the ICAC adjudication. For these site-reported statistics I also implemented two variations from **the sponsor's classification of CV deaths: (1) The** sponsor counted bleeding deaths as CV deaths. While that is reasonable for the primary endpoint (PEP) to estimate a net benefit, for an endpoint to explore efficacy effects alone I believe that it is preferable to exclude bleeding events not related to a cardiovascular or cerebrovascular event. Hence I excluded gastrointestinal bleeds but included non-traumatic intracranial hemorrhages. (2) The sponsor counted all unknown deaths as CV deaths, again reasonable for a PEP for net benefit. I counted sudden unknown deaths as CV deaths but excluded completely unknown deaths. I show the K-M plot for this site-reported MACE in Figure 5.

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Figure 5: Time to Site-Reported First MACE

Number at risk							
rx = clopidogrel	9306	8097	7777	7524	6030	5175	4073
rx = ticagrelor	9336	8131	7752	7520	6042	5136	4085

rx = clopidogrel ———— rx = ticagrelor ‒ ‒ ‒ ‒

The possible benefit of ticagrelor is much less impressive for site-reported events and not statistically significant (p about 0.095 by log rank). For site-reported events there is only a slight benefit regarding MIs (relative risk (RR) about 0.94), a detriment regarding strokes (RR about 1.2), with the best benefit regarding CV deaths (RR 0.85). Note that the curves do not diverge early. In fact, there is little divergence for the first 30 days as shown in Figure 6.

Figure 6: Time to Site-Reported First MACE – 30 Days

Number at risk							
rx = clopidogrel	9306	8759	8609	8535	8489	8441	8383
rx = ticagrelor	9336	8773	8633	8561	8519	8475	8417

The time course in Figure 5 and Figure 6 is quite different from what we have seen with the thienopyridines in ACS. Typically there has been an almost immediate benefit that rapidly accrues during the early days. The benefit beyond 30 days is harder to establish. For ticagrelor there appears to be little variation early by type of index event as shown in Figure 7.

Figure 7: Time to Site-Reported First MACE by Index Event Type

For all three types of index event ticagrelor appears to show beneficial effects longer term. The short term effects for ticagrelor are the opposite of what we've seen with prasugrel compared to clopidogrel: For prasugrel there was an immediate and dramatic benefit in STEMI patients in the TRITON trial but, at least for site-reported events, modest benefit for NSTEMI patients. There are three significant differences of TRITON compared to PLATO: (1) TRITON excluded patients with prior thienopyridine use; PLATO included them. (2) In TRITON all patients underwent percutaneous coronary intervention (PCI); in PLATO about 55% of patients had a PCI within the first 7 days after study drug administration. (3) In TRITON administration of study drug was delayed until after coronary angiography in all but the STEMI patients who presented within 12 hours of symptom onset; in PLATO the investigator was to give study drug immediately after randomization regardless of angiography having being done and prior to PCI. However, the investigator could delay randomization until after angiography at his or her discretion.

Relationship to Subsequent Percutaneous Coronary Intervention (PCI)
About 61% of PLATO patients had at least one PCI after study drug administration at some time during the study, virtually identical rates in both arms. I examined MACE rates in patients who did or did not have a subsequent PCI but did not find any discernible differences. However, about 43% of the patients had a PCI on the day of randomization and only 25% had a first or subsequent PCI after the day of randomization. Analyzing MACE rates by PCIs after day 1 produces some interesting results. I show the MACE rates by PCI anytime after day 1 in Figure 8, by PCI days 2 to 7 in Figure 9, and by PCI or death day 1 without a subsequent PCI with 30 days in Figure 10 .

Figure 8: Time to Site-Reported First MACE by PCI Anytime after Day 1

9
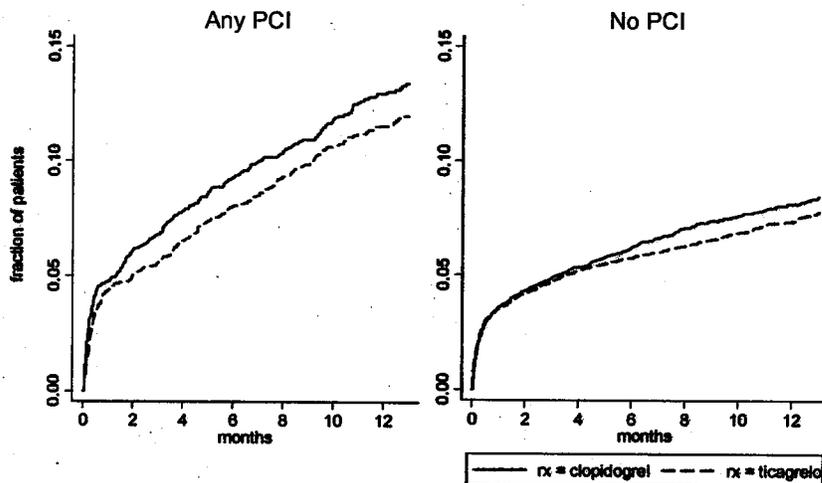
Figure 9: Time to Site-Reported First MACE by PCI Days 2 to 7
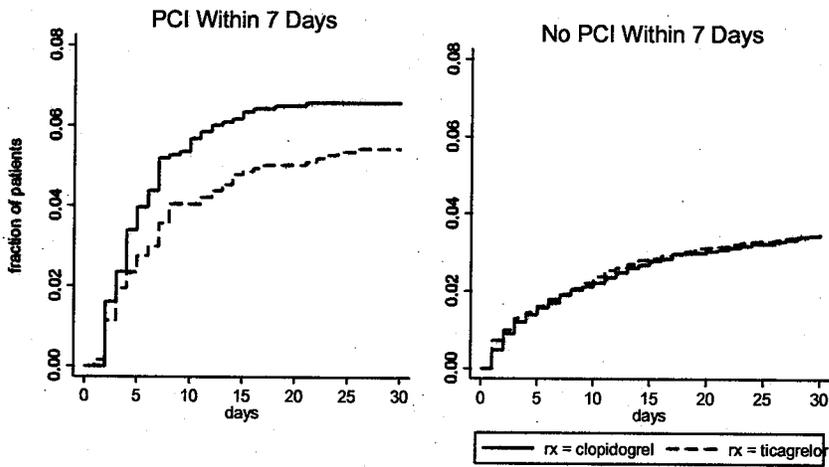
Figure 10: Time to Site-Reported First MACE in Patients with a PCI or Death Day 1 but No Subsequent PCI through Day 30

There appears to be no short term and limited long term benefit of ticagrelor in patients who did not have a subsequent PCI, while there is an apparent good benefit in patients who needed a subsequent PCI within 2 to 7 days of randomization. These findings alone might be interpreted

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as that ticagrelor shows greater benefit in the sicker patients requiring PCI. Furthermore, the determination of the need for PCI is a post-randomization decision subject to biases—and PCI itself can be considered to be a CV endpoint. However, that ticagrelor may show a detrimental effect in patients with PCIs on day 1 suggests an alternative explanation: Ticagrelor may have a delayed onset of platelet inhibition compared to clopidogrel. Attempting to analyze timing of study drug administration is complicated by the usual problems of inaccuracies with dates and times in clinical trials, e.g., I count 725 cases for which the study drug was administered prior to randomization. It is also confounded by another factor: 48% of the ticagrelor patients were on clopidogrel or received clopidogrel within the first 24 hours and the timing of administration of the clopidogrel was not captured.

The measured pharmacokinetics (PK) and pharmacodynamics of ticagrelor do not provide a consistent explanation for a delayed onset. Per the FDA clinical pharmacology review, the median T_{max} for ticagrelor levels after oral administration is 2.65 hours. This number suggests that some patients could be at risk for delayed effect. Furthermore, ticagrelor is >99% bound to plasma protein and total (not free) ticagrelor levels were measured in most PK studies, representing another source of variation between patients. However, the clinical pharmacology review notes that "The rate of offset of pharmacodynamic effect (%IPA [inhibition of platelet aggregation]) of ticagrelor is faster than that in clopidogrel in CAD patients on aspirin. However, given the higher antiplatelet activity and longer half-life of ticagrelor and its active metabolite, the time to conduct surgery following stopping of ticagrelor and clopidogrel may not be much different (5 days)." The half-life of ticagrelor is about 8 hours so that its half-life does not explain the delayed offset. Because we do not understand the delayed offset I question whether we really understand the timing of onset as well.

United States (US) vs. Outside United States (OUS) Efficacy
Another issue regarding the efficacy of ticagrelor is the quandary of the unfavorable results in the US that are inconsistent with the results in most other countries represented in PLATO. The funnel plot from the FDA Statistical Review reproduced in Figure 11 depicts the inconsistency well.

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Figure 11: Funnel Plot of Log Hazard Ratio by Events per Country (from FDA Statistical Review)

The US has worse results with ticagrelor for all efficacy measures, including MACE, MI, stroke, CV death, and all-cause mortality and is an outlier for all of them except stroke. Stroke rates are at least numerically higher with ticagrelor in all regions.

The sponsor has proposed one mechanism for explaining the disparate US vs. OUS results: aspirin dosage. Aspirin dosages in the US were split between 325 mg and 82 mg while OUS the vast majority of the dosing was 75 or 100 mg. The sponsor proposes that ticagrelor patients did worse with the high 325 mg dosage. Please see the FDA primary clinical efficacy and statistical reviews for exhaustive analyses of the aspirin dosage. I agree with those reviews' conclusions that, because of multiple problems with the analyses (aspirin dosage and region are highly correlated, the sponsor's analyses are sensitive to reclassification of small numbers of cases regarding loading vs. maintenance aspirin dosing and events in high dose aspirin OUS, biologic plausibility, etc.) aspirin dosing does not explain the disparate results.

Because I identified the issue of a delayed onset for ticagrelor effect after the primary reviewers had finished their reviews, we have not yet incorporated parameters relevant to delayed onset into any of our US vs. OUS analyses. These parameters include ones such as all clopidogrel use prior to PCI, timing of study drug administration relative to PCI, and early PCI vs. no early PCI. We will complete these analyses and forward them to advisory committee members when available or present them at the meeting. I do have the following quick observation: From prior ACS studies we have observed that there are practice differences between the US and Europe regarding antiplatelet drug use in ACS. Many US practitioners prefer to delay giving antiplatelet drugs until after angiography to determine whether the coronary anatomy is suitable for PCI or for coronary artery bypass surgery. European practitioners prefer to administer the antiplatelet drugs early so that platelet inhibition is maximal at the time of PCI. If US investigators delayed

study drug administration and if ticagrelor does have a delayed onset relative to clopidogrel, I would expect to see the results that PLATO has produced including the US-OUS disparity.

Long Term Benefit
The late divergence of the curves in Figure 5 and Figure 8 do suggest that ticagrelor may have a long term benefit and one that tracks differently than for the thienopyridines. Ticagrelor by *in vitro* testing does appear to produce greater platelet inhibition than clopidogrel at the dosages used in PLATO. The greater bleeding rates with ticagrelor in PLATO (see Safety below) confirm the greater platelet inhibition clinically. Hence greater platelet inhibition could explain the long term benefit. However, there are at least two other alternative or contributory mechanisms: (1) Ticagrelor is a moderate CYP3A inhibitor and increases the exposures of both simvastatin and atorvastatin, which account for the majority of the statin use in PLATO. PLATO did not capture statin dosages so we are unable to analyze them. We have not yet finished our analyses of lipid levels, which were captured. The one indication I have now that ticagrelor may have increased statin exposure is that rhabdomyolysis/myopathy AEs were greater with ticagrelor (8 vs. 2), although there was only one rhabdomyolysis SAE in each arm. (2) Ticagrelor blocks the uptake of adenosine into erythrocytes, potentially increasing local concentrations of endogenous adenosine and prolonging its effects. The sponsor has proposed this mechanism as a possible cause of the ventricular pauses seen with ticagrelor administration. Because adenosine also depresses ventricular automaticity and attenuates the cardiac stimulatory action of catecholamines and the release of norepinephrine from nerve terminals, this mechanism could also have a beneficial impact upon ventricular arrhythmias. I examine ventricular arrhythmia rates in Safety below.

Efficacy Evaluation Complexity
The previous sections should be convincing that efficacy evaluation in PLATO is extremely complex. I could argue that PLATO tried to do too much: *A priori* it attempted to evaluate three different conditions (i.e., STEMI, NSTEMI, and UA), two different management approaches (invasive and non-invasive), and two different pre-treatments (prior antiplatelet and no prior antiplatelet use). The complexity, e.g., 3 x 2 x 2 x 2 (study drug) = 24 different treatment cells was then increased 4 to 8-fold by the US vs. OUS discrepancies, with the issues of aspirin dosage and study drug timing, and the short term vs. long term effects. The evaluation is complicated further at least qualitatively by the issues of statin exposure and completeness of follow-up. As of the date of this review we have not successfully identified clear patterns among this complexity.

Safety
The major approvability issues for ticagrelor appear to be efficacy related. However, there are some common and some unique safety issues that warrant discussion.

Bleeding
The safety issue common to platelet inhibitors is bleeding. Ticagrelor did produce more bleeding than clopidogrel as shown **by the sponsor's statistics in** Figure 12.

Figure 12: Sponsor's Hazard Ratio Estimates of Non-procedural Bleeds
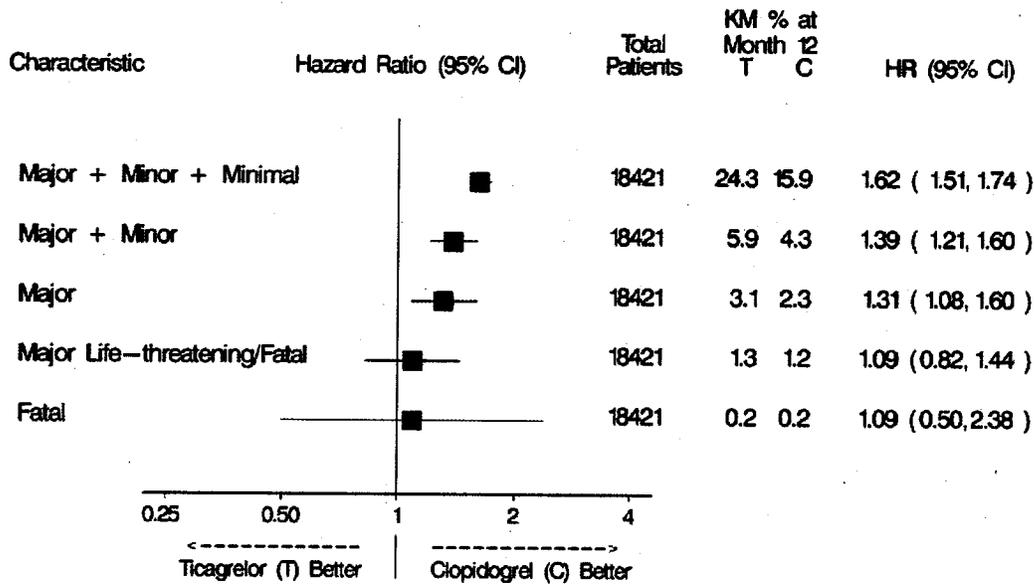
Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12		HR (95% CI)
			T	C	
Major + Minor + Minimal		18421	24.3	15.9	1.62 (1.51, 1.74)
Major + Minor		18421	5.9	4.3	1.39 (1.21, 1.60)
Major		18421	3.1	2.3	1.31 (1.08, 1.60)
Major Life—threatening/Fatal		18421	1.3	1.2	1.09 (0.82, 1.44)
Fatal		18421	0.2	0.2	1.09 (0.50,2.38)

```
        0.25      0.50    1     2      4
              <-------------  --------------->
              Ticagrelor (T) Better | Clopidogrel (C) Better
```

CI Confidence interval; HR Hazard ratio; KM% Kaplan-Meier estimate of % of patients with an event at 12 months.

While major bleeds and less serious bleeds were substantially increased with ticagrelor, life-threatening and fatal bleeds were not significantly increased. The FDA primary clinical safety reviewer commented that most patients with major bleeds had major CABG-related bleeds (~ 67%) and most CABG bleeds were major (~80%). The risk of CABG-bleeding was increased in ticagrelor patients who did not wait until day 5 after stopping treatment to have CABG. Besides confirming that the offset for ticagrelor is substantially longer than the pharmacokinetics predict, these statistics suggest that delaying CABG and other major surgery for five days or more after stopping ticagrelor is the most important management principle for dealing with the increased bleeding risk of ticagrelor.

Strokes, Intracerebral Hemorrhages, and Embolism
Strokes were included in the sponsor's primary efficacy endpoint but, because rates of stroke were higher with ticagrelor, they are also safety issues. Site-reported stroke rates were higher, but not significantly higher, with ticagrelor (1.5% vs. 1.2%). One possibility is that higher platelet inhibition could convert a small, subclinical ischemic stroke into a clinically apparent hemorrhagic one. The sponsor reported that with ticagrelor more patients had non-procedural intracranial hemorrhage (ICH, 26 vs. 14) and fatal ICH (11 vs. 2). The FDA primary clinical safety reviewer has raised the possibility of another mechanism: Pulmonary embolism and embolic events in general were slightly more frequent with ticagrelor. She also observes that strokes and pulmonary emboli were very slightly more frequent with prasugrel than clopidogrel in the TRITON trial. She hypothesizes that higher platelet inhibition might lead to clots that are more friable and likely to embolize. While the stroke rate is slightly higher with ticagrelor, the lower MACE rate (including the strokes) mitigate any concerns that I have about strokes.

Dyspnea

Dyspnea events in PLATO were reported more frequently in ticagrelor patients than in clopidogrel patients, about 14% vs. 8% by the sponsor's statistics. Dyspnea leading to discontinuation was uncommon but more frequent with ticagrelor (0.9% vs. 0.1%) as were dyspnea serious adverse events (SAEs, 0.7% vs. 0.4%). About half of the dyspnea AEs resolved within one week while a third were continuing at study termination. PLATO included a pulmonary function substudy that did not reveal any differences between treatment groups, although the FDA primary clinical safety reviewer questions that it was designed, conducted and analyzed in such ways that might have obscured differences if they existed. The sponsor hypothesizes that dyspnea may be another AE, like ventricular pauses, potentially related to adenosine. The sponsor proposes that if a patient reports dyspnea, physicians should evaluate the patient for underlying causes of dyspnea. If no cause is identified, patients should continue on ticagrelor treatment unless they cannot tolerate the dyspnea. I agree that this proposal is reasonable.

Ventricular Pauses and Ventricular Arrhythmias

Phase 2 studies suggested ticagrelor increased slightly the rate of sinus pauses. Because of this observation PLATO included a Holter monitoring substudy. The Holter monitoring confirmed that more ticagrelor patients had ventricular pauses ≥3 seconds and ≥5 seconds compared to clopidogrel; this difference was statistically significant for ventricular pauses ≥3 seconds at visit 1 only (relative risk 1.7, 95% confidence limits 1.15 to 2.64).

Reported AEs also do not suggest a clinical problem from ventricular pauses or bradycardia. Sinus pause AEs were uncommon and only slightly more frequent with ticagrelor (20 vs. 17). Bradycardia was similarly slightly more frequent (4.3% vs. 4.0%). Because of the slightly higher rate of stroke with ticagrelor, I recoded all atrial fibrillation events. By my recoding patients with atrial fibrillation events were virtually perfectly balanced between the two arms (both 5.2%). (My rates of atrial fibrillation are higher than those coded by the sponsor because I included reports of "absolute arrhythmia" and "arrhythmia", European terms for atrial fibrillation, as well as the reports of atrial fibrillation.)

I also recoded ventricular tachycardia and ventricular fibrillation events. Both types of serious ventricular arrhythmias appear to be less frequent with ticagrelor, combined about 1.5% of ticagrelor patients and 1.8% of clopidogrel patients. Only about 13% of these arrhythmias were reported in patients who also suffered an MI, so the slightly lower rate of MIs with ticagrelor may not explain the difference. The lower rate of ventricular arrhythmias may be another adenosine-related effect of ticagrelor and one that could contribute to the long term benefit.

Sex Hormonal Adverse Effects

Ticagrelor has signals of sex hormonal activity from its pre-clinical animal studies. The short summary from the FDA pharmacology and toxicology review is the following: There were reported drug-related effects on the reproductive organs of both sexes. In male mice, very high doses caused seminiferous epithelial degeneration of the testes. Female mice had an absence of corpora lutea at very high doses. In rats, endocrine effects were manifested as dose-related decreases in regular estrus cycles at relatively low doses ≥10 mg/kg. The relatively non-specific

finding of irregular estrus cycles became more important in light of the carcinogenicity study where female rats showed statistically significant incidences of uterine adenocarcinoma and uterine squamous cell carcinoma.

Because of these findings we scrutinized all adverse effects that could be related to sex hormonal activity, including malignancies of sexual organs. The one signal we found was regarding gynecomastia. For more details see the FDA primary clinical safety review, but the K-M plot of time to first gynecomastia is striking, as shown in Figure 13.

Figure 13: Time to First Gynecomastia in Men

Note that the absolute rate of gynecomastia is low, about 3 per 1,000 men at one year. The sponsor has commented that the use of other drugs associated with gynecomastia, such as spironolactone, confounds some of these cases. However, this is still a randomized comparison and, that ticagrelor may potentiate gynecomastia effects of other drugs, is not reassuring.

On the other hand, in this relatively short study we did not find any evidence for effects upon rates of sex organ malignancies. One testicular cancer was reported in a ticagrelor patient while prostate cancer was evenly balanced (13 vs. 12). Breast cancer events favored ticagrelor (4 vs. 10) while ovarian cancer was relatively balanced (2 vs. 1) and no uterine or cervical cancer events were reported. Given an observed favorable overall impact of ticagrelor upon CV events and total mortality, a potential increased risk of some sex hormone-related adverse effects is acceptable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

THOMAS A MARCINIAK
07/16/2010

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 29, 2010

From: Thomas A. Marciniak, M.D.
               Medical Team Leader

Subject: Ticagrelor for acute coronary syndromes, NDA 22-433

To: Advisory Committee Members

Ticagrelor (Brilinta™) is a novel $P2Y_{12}$ platelet receptor inhibitor submitted for approval for the indication of reducing the rate of thrombotic events in patients with acute coronary syndromes (ACS, including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI)). Two other drugs (clopidogrel, prasugrel) are approved for similar indications and a third (ticlopidine) is approved for related indications. All three have both common and individual limitations: The common limitations are that the approved drugs are all members of the thienopyridine structural class administered as pro-drugs requiring metabolic activation for effect and binding irreversibly to the $P2Y_{12}$ receptor. Ticagrelor does not require metabolic activation and binds reversibly. The individual limitations are that ticlopidine is rarely used because of a higher rate of neutropenia, clopidogrel may be less effective in some patients because of reduced activation due to genetic or drug-interaction factors, and prasugrel is associated with higher rates of bleeding and a question of cancer promotion. A novel drug without these limitations would be a therapeutic advance.

We have provided detailed primary reviews of clinical efficacy and of clinical safety in the FDA briefing package. In this memo I will highlight the significant clinical efficacy and safety questions that we have identified, referencing the preclinical and clinical pharmacological findings when relevant.

PLATO Study Design
The substantial evidence submitted to support the approval of ticagrelor comes from PLATO, a large, international, multi-center, randomized, double-blind, active-controlled trial. The primary reviews summarize well the details of protocol and study design. In general the trial was well-designed. In retrospect I have identified the following issues:

- Ticagrelor is a moderate inhibitor of cytochrome P450 CYP3A. Because several statins are metabolized by CYP3A and statins are commonly administered to ACS patients, the

sponsor proposed at the end-of-phase 2 meeting in December 2005 that concomitant therapy with either simvastatin or lovastatin at doses higher than 40-mg should be avoided. We accepted this proposal as reasonable. The protocol states that "As simvastatin has recommended restrictions for concomitant therapy with inhibitors of CYP3A due to increased reporting of myopathy, concomitant study therapy with simvastatin or lovastatin (which is very similar pharmacokinetically to simvastatin) at doses higher than 40mg should be avoided." In hindsight this restriction on a class of drugs with a mortality benefit appears inappropriate. There is no reason to restrict statin dosage in the clopidogrel arm.

Simvastatin was the most frequently used statin in PLATO—about 54% of patients took it at some time. Atorvastatin usage was very similar. Rosuvastatin usage was a distant third at about 9%. Note that ticagrelor also affects atorvastatin pharmacokinetics, increasing its AUC by a mean of 36%. These changes in statin exposure may be relevant to the time course of the presumed ticagrelor benefit that I discuss below.

Because of the restriction of simvastatin dosage the protocol should have specified collecting the dosages of statins used in the trial. Unfortunately the protocol failed to do so. The protocol did specify measuring blood lipid levels.

- PLATO was double-blinded but it was trivial to break the blind at the sites. The clopidogrel formulation used was a clopidogrel tablet cut into two and stuffed into a capsule. The dummy was identical in appearance. However, the sites could unblind any patient by breaking one of the patient's clopidogrel/dummy capsules and examining its contents. The protocol submitted in August 2006 described this clopidogrel formulation but the reviewing FDA medical officer did not identify the formulation as problematic. The sponsor did not submit the protocol for a Special Protocol Assessment. In 2006 we might have complained about but accepted the clopidogrel formulation even if we had identified it as problematic. Because of bad experiences with open label trials since 2006, we should be more cautious about such formulations today.

PLATO Study Conduct
Most aspects of the PLATO study conduct also appear to be good. The structure and processes of the trial, e.g., randomization by interactive voice or web response system, unblinded DSMB, blinded event adjudication committee, etc., are ones that we favor. The trial documentation submitted appears to be well-prepared and complete. The CRFs submitted are computer printouts from a data capture computer system. They are highly legible and appear complete but are difficult to read because of the computer formatting. However, we requested and the sponsor provided quickly the audit trail of all changes to the CRF data base—a 16.5GB file. We could analyze this file with standard statistical packages; I found it helpful in understanding changes in CRF data. The sponsor also submitted adjudication packages that were predominantly in an easier to read document format. These adjudication packages included investigator notes, hospital discharge summaries, ECG tracings, etc., that were helpful in understanding the adjudications.

There was one aspect of PLATO study conduct that was not good: the follow-up rate. By the sponsor's statistics, about 5% of the patients died while about 82% had a final study visit ("completers" per the sponsor's terminology). Hence about 13% of the patients (100% - 5% - 82%) had incomplete follow-up for determining the primary endpoint of CV death, myocardial infarction (MI), or stroke by the sponsor's tallying.

For PLATO the maximum targeted follow-up was one year. Patients randomized less than one year prior to study termination were to have their final study visit at the time of a planned quarterly visit based on their quarter of randomization to insure a 6-month minimum follow-up. The sponsor's short summary of this rolling termination is the following: "In effect, patients were phased out uniformly over a 3-month period starting on 18 October 2008." A communication to the sites recommended a -10 day window. Hence I counted patients as having good CV follow-up if they had an adjudicated death or they had a CV event or study visit on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria about 15% of patients had incomplete CV follow-up, with slightly but significant more ticagrelor than clopidogrel patients having incomplete follow-up (15.9% vs. 14.7%). The distributions of days of missing follow-up were similar in both arms, with the overall distribution shown in Figure 1.

Figure 1: Distribution of Days of CV Follow-up Missing in PLATO

The peaks at 180, 270, and 360 days are due to patients withdrawing shortly after randomization, allowing for the rolling phase-out. The median days of CV follow-up missing were 241 days.

I analyzed vital status follow-up similarly, counting vital status follow-up as good if the patient died or had a last visit or contact on or after 8 October 2008 or 355 days on-study (whichever came first). By these criteria 6.5% of ticagrelor and 5.2% of clopidogrel patients had incomplete vital status follow-up. The median days of vital status follow-up missing were 179 days in both arms.

These rates of incomplete follow-up are concerning. They greatly exceed the differences between arms in rates for any of the endpoints. If the endpoint results were consistent, then we would be less concerned about the follow-up rates. However, the efficacy results are inconsistent by region and the time course of the effects are inconsistent with those from the thienopyridine ACS trials.

This problem with incomplete follow-up rates has been an issue for other recent CV outcome trials. While we are sympathetic to the difficulties of performing outcome trials in the modern era of increased patient awareness of medical treatments and mounting privacy concerns, if this trend continues we will not be able to interpret CV outcome trial results. This problem is the number one study conduct problem today threatening the integrity of CV outcome trials.

Efficacy
The PLATO efficacy analyses are time-to-first-event analyses. Before presenting my analyses, I have one analytic issue to discuss. The sponsor, for its time-to-event analyses, used censoring dates for patients without the event of interest based on the last study visit date for the "completers" but projected based on either a future planned visit date plus 30 days for withdrawals or upon the last dispense date plus 90 days for patients who continued on study medication after a "last" visit. While the use of these strange censoring rules does not change the statistics greatly, I can not see the validity of projecting follow-up. I censored patients at the time of an event or the time of the last study visit (for CV events) or the last vital status follow-up (for all-cause mortality).

Sponsor's Primary Adjudicated Results
The sponsor contracted with an academic center to perform blinded adjudications of CV and bleeding events. The sponsor named this adjudication group the Independent Central Adjudication Committee (ICAC). While the use of a blinded adjudication process is good, it does not guarantee that the adjudications are unbiased. Someone still has to decide what events to refer and what documents to include in the adjudication packages. All of these processes are subject to surreptitious unblinding. For example, besides the DSMB the sponsor reported in Serial 008 that four groups within its organization had treatment codes as well as two contractors, i.e., ⬛⬛ (b) (4) had access to a password protected list of the randomization code which was known to only named personnel. This was used for the identification of PK samples . . ." and a second contractor had treatment codes for the IVRS system. With so many groups having access to treatment codes I am not reassured that the blind was properly maintained.

I show the Kaplan-Meier (K-M) plot for the sponsor's first primary endpoint event (CV death, MI, or stroke - MACE) in Figure 2 and for death in Figure 3.

Figure 2: Time to Sponsor's First Primary Endpoint Event (MACE)

Number at risk							
rx = clopidogrel	9306	7941	7609	7352	5879	5042	3962
rx = ticagrelor	9336	8021	7634	7395	5927	5035	3999

rx = clopidogrel   rx = ticagrelor

Figure 3: Time to Death from Any Cause

Number at risk							
rx = clopidogrel	9310	8815	8664	8526	6994	6037	4824
rx = ticagrelor	9345	8867	8674	8525	6970	5976	4809

rx = clopidogrel   rx = ticagrelor

Both time-to-first event analyses are highly statistically significant by the log rank test. One relevant question is that, given the incompleteness of follow-up, are the results real?

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Site-Reported MACE

As a check I counted CV death, MI, and stroke events (MACE) as reported by the sites without the ICAC adjudication. For these site-reported statistics I also implemented two variations from the sponsor's classification of CV deaths: (1) The sponsor counted bleeding deaths as CV deaths. While that is reasonable for the primary endpoint (PEP) to estimate a net benefit, for an endpoint to explore efficacy effects alone I believe that it is preferable to exclude bleeding events not related to a cardiovascular or cerebrovascular event. Hence I excluded gastrointestinal bleeds but included non-traumatic intracranial hemorrhages. (2) The sponsor counted all unknown deaths as CV deaths, again reasonable for a PEP for net benefit. I counted sudden unknown deaths as CV deaths but excluded completely unknown deaths. I show the K-M plot for this site-reported MACE in Figure 4.

Figure 4: Time to Site-Reported First MACE
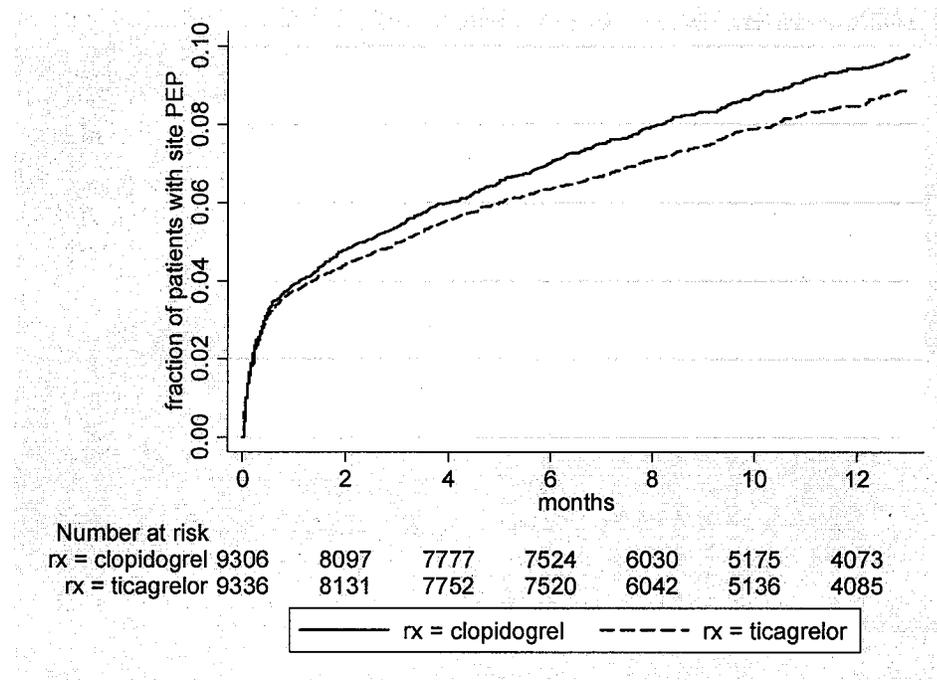
Number at risk							
rx = clopidogrel	9306	8097	7777	7524	6030	5175	4073
rx = ticagrelor	9336	8131	7752	7520	6042	5136	4085

——— rx = clopidogrel   – – – – – rx = ticagrelor

The possible benefit of ticagrelor is much less impressive for site-reported events and not statistically significant (p about 0.095 by log rank). For site-reported events there is only a slight benefit regarding MIs (relative risk (RR) about 0.94), a detriment regarding strokes (RR about 1.2), with the best benefit regarding CV deaths (RR 0.85). Note that the curves do not diverge early. In fact, there is little divergence for the first 30 days as shown in Figure 5.

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Figure 5: Time to Site-Reported First MACE – 30 Days

Number at risk

rx = clopidogrel	9306	8759	8609	8535	8489	8441	8383
rx = ticagrelor	9336	8773	8633	8561	8519	8475	8417

——— rx = clopidogrel   – – – – – rx = ticagrelor
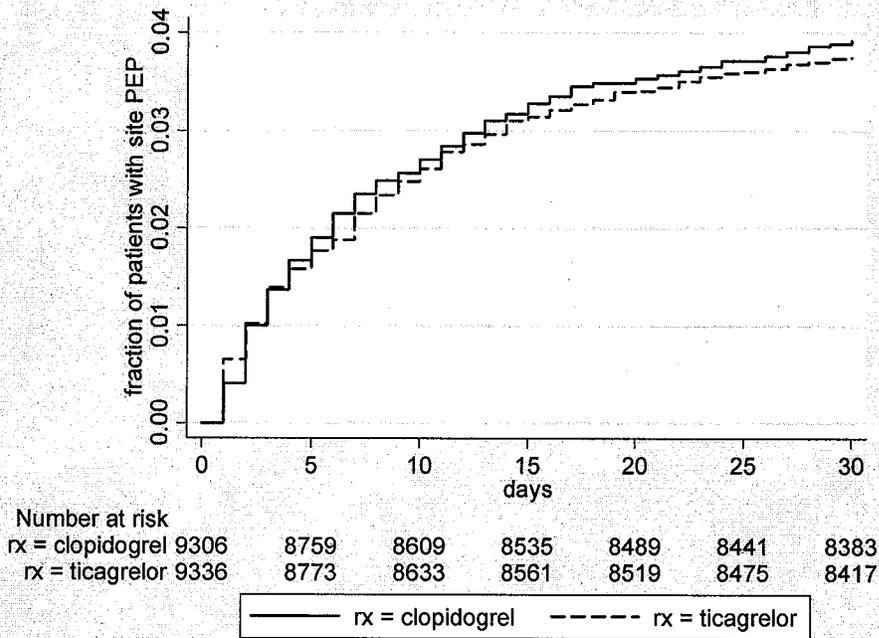
The time course in Figure 4 and Figure 5 is quite different from what we have seen with the thienopyridines in ACS. Typically there has been an almost immediate benefit that rapidly accrues during the early days. The benefit beyond 30 days is harder to establish. For ticagrelor there appears to be little variation early by type of index event as shown in Figure 6.

Figure 6: Time to Site-Reported First MACE by Index Event Type

For all three types of index event ticagrelor appears to show beneficial effects longer term. The short term effects for ticagrelor are the opposite of what we've seen with prasugrel compared to clopidogrel: For prasugrel there was an immediate and dramatic benefit in STEMI patients in the TRITON trial but, at least for site-reported events, modest benefit for NSTEMI patients. There are three significant differences of TRITON compared to PLATO: (1) TRITON excluded patients with prior thienopyridine use; PLATO included them. (2) In TRITON all patients underwent percutaneous coronary intervention (PCI); in PLATO about 55% of patients had a PCI within the first 7 days after study drug administration. (3) In TRITON administration of study drug was delayed until after coronary angiography in all but the STEMI patients who presented within 12 hours of symptom onset; in PLATO the investigator was to give study drug immediately after randomization regardless of angiography having being done and prior to PCI. However, the investigator could delay randomization until after angiography at his or her discretion.

Relationship to Subsequent Percutaneous Coronary Intervention (PCI)
About 61% of PLATO patients had at least one PCI after study drug administration at some time during the study, virtually identical rates in both arms. I examined MACE rates in patients who did or did not have a subsequent PCI but did not find any discernible differences. However, about 43% of the patients had a PCI on the day of randomization and only 25% had a first or subsequent PCI after the day of randomization. Analyzing MACE rates by PCIs after day 1 produces some interesting results. I show the MACE rates by PCI anytime after day 1 in Figure 7, by PCI days 2 to 7 in Figure 8, and by PCI or death day 1 without a subsequent PCI with 30 days in Figure 9 .

Figure 7: Time to Site-Reported First MACE by PCI Anytime after Day 1
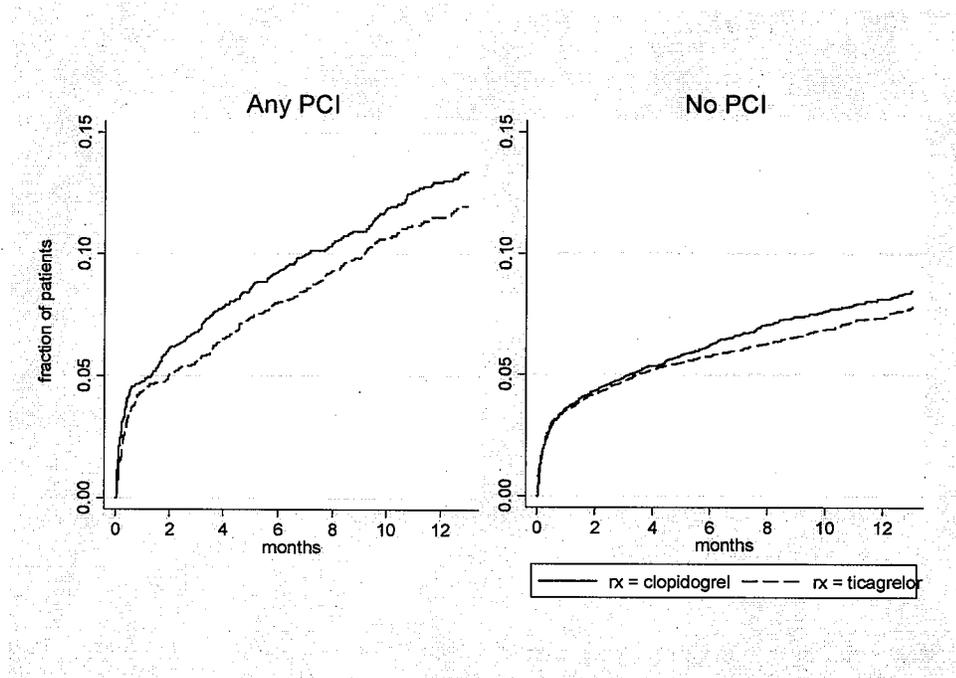
Figure 8: Time to Site-Reported First MACE by PCI Days 2 to 7
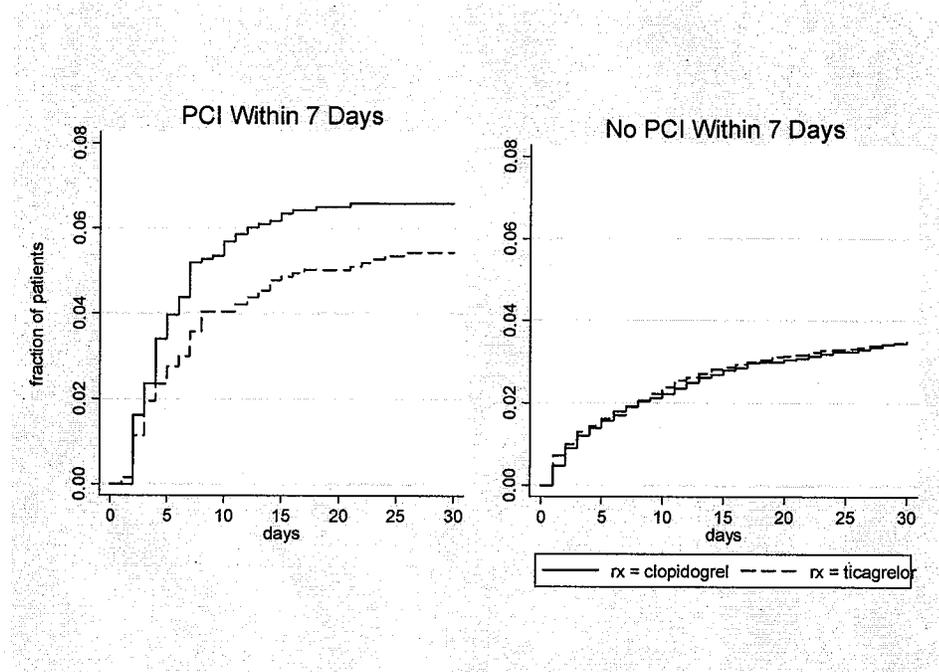
Figure 9: Time to Site-Reported First MACE in Patients with a PCI or Death Day 1 but No Subsequent PCI through Day 30

There appears to be no short term and limited long term benefit of ticagrelor in patients who did not have a subsequent PCI, while there is an apparent good benefit in patients who needed a subsequent PCI within 2 to 7 days of randomization. These findings alone might be interpreted

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as that ticagrelor shows greater benefit in the sicker patients requiring PCI. Furthermore, the determination of the need for PCI is a post-randomization decision subject to biases—and PCI itself can be considered a CV endpoint. However, that ticagrelor may show a detrimental effect in patients with PCIs on day 1 suggests an alternative explanation: Ticagrelor may have a delayed onset of platelet inhibition compared to clopidogrel.

The measured pharmacokinetics (PK) and pharmacodynamics of ticagrelor do not provide a consistent explanation for a delayed onset. Per the FDA clinical pharmacology review, the median T_{max} for ticagrelor levels after oral administration is 2.65 hours. This number suggests that some patients could be at risk for delayed effect. Furthermore, ticagrelor is >99% bound to plasma protein and total (not free) ticagrelor levels were measured in most PK studies, representing another source of variation between patients. However, the clinical pharmacology review notes that "The rate of offset of pharmacodynamic effect (%IPA [inhibition of platelet aggregation]) of ticagrelor is faster than that in clopidogrel in CAD patients on aspirin. However, given the higher antiplatelet activity and longer half-life of ticagrelor and its active metabolite, the time to conduct surgery following stopping of ticagrelor and clopidogrel may not be much different (5 days)." The half-life of ticagrelor is about 8 hours so that its half-life does not explain the delayed offset. Because we do not understand the delayed offset I question whether we really understand the timing of onset as well.

United States (US) vs. Outside United States (OUS) Efficacy
Another issue regarding the efficacy of ticagrelor is the quandary of the unfavorable results in the US that are inconsistent with the results in most other countries represented in PLATO. The funnel plot from the FDA Statistical Review reproduced in Figure 10 depicts the inconsistency well.

Figure 10: Funnel Plot of Log Hazard Ratio by Events per Country (from FDA Statistical Review)

The US has worse results with ticagrelor for all efficacy measures, including MACE, MI, stroke, CV death, and all-cause mortality and is an outlier for all of them except stroke. Stroke rates are at least numerically higher with ticagrelor in all regions.

The sponsor has proposed one mechanism for explaining the disparate US vs. OUS results: aspirin dosage. Aspirin dosages in the US were split between 325 mg and 82 mg while OUS the vast majority of the dosing was 75 or 100 mg. The sponsor proposes that ticagrelor patients did worse with the high 325 mg dosage. Please see the FDA primary clinical efficacy and statistical reviews for exhaustive analyses of the aspirin dosage. I agree with those reviews' conclusions that, because of multiple problems with the analyses (aspirin dosage and region are highly correlated, the sponsor's analyses are sensitive to reclassification of small numbers of cases regarding loading vs. maintenance aspirin dosing and events in high dose aspirin OUS, biologic plausibility, etc.) aspirin dosing does not explain the disparate results.

Because I identified the issue of a delayed onset for ticagrelor effect after the primary reviewers had finished their reviews, we have not yet incorporated parameters relevant to delayed onset into any of our US vs. OUS analyses. These parameters include ones such as all clopidogrel use prior to PCI, timing of study drug administration relative to PCI, and early PCI vs. no early PCI. We will complete these analyses and forward them to advisory committee members when available or present them at the meeting. I do have the following quick observation: From prior ACS studies we have observed that there are practice differences between the US and Europe regarding antiplatelet drug use in ACS. Many US practitioners prefer to delay giving antiplatelet drugs until after angiography to determine whether the coronary anatomy is suitable for PCI or for coronary artery bypass surgery. European practitioners prefer to administer the antiplatelet drugs early so that platelet inhibition is maximal at the time of PCI. If US investigators delayed study drug administration and if ticagrelor does have a delayed onset relative to clopidogrel, I would expect to see the results that PLATO has produced including the US-OUS disparity.

Long Term Benefit
The late divergence of the curves in Figure 4 and Figure 7 do suggest that ticagrelor may have a long term benefit and one that tracks differently than for the thienopyridines. Ticagrelor by *in vitro* testing does appear to produce greater platelet inhibition than clopidogrel at the dosages used in PLATO. The greater bleeding rates with ticagrelor in PLATO (see Safety below) confirm the greater platelet inhibition clinically. Hence greater platelet inhibition could explain the long term benefit. However, there are at least two other alternative or contributory mechanisms: (1) Ticagrelor is a moderate CYP3A inhibitor and increases the exposures of both simvastatin and atorvastatin, which account for the majority of the statin use in PLATO. PLATO did not capture statin dosages so we are unable to analyze them. We have not yet finished our analyses of lipid levels, which were captured. The one indication I have now that ticagrelor may have increased statin exposure is that rhabdomyolysis AEs were greater with ticagrelor (8 vs. 2), although there was only one rhabdomyolysis SAE in each arm. (2) Ticagrelor blocks the uptake of adenosine into erythrocytes, potentially increasing local concentrations of endogenous adenosine and prolonging its effects. The sponsor has proposed this mechanism as a possible cause of the ventricular pauses seen with ticagrelor administration. Because adenosine also depresses ventricular automaticity and attenuates the cardiac stimulatory action of catecholamines and the release of norepinephrine from nerve terminals, this mechanism

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could also have a beneficial impact upon ventricular arrhythmias. I examine ventricular arrhythmia rates in Safety below.

Safety

The major approvability issues for ticagrelor appear to be efficacy related. However, there are some common and some unique safety issues that warrant discussion.

Bleeding

The safety issue common to platelet inhibitors is bleeding. Ticagrelor did produce more bleeding than clopidogrel as shown by the sponsor's statistics in Figure 11.

Figure 11: Sponsor's Hazard Ratio Estimates of Non-procedural Bleeds
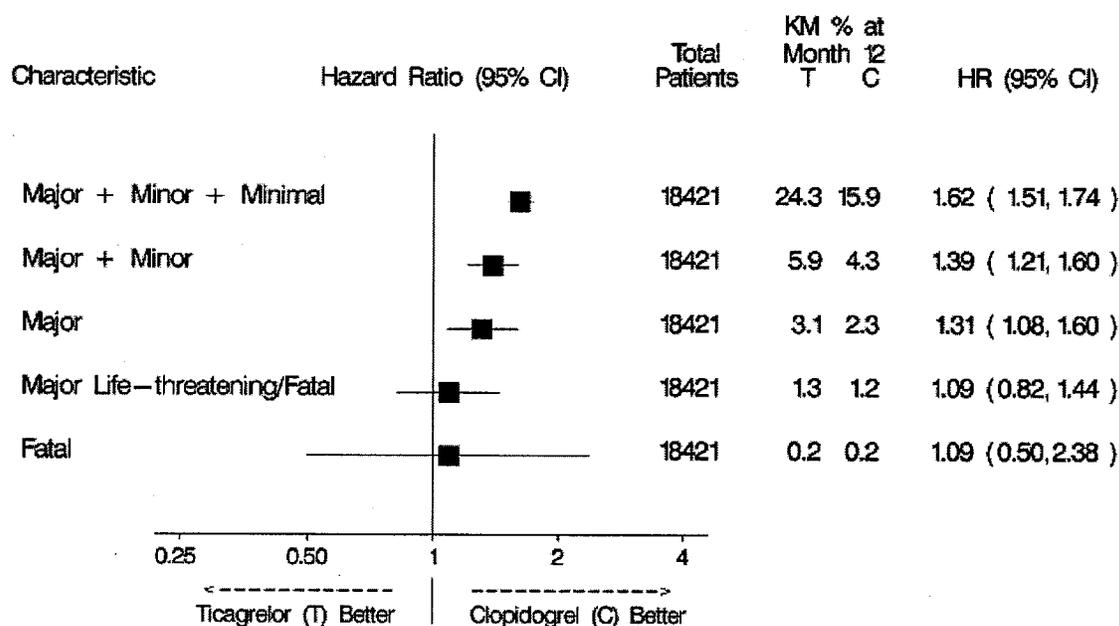
Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 T	KM % at Month 12 C	HR (95% CI)
Major + Minor + Minimal		18421	24.3	15.9	1.62 (1.51, 1.74)
Major + Minor		18421	5.9	4.3	1.39 (1.21, 1.60)
Major		18421	3.1	2.3	1.31 (1.08, 1.60)
Major Life-threatening/Fatal		18421	1.3	1.2	1.09 (0.82, 1.44)
Fatal		18421	0.2	0.2	1.09 (0.50, 2.38)

0.25   0.50   1   2   4

<─────────   │   ─────────>
Ticagrelor (T) Better   │   Clopidogrel (C) Better

CI Confidence interval; HR Hazard ratio; KM% Kaplan-Meier estimate of % of patients with an event at 12 months.

While major bleeds and less serious bleeds were substantially increased with ticagrelor, life-threatening and fatal bleeds were not significantly increased. The FDA primary clinical safety reviewer commented that most major bleeds were CABG-related (~ 75%) and most CABG bleeds were major (~85%). The risk of CABG-bleeding was increased in ticagrelor patients who did not wait until day 5 after stopping treatment to have CABG. Besides confirming that the offset for ticagrelor is substantially longer than the pharmacokinetics predict, these statistics suggest that delaying CABG and other major surgery for five days or more after stopping ticagrelor is the most important management principle for dealing with the increased bleeding risk of ticagrelor.

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Strokes, Intracerebral Hemorrhages, and Embolism

Strokes were included in the sponsor's primary efficacy endpoint but, because rates of stroke were higher with ticagrelor, they are also safety issues. Site-reported stroke rates were higher, but not significantly higher, with ticagrelor (1.5% vs. 1.2%). One possibility is that higher platelet inhibition could convert a small, subclinical ischemic stroke into a clinically apparent hemorrhagic one. The sponsor reported that with ticagrelor more patients had non-procedural intracranial hemorrhage (ICH, 26 vs. 14) and fatal ICH (11 vs. 2). The FDA primary clinical safety reviewer has raised the possibility of another mechanism: Pulmonary embolism and embolic events in general were slightly more frequent with ticagrelor. She also observes that strokes and pulmonary emboli were very slightly more frequent with prasugrel than clopidogrel in the TRITON trial. She hypothesizes that higher platelet inhibition might lead to clots that are more friable and likely to embolize. While the stroke rate is slightly higher with ticagrelor, the lower MACE rate (including the strokes) minimize any concerns that I have about strokes.

Dyspnea

Dyspnea events in PLATO were reported more frequently in ticagrelor patients than in clopidogrel patients, about 14% vs. 8% by the sponsor's statistics. Dyspnea leading to discontinuation was uncommon but more frequent with ticagrelor (0.9% vs. 0.1%) as were dyspnea serious adverse events (SAEs, 0.7% vs. 0.4%). About half of the dyspnea AEs resolved within one week while a third were continuing at study termination. PLATO included a pulmonary function substudy that did not reveal any differences between treatment groups, although the FDA primary clinical safety reviewer questions that it was designed, conducted and analyzed in such ways that might have obscured differences if they existed. The sponsor hypothesizes that dyspnea may be another AE, like ventricular pauses, potentially related to adenosine. The sponsor proposes that if a patient reports dyspnea, physicians should evaluate the patient for underlying causes of dyspnea. If no cause is identified, patients should continue on ticagrelor treatment unless they cannot tolerate the dyspnea. I agree that this proposal is reasonable.

Ventricular Pauses and Ventricular Arrhythmias

Phase 2 studies suggested ticagrelor increased slightly the rate of sinus pauses. Because of this observation PLATO included a Holter monitoring substudy. The Holter monitoring confirmed that more ticagrelor patients had ventricular pauses ≥ 3 seconds and ≥ 5 seconds compared to clopidogrel; this difference was statistically significant for ventricular pauses ≥ 3 seconds at visit 1 only (relative risk 1.7, 95% confidence limits 1.15 to 2.64).

Reported AEs also do not suggest a clinical problem from ventricular pauses or bradycardia. Sinus pause AEs were uncommon and only slightly more frequent with ticagrelor (20 vs. 17). Bradycardia was similarly slightly more frequent (4.3% vs. 4.0%). Because of the slightly higher rate of stroke with ticagrelor, I recoded all atrial fibrillation events. By my recoding patients with atrial fibrillation events were virtually perfectly balanced between the two arms (both 5.2%). (My rates of atrial fibrillation are higher than those coded by the sponsor because I included reports of "absolute arrhythmia" and "arrhythmia", European terms for atrial fibrillation, as well as the reports of atrial fibrillation.)

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I also recoded ventricular tachycardia and ventricular fibrillation events. Both types of serious ventricular arrhythmias appear to be less frequent with ticagrelor, combined about 1.5% of ticagrelor patients and 1.8% of clopidogrel patients. Only about 13% of these arrhythmias were reported in patients who also suffered an MI, so the slightly lower rate of MIs with ticagrelor may not explain the difference. The lower rate of ventricular arrhythmias may be another adenosine-related effect of ticagrelor and one that could contribute to the long term benefit.

Sex Hormonal Adverse Effects

Ticagrelor has signals of sex hormonal activity from its pre-clinical animal studies. The short summary from the FDA pharmacology and toxicology review is the following: There were reported drug-related effects on the reproductive organs of both sexes. In male mice, very high doses caused seminiferous epithelial degeneration of the testes. Female mice had an absence of corpora lutea at very high doses. In rats, endocrine effects were manifested as dose-related decreases in regular estrus cycles at relatively low doses ≥ 10 mg/kg. The relatively non-specific finding of irregular estrus cycles became more important in light of the carcinogenicity study where female rats showed statistically significant incidences of uterine adenocarcinoma and uterine squamous cell carcinoma.

Because of these findings we scrutinized all adverse effects that could be related to sex hormonal activity, including malignancies of sexual organs. The one signal we found was regarding gynecomastia. For more details see the FDA primary clinical safety review, but the K-M plot of time to first gynecomastia is striking, as shown in Figure 12.

Figure 12: Time to First Gynecomastia in Men

Note that the absolute rate of gynecomastia is low, about 3 per 1,000 men at one year. The sponsor has commented that the use of other drugs associated with gynecomastia, such as

spironolactone, confounds some of these cases. However, this is still a randomized comparison and, that ticagrelor may potentiate gynecomastia effects of other drugs, is not reassuring.

On the other hand, in this relatively short study we did not find any evidence for effects upon rates of sex organ malignancies. One testicular cancer was reported in a ticagrelor patient while prostate cancer was evenly balanced (13 vs. 12). Breast cancer events favored ticagrelor (4 vs. 10) while ovarian cancer was relatively balanced (2 vs. 1) and no uterine or cervical cancer events were reported. Given an observed favorable overall impact of ticagrelor upon CV events and total mortality, a potential increased risk of some sex hormone-related adverse effects is acceptable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

THOMAS A MARCINIAK
06/29/2010

CLINICAL EFFICACY REVIEW

Application Type	NDA
Application Number	022433
Priority or Standard	Standard
Submit Date	November 13, 2009
Received Date	November 16, 2009
PDUFA Goal Date	September 16, 2010
Division / Office	DCRP / ODE-1
Reviewer Name	Robert Fiorentino, MD MPH
Review Completion Date	June 25, 2010
Established Name	Ticagrelor
(Proposed) Trade Name	Brilinta
Therapeutic Class	Antiplatelet agent
Applicant	AstraZeneca
Formulation	film-coated tablet, 90 mg
Dosing Regimen	90mg twice daily
Indication	**Reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be managed medically or managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG.**
Intended Population	Acute Coronary Syndrome (ACS)

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1 Efficacy Review: Executive Summary

The sponsor has submitted an NDA to support the marketing of ticagrelor with an indication to reduce the rate of thrombotic events, including stent thrombosis, for patients with ACS (unstable angina [UA], non ST elevation myocardial infarction [NSTEMI] or ST elevation myocardial infarction [STEMI] (b) (4)

Platelet aggregation following disruption of an atherosclerotic plaque is the key process underlying ACS. Adenosine diphosphate (ADP) mediates platelet activation and aggregation and the use of ADP receptor inhibitors, such as the currently approved medications clopidogrel (Plavix) or prasugrel (Effient), have contributed to a substantial improvement in outcomes with an acceptable bleeding profile.

Ticagrelor, notable for having the first NDA for a *reversibly* binding oral ADP receptor antagonist, acts via the $P2Y_{12}$ receptor to block ADP-mediated platelet activation and aggregation.

PLATO is the single phase III clinical trial intended to support the approval ticagrelor for the proposed indication.

PLATO was conducted from October 2006 to February 2009 in 43 countries and was a double-blind, double-dummy, parallel group, randomized, multicenter study. The primary objective of PLATO was to test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events in patients with non-ST or ST elevation ACS. The primary efficacy endpoint was the time to first occurrence of any event from the composite of death from vascular causes, MI and stroke. PLATO compared the efficacy and safety of ticagrelor 90mg twice daily with clopidogrel 75mg once daily in the prevention of vascular events in patients with non-ST or ST elevation ACS.

A notable strength of PLATO was that the protocol required subjects to take the first dose of study medication directly after randomization and before any PCI. Subjects could also be medically managed without planned intervention (PCI) for the index event, and hence PLATO provides valuable information regarding this subgroup of patients.

PLATO randomized 18,624 subjects. Of those, 15,187 (82%) made a final study visit and 931 (5%) died. Of those who did not make it to a final study visit and did not die, (1,944) 78% had vital status assessed. Although inadequate follow-up can affect the validity of study outcome, sensitivity analyses did not significantly alter the reported results.

Overall, ticagrelor was superior in the prevention of thrombotic events in the composite efficacy endpoint (CV death, MI, and stroke) over 12 months in patients with ACS events compared to clopidogrel (9.8% vs. 11.7%, HR: 0.84; p=0.0003). The reduction in primary events was driven primarily by significant reductions in the rates of myocardial infarction (5.8% vs. 6.9%, HR:0.84, p=0.0045) and cardiovascular death (4.0% vs. 5.1%, HR:0.79, p=0.0013). Strokes were

numerically higher in the ticagrelor arm but did not reach statistical significance (1.5% vs. 1.3%, HR: 1.17, p=0.22).

The sponsor is also seeking to claim that ticagrelor reduces the risk of stent thrombosis. Although the data does appear to suggest relatively lower rates of stent thrombosis in the ticagrelor arm, stent thrombosis was an exploratory analysis.

In the primary analysis, the overall benefit of ticagrelor compared to clopidogrel was seen early following randomization and tended to accrue over time. The apparent accrual of relative benefit out to one year is an important finding, and suggests a longer-term benefit not directly attributable to the avoidance of early events. It is possible that the inclusion of a medically managed population into PLATO, as apposed to only a post-PCI population, explains some of these findings, given that peri-procedural events are avoided (or delayed). Regardless, in the overall PLATO population, comparative benefit with ticagrelor was observed in both medically managed (HR=0.85) and planned invasive (HR=0.84) subgroups (similar results in PCI and no-PCI subgroups). Comparative benefit was also preserved across the index event types of STEMI [HR=0.84 (0.72, 0.98)] and NSTEMI [HR=0.83 (0.73, 0.94)], with some attenuation of benefit in UA [HR=0.96 (0.75, 1.22)]. Overall, PLATO suggested a 22% relative reduction [HR=0.78 (0.69, 0.89)] in all-cause mortality with ticagrelor, however, type-1 statistical error was not controlled for this analysis.

A prespecified regional subgroup analysis suggested that in North America, there was a trend toward worse outcomes with ticagrelor compared to clopidogrel, which accounted for a significant interaction between region and treatment (p=0.045). However, only two countries comprised the North American subgroup, Canada (n=401) and the United States (n=1,413) and both had primary outcomes unfavorable towards ticagrelor, US: HR = 1.27, 95%CI(0.92, 1.75) and Canada: HR=1.17, 95%CI(0.59, 2.31). Although there were 10 other countries with HR>1.0, representing a combined population of 3,222 subjects (17% of PLATO), individually none showed statistically significant outcome. The US contributed the 2nd highest number of subjects of the 43 countries representing PLATO.

A detailed analysis of outcomes in the US showed that myocardial infarctions were the principal contributor to the overall (unfavorable) outcome [HR=1.38, 95%CI(0.95,2.01)]; however none of the component endpoints suggested a strong trend towards significance. Notable is that the numerically higher stroke rate seen in ticagrelor compared to clopidogrel was the only outcome that trended in the same direction across the US (HR=1.75) and non-US (HR=1.15) subgroups, albeit with infrequent (≤1.5%) event rates.

The most pronounced initial observation from attempts to explain the regional differences in outcome was that of a potential treatment interaction between aspirin (ASA) and study treatment, such that higher-dose aspirin was associated with comparatively unfavorable outcomes for ticagrelor. In fact, the ASA-by-treatment interaction explained virtually the entirety of the treatment-by-region interaction. Importantly, the United States, virtually alone among other countries, took a substantially higher dose of concomitant aspirin (on average) compared to the rest of the world (~220mg US vs. ~100mg non-US). Over half of the US study population received concomitant daily doses of 325mg aspirin, with a lesser number receiving 81mg. In stark contrast, the overwhelming majority of subjects outside the US took ≤100mg of aspirin

concomitantly with study drug, with only a small proportion of non-US subjects exceeding that dose.

Initially, the FDA review team entertained the possibility of a ticagrelor-aspirin interaction, given that event rates in the clopidogrel arm were fairly consistent across aspirin doses, whereas event rates in the ticagrelor arm appeared to increase. However, no clear pathophysiological, pharmacodynamic or pharmacokinetic explanation for an ASA-ticagrelor interaction was discernible in the data submitted.

Our review then focused on a large number of univariate and multivariate analyses that attempted to, 1) compare and contrast characteristics between the US and non-US populations, 2) identify other factors that might explain the divergent outcomes, and 3) investigate the possibility of other treatment interactions that correlate with high-dose aspirin use.

We observed that the US population differed somewhat from the non-US population on certain baseline characteristics. Among these are that the US population on average was heavier by approximately 10kg (22lbs), had higher rates of diabetes (33% vs. 24%), and more likely to have had a previous PCI (29% vs. 12%) and CABG (17% vs. 5%). The US also appeared to have greater use of clopidogrel and/or ASA at baseline, possibly reflecting their more prevalent cardiac history. Importantly, the index event characteristics differed substantially, with the US having a higher proportion of NSTEMI (67% vs. 41%) and lower proportion of subjects with STEMI (16% vs.40%) than non-US subjects. Furthermore, the US had a higher proportion of subjects with ≥12 hours from index event to study drug (63% vs. 46%), reflecting the lower proportion of STEMI subjects who have more urgent treatment demands. However, the US also had higher proportions of intent to invasively manage with PCI (94% vs. 70%), more frequent early PCI (61% vs. 49%), more frequent use of drug eluting stents (46% vs. 19%), less frequent use of bare metal stents (23% vs. 46%) and higher rates of GP IIb/IIIa use during index hospitalization (50% vs. 25%). The US population also had lower rates of compliance with study drug (86% vs. 95%).

These analyses suggest that the US population had different baseline factors at the time of enrollment and subsequently underwent dissimilar treatment strategies compared to the average non-US population.

Furthermore, by one analysis, it was observed that the US subjects who received higher-dose, 325mg ASA (n=667) when compared to those with 81mg (n=545), were more likely to have PCI on-study (77% vs. 61%), with more stents implanted (74% vs. 58%) and more frequent use of GPIIb/IIIa inhibitors during index hospitalization (57% vs. 45%). These factors, as expected, are clinically inter-related.

Further analyses also suggested that US subjects who received ASA 81mg had numerically better outcomes that those on 325mg. However the hazard ratios for these subgroups were sensitive to the method used to define and derive a given subject's daily mean or median dose. For example, the original data submitted with the NDA estimated a HR=0.96 (0.57, 1.63) in the US 81mg group, compared with HR=1.56 (1.01, 2.41) in the US 325mg group. The sponsor subsequently (and appropriately) corrected a programming error and discussed with the FDA other methods by which ASA dose could be more reliably and robustly defined. In general, the FDA and sponsor agreed that the methods by which ASA dose was derived could contain a

number of potential confounders that should be addressed. However, after this was implemented the association between ASA dose and outcome in the US was altered; whereby the revised data estimated a HR=0.76 (0.57, 1.63) in the US 81mg subgroup that was now more favorable towards ticagrelor.

Subsequent to this observation, we became aware that even small switching of events between the two study arms in the US could cause the treatment-by-region interaction to become non-significant. Additional statistical models attempting to estimate US outcomes extrapolated from non-US observations were also sensitive to small changes in events and the methods by which a subject's daily aspirin dose was derived from the data. A major limitation of these models was that there were so few subjects outside the US who took ASA >100mg, including 325mg daily.

In the end, irrespective of aspirin dose, there was no other factor identified that could, by itself, account for the unfavorable study outcome in the US population. Although the US population, as discussed above, had key differences from the rest of the PLATO population, none of these differences appeared to have a strong treatment interaction with ticagrelor. Further complicating this analysis was the observation that subjects who received higher-dose aspirin in the US had numerically unfavorable outcomes. One could argue that the baseline and treatment characteristics of US population, including the use of higher-dose aspirin, were confounded with the primary outcome in a manner (through multicollinearity) that could not be teased apart by *post hoc* multivariate analyses.

One difficulty in accepting the aspirin-ticagrelor interaction premise is that there exists no known explanation for why ticagrelor and aspirin should interact *in vivo.* Conversely, there is no self-evident reason for why ticagrelor should be expected to perform differently in any specific region or country.

Finally, the data that supports the relationship between higher-dose ASA and unfavorable outcomes does not appear considerably robust. I remain concerned that the validity of the statistical models is limited by the different methods used to derive ASA dosages, to random or systematic processes across regions that could be related to outcome and to the lack of higher-dose ASA subgroups outside the US. I am unconvinced that un-measureable (or unknowable) confounders are not confusing our analyses, which also makes it somewhat unreasonable to place blame for the unfavorable US outcome entirely on any single factor alone, including aspirin. Ever present is the unknown contribution that human bias has had to any of these post-hoc analyses and findings. Finally, although the results of PLATO suggest at least some level of internal inconsistency with respect to the US findings, it seems difficult to discount outcomes, particularly a benefit in all-cause mortality, observed in over 17,000 subjects outside the US.

2 Introduction and Regulatory Background

2.1 Product Information

Ticagrelor (formerly AZD6140; proposed trade name, Brilinta), is a new molecular entity (NME) that acts as an oral adenosine diphosphate (ADP) receptor antagonist, reversibly binding to the $P2Y_{12}$ receptor on platelet surfaces and blocking ADP-mediated platelet activation and aggregation. Ticagrelor does not require hepatic or other metabolic activation.

Platelet aggregation following disruption of an atherosclerotic coronary plaque is the key process underlying acute coronary syndromes (ACS). The term ACS encompasses a range of clinical conditions that includes unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI).

Adenosine diphosphate (ADP) mediates platelet activation and aggregation and the use of an ADP receptor inhibitor in the management of ACS, in addition to other therapeutic advancements, has contributed to a substantial improvement in outcomes.

Current clinical practice guidelines include recommendations for initiation of therapy with clopidogrel plus acetylsalicylic acid (ASA) as early as possible following the ACS event, including prior to angiography, and this treatment regimen should ideally be maintained for 9 to 12 months for all ACS patients. ACS patients undergoing percutaneous coronary intervention (PCI) should receive dual antiplatelet therapy for at least 1 month and ideally up to a year after bare metal stent (BMS) implantation, and at least 12 months for drug-eluting stents (DES).

The applicant is seeking a claim that ticagrelor reduces the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be managed medically or managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG.

Treatment would be initiated with 180 mg (two doses of 90 mg) oral loading dose, followed by maintenance therapy of 90 mg twice daily. In chronic treatment, sponsor proposes that BRILINTA be used with low dose aspirin (75-150 mg).

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently Available Treatments for Proposed Indication

Drug	Indication	Mechanism of Action
Aspirin	Reduce the risk of vascular mortality in patients with a suspected acute MI. Reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris.	Irreversibly blocks the formation of thromboxane-A2 in platelets via the irreversible inactivation of the cyclooxygenase (COX) enzyme, producing an inhibitory effect on platelet aggregation
Clopidogrel (Plavix)	Clopidogrel bisulfate is indicated for the reduction of atherothrombotic events as follows: **Recent MI, Recent Stroke or Established Peripheral Arterial Disease** For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, clopidogrel bisulfate has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death. **Acute Coronary Syndrome** For patients with acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, clopidogrel bisulfate has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.	Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets.
Prasugrel (Effient)	Prasugrel is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows: Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI). Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.	Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets.

Source: R. Fiorentino, Clinical Reviewer

Ticlopidine (Ticlid) is another irreversible ADP $P2Y_{12}$ platelet inhibitor not listed above. However, ticlopidine is indicated in the U.S. for reducing the risk of thrombotic stroke (fatal or nonfatal) in

patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. It is also indicated for adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation. Ticlopidine does not carry a secondary prevention indication for ACS or MI and its use has largely been supplanted by clopidogrel.

2.3 Availability of Proposed Active Ingredient in the United States

Ticagrelor is currently not marketed in the United States (or outside the US).

2.4 Important Safety Issues With Consideration to Related Drugs

An increased risk of bleeds is a known complication of antiplatelet therapy, particularly gastrointestinal and intracranial hemorrhage. The bleeding risk of any antiplatelet regimen is commonly weighed against the effectiveness in preventing "hard" clinical events such as myocardial infarction (MI), stroke or death. However the benefit-to-risk ratio is complicated by varying definitions of bleed severity across clinical studies and no clear metric by which an observed level of bleeding risk would negate a given improvement in hard clinical outcomes. Regardless, the prevention of a stroke, MI or death is of considerably greater importance than that of either "nuisance" bleeds or severe bleeds that do not result in one of these outcomes.

Other ADP receptor antagonists such as ticlopidine hydrochloride and clopidogrel bisulfate have been associated with neutropenia, agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

December 5, 2002: Pre-IND meeting
AstraZeneca requested a Pre-IND meeting to discuss AZD6140 Tablets, an oral adenosine diphosphate (ADP) receptor agonist. The Sponsor was seeking to study AZD6140 for secondary event prevention after stroke. Preclinical findings discussed included phospholipidosis in rat lung during pre-clinical toxicity studies. Also pre-clinical findings of potential liver injury division responded that adequate monitoring will be critical.

May 28, 2003: 30 Day Safety Meeting
Original target indication was for secondary event prevention after stoke or transient ischemic attack. No clinical hold issues were identified. It was noted that a "substantial number" of non-US subjects had already been exposed to AZD6140. The medical officer expressed concerns about liver enzyme elevation observed during human exposure, and the potential of QT interval prolongation documented in animal data. Observations at the time indicated that "liver abnormalities reverted to normal levels after discontinuation of the drug."

May 27, 2004: Type C Guidance meeting
At this time, the drug was being developed for the treatment of acute coronary syndrome and for secondary event prevention following a stroke or transient ischemic attack. AstraZeneca proposed a Phase 2 dose-ranging study (DISPERSE2) to investigate the pharmacodynamic and pharmacokinetic properties of AZD6140 plus aspirin as compared to clopidogrel plus aspirin in patients with atherosclerosis. AstraZeneca provided a draft protocol for DISPERSE2 and they sought guidance for the design of DISPERSE2 as the data from both studies would guide dose selection for their Phase 3 program. Sponsor summarized the results from their DISPERSE1 study. Results showed that dyspnea events are greater on the drug arm than with clopidogrel. Choice and definitions of endpoints for future studies was also discussed with the Division. AstraZeneca stated that they intended to repeat an adenosine agonist and antagonist study, although they clarified that this was a screening pharmacology study and not one looking to determine the mechanism of action. Sponsor noted that they would continue to work on possible effects of the drug on other receptors

December 8, 2005: Type B End of Phase 2 meeting
Ticagrelor was being developed for the treatment of acute coronary syndrome, and secondary event prevention following a stroke or transient ischemic attack. The planned Phase 3 study, PLATO, was described as a randomized, double-blind, parallel study of ACS patients comparing AZD6140 (180 mg bid) and clopidogrel (75 mg qd) on time to vascular death, MI, or stroke. The planned enrollment was 16,000, but the study would be event-driven (1800 events). The Division agreed that the non-clinical data presented supported the proposed dosing for the Phase 3 PLATO study. The Division found it "reasonable" that because AZD6104 is a moderate inhibitor of CYP3A, concomitant therapy with either simvastatin or lovastatin at doses higher than 40-mg should be avoided. Division agreed that strong CYP3A inhibitors (antifungals, protease inhibitors, etc.) are prohibited, the dose of CYP3A-dependent statins (simvastatin, lovastatin) be limited to 40 mg and other narrow therapeutic index drugs metabolized by CYP3A (cyclosporine, quinidine) be prohibited. Agency agreed that because the effect of AZD6140 on digoxin is about a 30% increase (at trough), that "close monitoring" of digoxin be planned around times of changes in AZD6140.

The Agency found it acceptable to use a 600-mg loading as standard practice and proposed to leave this up to investigator discretion. FDA argued that if there is an early effect, similar to ACS trials where most of the benefit was observed within the first two weeks, AZ will be unable to secure a comparative claim by beating an inadequate dose of clopidogrel. An effective dose should be used, particularly if early effects are expected.

April 20, 2009: Type B Pre-NDA meeting
AstraZeneca planned to submit a NDA for ticagrelor during the second half of 2009. The goal of the sponsor for this pre-NDA meeting was to gain agreement with the Division regarding the proposed format, data, and analyses planned to be included in the NDA to support the approval of ticagrelor.

August 5, 2009: Type 3 Phase 3 Results meeting
The goal for this meeting was to provide preliminary results from the Phase 3 PLATO study and to obtain the Division's initial impressions of the data.

AstraZeneca agreed to analyze and present the results for the subgroups of subjects with NSTEMI ACS and STEMI. The sponsor explained that the nominal p-value was 0.0003 for all cause mortality was not considered statistically significant because the p-value for the secondary endpoint above it in the hierarchical analysis, reduction in stroke, was not less than 0.05. CV mortality, however, was significant. FDA noted that this would be considered further.

The consistency of treatment effect from 1-30 and 31-360 days was explored. AstraZeneca agreed to explore other time periods in the NDA submission.

AstraZeneca explained that dose dependent bradycardia was observed in Phase 2 but not in PLATO. AstraZeneca added that bradycardia did not appear to be due to a drug-drug interaction. An increase in frequency in bradycardia episodes was observed in overweight patients as well as at night.

A mild increase in uric acid was also observed in slightly more subjects randomized to ticagrelor than clopidogrel. AstraZeneca noted that after stopping ticagrelor, uric acid levels decrease but do not normalize. No other markers for kidney injury were explored. The sponsor suggested that it is likely due to inhibition of organic anion transporter(s), but the only transporter-interaction study they have performed was with digoxin (P-glycoprotein transport substrate).

AstraZeneca stated that no potential Hy's law cases were observed in PLATO. Two subjects' lab tests on Day 1 of treatment met criteria for a potential Hy's law case but both had readily identifiable reasons for the lab abnormalities.

AstraZeneca indicated that the results in the subgroup of subjects enrolled in North America (NA) were notably different from the rest of the world, favoring clopidogrel on the primary endpoint (20 fewer MIs/strokes/CV deaths, with no one component predominating). AstraZeneca indicated they had extensively reviewed the data for an explanation. There did not seem to be major differences in the standard of care between North America and the rest of the world. One difference found was that in NA the dose of aspirin tended to be 325 mg while the dose in the rest of the world was less. Dr. Temple observed that the evidence for dose-response for aspirin indicated that dose of aspirin does not appear to have much dose related effect on MACE outcomes. AstraZeneca agreed to explore possible interactions with aspirin/ticagrelor.

3 Ethics and Good Clinical Practices

Refer to the separate review conducted by Dr. Melanie Blank.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Molecular Formula: $C_{23}H_{28}F_2N_6O_4S$
Relative Molecular Mass: 522.57

Ticagrelor tablets are presented as round, biconvex, yellow, film-coated tablets containing 90 mg of ticagrelor.

No other relevant issues.

4.2 Clinical Microbiology

No relevant issues.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the separate review of Safety performed by Dr. Melanie Blank (FDA).

4.4 Clinical Pharmacology

The following sections contain information reproduced from the separate Clinical Pharmacology review performed by Dr. Islam Younis (FDA).

4.4.1 Mechanism of Action

Ticagrelor is a selective and reversible $P2Y_{12}$ ADP-receptor antagonist.

4.4.2 Pharmacodynamics

- The rate of onset of pharmacodynamic effect of ticagrelor measured by % inhibition of platelet aggregation (%IPA) is faster than that of clopidogrel in stable coronary artery disease (CAD) patients on aspirin
- The rate of offset of pharmacodynamic effect (%IPA) of ticagrelor is faster than that in clopidogrel in CAD patients on aspirin
- Switching from clopidogrel results in a statistically significant increase in %IPA of at least 16.8 units in CAD patients on aspirin and vice versa. The effect is more pronounced in CAD patients on aspirin who are less responsive to clopidogrel
- Ticagrelor increases serum uric acid by 10% in healthy male volunteers and patients with acute coronary artery disease
- Ticagrelor does not induce bronchospasm and does not cause changes in respiratory parameters in healthy elderly, patients with mild asthma, and patients with COPD

4.4.3 Pharmacokinetics

- The plasma concentration of ticagrelor decline mono-exponentially
- Ticagrelor $t_{1/2}$ is 8 hours

- Ticagrelor is rapidly absorbed with median T_{max} of 1.5 hours
- Ticagrelor is > 99% bound to plasma protein
- Ticagrelor is metabolized mainly by CY3A4/5 to produce AR-C124910XX and ARC133913XX.
- The major metabolite AR-C124910XX is rapidly formed with median T_{max} 2.5 h. It is also equipotent as $P2Y_{12}$ inhibitor as ticagrelor, >99% bound to plasma protein, and metabolized by CYP3A4/5. AR-C124910XX to ticagrelor ratio is 36% – 52%. AR-C133913XX (inactive metabolite) to ticagrelor ratio is 12%
- Less than 1% of ticagrelor is excreted unchanged in the urine
- The PK of ticagrelor is slightly more than dose proportional over the dose range 50 – 400 mg in healthy volunteers and patients with stable atherosclerotic disease

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The present submission includes clinical study reports of 47 clinical studies, including *in vitro* clinical pharmacology, biopharmaceutic, human PK and PD studies and one pivotal study. A tabulated summary of the phase 2 and 3 studies included in this review is provided in Table 2.

Table 2. Phase 2 and 3 Studies

Study ID / Title	Population	Primary objective	Subjects Randomized/Arm	Dates
ID: D5130C00008 "DISPERSE": A 28-Day, Randomized, Double-blind, double-dummy, Parallel Group, Dose Finding Study to Investigate the Pharmacodynamics and Pharmacokinetics of AZD6140 plus Acetyl Salicylic Acid (ASA) Compared with Clopidogrel plus ASA in Subjects with Atherosclerosis	Male and female patients with documented atherosclerotic disease	To assess the PD effects of AZD6140 at doses of 50 mg twice daily (bd), 100 mg bd, 200 mg bd and 400 mg once daily (od) in the presence of acetyl salicylic acid (ASA) compared to clopidogrel 75 mg od plus ASA, in subjects with documented atherosclerotic disease	Total rand = 201 (Completed = 185) Ticagrelor 50mg bd: 41 Ticagrelor 100mg bd: 40 Ticagrelor 200mg bid: 37 Ticagrelor 400mg od: 46 Clopidogrel 75mg od: 37	August 4, 2003 to November 27, 2003
ID: D5130C00002 "DISPERSE2": A Double-blind, Double-dummy, Parallel Group Randomised Dose Confirmation and Feasibility Study of AZD6140 + Acetyl Salicylic Acid (ASA) Compared with Clopidogrel + ASA in Patients with Non-ST Segment Elevation Acute Coronary Syndromes	Male and female patients with documented evidence of non-ST segment elevation ACS in the previous 48 hours	To assess the safety and tolerability of different doses of AZD6140 in the presence of acetyl salicylic acid (ASA), compared with clopidogrel plus ASA, in patients with non ST segment elevation ACS	Total randomized= 990 (Completed = 794) Ticagrelor 90mg bd: 334 Ticagrelor 180mg bd: 329 Clopidogrel 75mg qd: 327	October 03, 2004 to June 03, 2005
ID: D5130C05262 "PLATO": A Randomised, Double-blind, Parallel Group, Phase 3, Efficacy and Safety Study of AZD6140 Compared with Clopidogrel for Prevention of Vascular Events in Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS)	Male or female patients with a NSTEMI or STEMI ACS	Pivotal Study: The primary objective of this study was to test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events in patients with non-ST or ST elevation ACS. The primary efficacy endpoint was time to first occurrence of any event from the composite of death from vascular causes, MI and stroke.	Total randomized: 18,624 Ticagrelor 90mg bd: 9333 Clopidogrel 75mg bd: 9291	October 11, 2006 to February 27, 2009

Source: R. Fiorentino, Clinical Reviewer

5.2 Review Strategy

The submitted NDA is being reviewed by two clinical reviewers. Dr. Robert Fiorentino (this reviewer) has responsibility to provide the clinical review of efficacy, while Dr. Melanie Blank performed a review of safety.

The phase 3 PLATO study is the principal source of data supporting the determination of efficacy and safety of ticagrelor. The clinical review of efficacy is discussed in detail in Section 6.

Two phase 2 trials, DISPERSE and DISPERSE2, are also discussed in Section 8.2. These trials were reviewed by both efficacy and safety reviewers on a limited basis and information derived from these studies, when relevant to the discussion, is included in the respective reviews.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 PLATO [Study ID: D5130C05262]

5.3.1.1 Title

PLATO: A Study of PLATelet inhibition and Patient Outcomes.

A Randomised, Double-blind, Parallel Group, Phase 3, Efficacy and Safety Study of AZD6140 Compared with Clopidogrel for Prevention of Vascular Events in Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS)

5.3.1.2 Study Objectives

Primary objective:

The primary objective of this study was to test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events in patients with non-ST or ST elevation ACS.

Secondary objectives:

- To assess the safety and tolerability of ticagrelor compared with clopidogrel.

- To assess the efficacy and safety of ticagrelor compared with clopidogrel in those patients who underwent CABG surgery or PCI during the study and in relation to the timing of these interventions. The primary efficacy and safety endpoints were used for this assessment as well as the secondary efficacy and safety endpoints.

- To assess the occurrence of arrhythmic episodes detected by Holter monitoring with ticagrelor compared with clopidogrel both during the initial period after randomization

and at 1 month and the relation of these episodes to clinical outcomes. The primary variable of interest was the occurrence of ventricular pauses ≥3 seconds. Secondary variables included other lengths of pauses, other bradycardic episodes, heart rate, atrial tachyarrhythmias, and ventricular arrhythmias.

5.3.1.3   Endpoints

Primary Efficacy Endpoint
The primary efficacy endpoint was the time to first occurrence of any event from the composite of death from vascular causes, MI and stroke.

Secondary Efficacy Endpoints
The following endpoints were prespecified in the PLATO protocol:

- The time to first occurrence of any event from the composite of death from vascular causes, MI and stroke for the subgroup of patients with intent for invasive management at randomization (planned coronary angiography with revascularization if indicated during the index event hospitalization)

- The time to first occurrence of any event from the composite of all-cause mortality, MI, and stroke

- The time to first occurrence of any event from the composite of death from vascular causes, MI (including silent MI by electrocardiogram (ECG)), stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, transient ischemic attack (TIA) and other arterial thrombotic events

- The time to first occurrence of each component of the primary composite efficacy endpoint individually in the order of MI, death from vascular causes and then stroke

- The time to occurrence of all-cause mortality

- The other components of the secondary composite efficacy endpoints (i.e. silent MI, recurrent cardiac ischemia, severe recurrent cardiac ischemia, TIA and other arterial thrombotic events) were to be presented only descriptively.

Primary Safety Endpoint
The primary safety endpoint is the time to first occurrence of any total major bleeding event.

Secondary Safety Endpoints

- Non-CABG, non-procedure-related, coronary procedure-related and noncoronary procedure-related major bleeding events

- Total, non-CABG, non-procedure-related, coronary procedure-related and non-coronary procedure-related minor bleeding events.

- Combined major and minor bleeding events for each of the categories.

5.3.1.4 Study Design

PLATO was a double-blind, double-dummy, parallel group, randomized, international, multicenter study comparing the efficacy and safety of ticagrelor 90mg twice daily with clopidogrel 75mg once daily in the prevention of vascular events in patients with non-ST or ST elevation ACS.

The duration of treatment ranged from 6 to 12 months with planned study completion at 6, 9 and 12 months depending on date the patients entered the study (e.g., patients that entered towards the end of the enrolment period would have the shortest duration of treatment). To achieve the target of 1780 primary endpoint events (given the expected event rate and the recommendations for long-term antiplatelet therapy for ACS patients), the CSP specified a treatment duration maximum of 12 months and minimum of 6 months, with an expected average study duration of approximately 10 months per patient.

 An interim analysis was performed when approximately 1200 adjudicated events were available.

Figure 1. PLATO Study Flow Chart
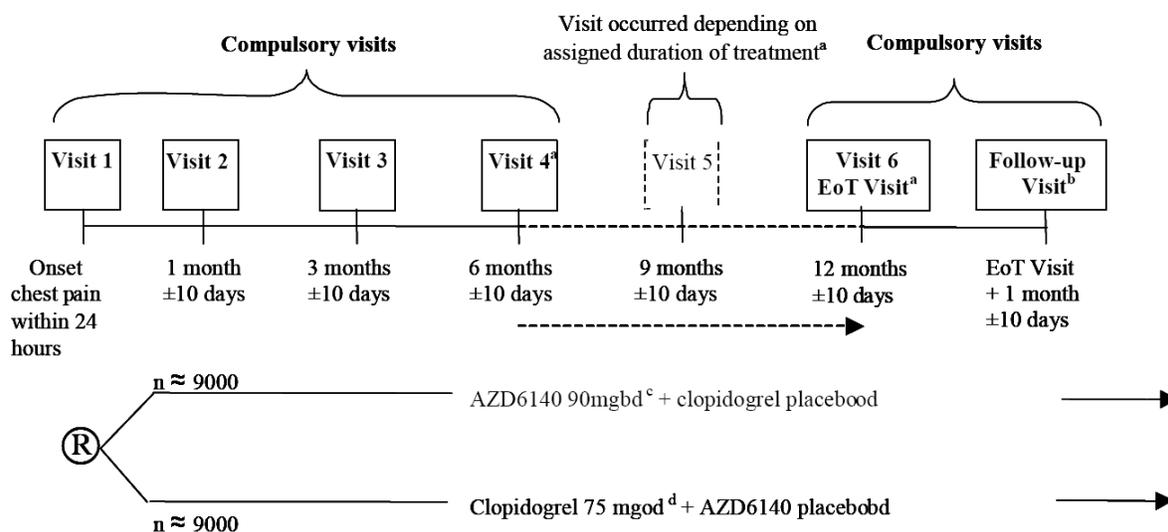
[a] The EoT visit when all measurements were performed could have been Visit 4 (6 months), Visit 5 (9 months), or Visit 6 (12 months), depending on when a patient was randomized; the last patients to enter the study had a minimum treatment duration of 6 months with a 30 day follow up visit.

[b] Patients who discontinued study drug prematurely and permanently had a Follow-up visit 1 month after the last dose of study drug and were then followed according to the visit schedule.

[c] A first (loading) dose of 180 mg ticagrelor was given. An additional 90 mg ticagrelor was given prior to any PCI if the intervention took place >24 hours after randomization. A 180 mg ticagrelor loading dose was administered if study drug therapy was interrupted for >5 days for patients treated in-hospital for an ACS event.

[d] A first (loading) dose of 300 mg clopidogrel was given unless the patient had already received clopidogrel prior to randomization. An additional loading dose of 300 mg clopidogrel was allowed, at the discretion of the investigator, if the patient had PCI later, regardless of the timing in relation to randomization.

ACS=Acute coronary syndromes; bd=Twice daily dosing; EoT=End of Treatment; od=Once daily dosing; PCI=Percutaneous coronary intervention; R=Randomization.
Source: Sponsor, PLATO protocol 10 April 2006, page 32

5.3.1.5   Study Population

5.3.1.5.1 Inclusion Criteria

For inclusion in the study patients had to fulfill all of the following criteria:

1. Index event of non-ST or ST segment elevation ACS. The patient was hospitalized for chest pain and potential ACS and the onset of the most recent cardiac ischemic symptoms of the index event had to occur within the 24 hours before randomization and

had to be documented by cardiac ischemic symptoms[1] of ≥10 minutes duration at rest[2] and:

a. Persistent ST segment elevation[3] ≥1mm (0.1 mV) in 2 or more contiguous leads and primary PCI planned, *OR,*

b. New or presumed new left bundle branch block (LBBB) and primary PCI planned, *OR,*

c. Cardiac ischemic symptoms[1] of ≥10 minutes duration at rest[2] (started spontaneously or with exercise but did not resolve with rest) and at least 2 of the following criteria:

    i. ST segment changes on ECG indicative of ischemia:
    Either
    ST segment depression[4] ≥1mm (0.1mV) in 2 or more contiguous leads
    or
    Transient ST segment elevation[5] ≥1 mm (0.1 mV) in 2 or more contiguous leads

    ii. Positive biomarker evidence of myocardial necrosis:
    Either
    Troponin T or I greater than the laboratory upper normal limit6 on at least 1 occasion in association with the index clinical event (i.e., any elevated troponin level)
    or
    Myocardial fraction of creatine kinase (CK-MB), preferably CK-MB mass, greater than the laboratory upper normal limit on at least 1 occasion in association with the index clinical event

    iii. Having at least 1 of the following risk factors:
        1. Aged 60 or over
        2. Previous MI or CABG
        3. Known multi-vessel coronary artery disease (CAD) (50% or more stenosis in 2 or more vessels)

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1 Cardiac ischemic symptoms: chest pain or discomfort or equivalent (eg, neck or jaw symptoms, dyspnea believed to represent an angina pectoris equivalent) believed due to impaired coronary flow secondary to atherosclerotic disease. If symptoms are found not to be due to atherosclerosis related myocardial ischemia before randomization then the patient should not be randomized (eg, pericarditis, myocarditis, normal coronary arteries by angiography).

2 At rest: started spontaneously or with exercise but did not resolve with rest.

3 ST segment elevation not known to be pre-existing or due to a co-existing disorder (eg acute pericarditis). Transient ST segment elevation <20 minutes is considered non-ST elevation ACS and persistent elevation is considered ST elevation ACS.

4 ST segment depression: Transient or persistent ST segment depression which is not known to be pre-existing nor is as a result of a co-existing disorder (eg, left ventricular hypertrophy) or medication (eg, digoxin).

5 ST segment elevation not known to be pre-existing or due to a co-existing disorder (eg acute pericarditis). Transient ST segment elevation <20 minutes is considered non-ST elevation ACS and persistent elevation is considered ST elevation ACS. Also see definitions of terms following the inclusion criteria below.

6 Laboratory upper normal limit: this is the value that is considered abnormal. For institutions that report an intermediate or indeterminate range for troponin I or T, these values are considered abnormal for this study.

    4. Previous ischemic stroke, TIA (hospital based diagnosis), carotid stenosis (50% or more) or cerebral revascularization
    5. Diabetes mellitus
    6. Peripheral arterial disease (intermittent claudication with prior objective confirmation, previous revascularization or ankle-brachial index less than 0.9)
    7. Chronic renal dysfunction (creatinine clearance [CrCL] calculated by Cockcroft-Gault equation is less than 60 mL/min).

2. Provision of signed ICF
3. Male or female aged at least 18 years
4. Females of child-bearing potential (i.e., females who were not chemically or surgically sterilized or females who were not post-menopause) must have had a negative urine or blood pregnancy test at enrolment and had been willing to use 2 methods of reliable contraception, 1 of which must have been a barrier method.

5.3.1.5.2 Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Contraindication or other reason that clopidogrel or ticagrelor was not to be administered (e.g., hypersensitivity, active bleeding, moderate or severe liver disease, history of previous intracranial bleed, gastrointestinal (GI) bleed within the past 6 months, major surgery within 30 days)
2. Index event was an acute complication of PCI
3. Patient had undergone PCI after the index event and before the first dose of study drug
4. Oral anticoagulation therapy that could not be stopped (i.e., patient requires chronic therapy)
5. Fibrinolytic therapy in the 24 hours prior to randomization, or planned fibrinolytic treatment following randomization (e.g., for STEMI or pulmonary embolus)
6. Increased risk of bradycardic events (e.g., no pacemaker and known sick sinus syndrome, second or third degree atrioventricular (AV) block or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker). The DSMB reviewed the Holter data in this study to assess the need to continue with this exclusion.
7. Patient required dialysis
8. Known clinically important thrombocytopenia
9. Known clinically important anemia
10. Participation in another investigational drug or device study in the last 30 days
11. Pregnancy or lactation
12. Concomitant oral or iv therapy (see examples below) with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers which could not be stopped for the course of the study
    a. Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir, over 1 liter daily of grapefruit juice.
    b. Substrates with narrow therapeutic index: cyclosporine, quinidine.

     c.   Strong inducers: rifampin/rifampicin, phenytoin, carbamazepine.

13. Any other condition which in the opinion of the investigator, may either put the patient at risk or influence the result of the study (e.g., cardiogenic shock or severe hemodynamic instability, active cancer, risk for non-compliance, risk for being lost to follow up)

14. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site)

15. Previous enrolment or randomization of treatment in the present study.

Generally, clinical exclusions represent contraindications to dual-antiplatelet therapy under current clinical management paradigms or to properties of ticagrelor.

Amendment 2 (dated 24 October 2006) modified exclusion criteria numbers 6, 8 and 9 shortly after the start of the study.

Criterion number 6 was changed to add the statement "unless treated with a pacemaker" so that patients who were at increased risk for bradycardic events were not excluded if they already had a pacemaker inserted.

The exclusion criteria 8 and 9 regarding platelet count and hemoglobin concentration were changed to exclude patients with known clinically important thrombocytopenia or anemia instead of excluding patients who had laboratory values of platelet count less than 100×10^9/L and hemoglobin (Hb) level less than 100 g/L. Sponsor stated that the purpose of this amendment was to allow inclusion of patients in PLATO without delaying indicated invasive therapy or otherwise compromising patient safety because.

5.3.1.6   Study Treatments

Study treatment was initiated within 24 hours of the index event since patients are at highest risk of recurrent events soon after the index event and therefore treatment guidelines recommend early onset of therapy.

At Visit 1 (randomization) eligible patients were randomly assigned to 1 of 2 treatment groups, ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, taken orally.

Randomization and treatment pack assignment was managed via a central Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) and subjects took the first dose of study medication directly after randomization at Visit 1. Patients took subsequent maintenance doses in the morning and evening, at approximately 12-hour intervals, for the remainder of the treatment period.

All patients in the ticagrelor arm received a loading dose of ticagrelor study medication (2 tablets of either 90 mg or matching placebo).

Table 3. Study treatment dosing

Study drug	Loading dose at randomisation	Maintenance dose	Loading dose for PCI <24 hours post randomisation	Loading dose for PCI >24 hours post randomisation
Ticagrelor blinded study medication	180 mg	90 mg bd	None	An additional 90 mg
Clopidogrel blinded study medication	300 mg for clopidogrel-naïve patients; 75 mg for patients who received open-label clopidogrel treatment prior to randomisation.	75 mg od	An additional 300 mg at the discretion of the investigator	An additional 300 mg at the discretion of the investigator

bd Twice daily dosing; od Once daily dosing; PCI Percutaneous coronary intervention.

Source: Sponsor, Clinical Study Report, page 36

Patients randomized to ticagrelor received an initial 180 mg loading dose, with an additional 90 mg in case of a PCI procedure if greater than 24 hours had elapsed since the loading dose at randomization. The proposed rationale for this loading dose was to ensure that they were protected during times when a high degree of platelet inhibition (IPA) was required, such as during PCI. Sponsor believed that pharmacodynamic data indicated that a 180 mg dose of ticagrelor would provide sufficient IPA and would be maintained for up to 24 hours. At any time beyond this first 24 hr an additional single 90 mg loading dose added to the 90 mg bd maintenance dose.

Therefore, investigators should have given subjects undergoing PCI during the treatment period an additional loading dose of 90 mg ticagrelor blinded study medication (active or placebo) if the intervention took place >24 h after randomization. At their discretion, investigators may also have given such patients an additional loading dose of 300 mg clopidogrel blinded study medication (active or placebo), irrespective of the timing in relation to randomization.

The clopidogrel group (control) received 75 mg clopidogrel daily and a 300 mg initial loading dose if previously not treated with clopidogrel. In addition, concomitant ASA (75 mg to 100 mg od) was given at the discretion of the investigator.

It should be noted that a Phase I AstraZeneca study (Study D5130C00020) indicated that clopidogrel tablets that were halved and over-encapsulated were bioequivalent to the original tablets based on PK properties. The percentage inhibition of platelet aggregation demonstrated for over-encapsulated clopidogrel was unaffected by the over-encapsulation process.

That being said, it would have been possible to unblind the study drug by opening the overencapsulated clopidogrel tablet, since the clopidogrel placebo capsule would have been empty.

Also, it had been shown in DISPERSE that IPA with 50 mg bd ticagrelor appeared equivalent to that with 75 mg daily clopidogrel.

Finally, during development, the mannitol-based 100 mg tablets showed a 17% higher area under the concentration-time curve than the lactose-based 100 mg tablets; therefore, a new mannitol-based IR tablet strength of 90 mg (used in DISPERSE2) was produced.

5.3.1.7   Concomitant Medications

The protocol prohibited or restricted oral anticoagulants, additional oral antiplatelet therapies, and fibrinolytic therapy pre-study and during the study due to increased risk of bleeding when administered simultaneously with dual antiplatelet therapy. If administration of a fibrinolytic agent was required, protocol stated that treatment with study medication should be temporarily stopped. Study medication could be re-started at least 24 hours after administration of the fibrinolytic agent. Approved parenteral anticoagulants and glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonists were allowed during the study.

CYP3A metabolizes ticagrelor and the active metabolite, AR-C124910XX. Therefore, treatment with strong CYP3A inhibitors, strong CYP3A inducers, and substrates of CYP3A that have a narrow therapeutic index was not allowed during treatment with study drug. If the subject required treatment with such therapies, the investigator should have interrupted study medication dosing and then resumed dosing if possible when administration of the inhibitor or inducer was no longer required. Moderate CYP3A inhibitors and inducers were allowed during the study.

In healthy volunteer studies, ticagrelor was found to increase simvastatin levels an average of approximately 50% with maximum individual increases of about 2- to 3 fold, and increase atorvastatin levels an average of approximately 35%. Simvastatin has recommended restrictions for concomitant therapy with inhibitors of CYP3A, due to increased reporting of myopathy; therefore, study medication and concomitant simvastatin or lovastatin at doses higher than 40mg was avoided. There were no restrictions for other statin therapies because they are not metabolized by CYP3A (pravastatin, rosuvastatin, fluvastatin) or have restrictions for concomitant use with mild or moderate inhibitors of CYP3A (atorvastatin).

5.3.1.8   Concomitant Aspirin

Investigators administered both ticagrelor and clopidogrel against a background of ASA therapy, unless contraindicated, because ASA is part of the standard therapy for prevention of CV events. The clinical study protocol specified a once daily ASA dose of 75 to 100 mg since previous clinical studies indicated this as a suitable daily dose range for ASA in combination therapy to protect against CV events.

For patients not previously taking ASA, the CSP allowed a first loading dose of 160 mg to 500 mg ASA (maximum loading dose of 325 mg preferred, however the CSP allowed 500 mg ASA where this was standard practice). Following stenting, the CSP allowed the use of 325 mg of

ASA for up to 6 months for bare metal or drug eluting stents according to American College of Cardiology (ACC)/American Heart Association (AHA) guidelines at the Investigator's discretion.

5.3.1.9 Discontinued Subjects

At their discretion, investigators could discontinue patients from study drug and assessments at any time. Patients were free to discontinue participation in the study at any time, without prejudice to further treatment. Once randomized into the study, investigators assessed patients until study closure (in accordance with intention-to-treat [ITT] principals) unless the patient withdrew informed consent for study participation (defined as permanent premature withdrawal from study).

For patients who discontinued study drug (temporary discontinuation or premature permanent discontinuation of study drug) the investigator noted whether they were assessed after study medication was stopped, and patients were asked about their reason(s) for discontinuation and about the presence of any AEs. If possible, they were seen and assessed by an investigator. The investigator followed AEs until the follow-up visit, End of Treatment plus 30 days, and the patient returned any investigational products and study materials.

5.3.1.10 Interruption of Medication

If a subject's treatment was interrupted for more than 5 days and if the subject was treated in hospital for an ACS, study drug was restarted, according to the randomization schedule, 180 mg ticagrelor or 300 mg clopidogrel. At their discretion investigators may have given patients a corresponding loading dose of 300 mg clopidogrel blinded study medication. Patients were not to make up missed doses of ticagrelor or clopidogrel blinded study medication (i.e., if a patient missed a dose, the patient should have taken the next regularly scheduled dose, which should not have been doubled). If a patient could not take oral medication then study drug should have been interrupted until oral therapy could be resumed.

At each study visit, the investigator assessed the patient's compliance and recorded it in the eCRF. If the patient reported taking more than 80% of the expected doses of study medication between each visit the investigator regarded the patient as compliant.

5.3.1.11 Adjudication of Clinical Endpoints

An Independent Central Adjudication Committee (ICAC), independent of the sponsor and investigators, adjudicated and evaluated all clinical primary and secondary efficacy events as described in the ICAC Charter. The investigator collected these events in the eCRF and identified the events using standard questioning of the patient at each visit or from information that the investigator received as part of standard medical practice. All cases adjudicated as CV death were evaluated to determine whether an MI was the cause of death.

Clinical MIs and periprocedural MIs detected by biomarkers were included in the primary variable, as adjudicated by the ICAC. Due to absence of symptoms, the date of occurrence of silent MIs detected by ECG usually cannot be determined. For these reasons, the primary efficacy variable time to event analysis does not include silent MIs. However, silent MIs are included in a secondary composite endpoint using date of ECG as date of occurrence, and are presented separately. In addition, a sensitivity analysis of the primary efficacy variable includes silent MI.

The ICAC documented all final adjudication decisions, which were entered in the study database. Analyses were based on events confirmed by the adjudication committee; unconfirmed reports of suspected events by investigators were not counted.

Nine clinical coordinators provided an initial assessment and processed the endpoints. Endpoints then went to pairs of physician adjudicators (from among a global team of 51), who received training on the review and adjudication process. Any disagreement between reviewers went to a senior ICAC committee. Several adjudicators could have adjudicated certain endpoint events. For example, a stroke could be adjudicated by a pair of ICAC adjudicators, and, separately, by the ICAC bleeding group, and the ICAC stroke group.

Quality assurance or blinded medical review of ICAC adjudicated events was performed on 5.4% (586) of randomly-selected clinical endpoint events. This was in keeping with the ICAC Charter, which recommended quality assurance of 5% of randomly-selected clinical endpoint events.

The ICAC adjudicated bleeding events according to the PLATO definitions. The analyses show bleeding events categorized using PLATO definitions. Another analysis algorithmically reassigned these events to TIMI-defined bleeding categories. Bleeding events were not adjudicated a second time using TIMI bleeding definitions.

The ICAC evaluated the clinical study data of every patient who underwent CABG during the study to adjudicate for a possible bleeding event, whether or not the investigator designated an event. The ICAC also evaluated all bleeding events designated by investigators as 'Major' or 'Minor', as described in the ICAC Charter. ICAC reviewed the information provided by Investigators and applied consistent criteria to categorize each event as 1 of the following: 'Major Fatal/Life-threatening', 'Major Other', 'Minor' and 'Minimal'. Non-CABG bleeding events reported by investigators as 'Minimal' were not adjudicated by ICAC, and were combined for analysis with events adjudicated by ICAC to be 'Minimal'. ICAC determined that some events reported by Investigators did not qualify as bleeding events. On occasion, ICAC identified additional events and directed the sponsor to query a site to register the events for official adjudication. If the Investigator agreed, the event was registered and processed by ICAC.

5.3.1.12 Protocol Changes

Several amendments and additional changes to the protocol affected study design. The key amendments are summarized below:

Amendment 1 changed the ticagrelor dose to 90 mg twice daily and added a loading dose of an additional 90 mg at randomization and prior to PCI. This amendment also included some other procedural changes (see Section 5.8.1 for further details). This amendment was implemented prior to the start of the study (on 13 July 2006, first patient enrolled on 11 October 2006) so all patients followed the same dosing regimen.

Amendment 2 included some additional changes to and clarification of the study procedures, including changes to exclusion criterion 2, as shown in Section 5.8.1. This amendment was implemented after the start of the study (on 24 October 2006, first patient enrolled on 11 October 2006). The amendment was made primarily to clarify study conduct and did not fundamentally alter the study design.

Amendment 3 added the Pulmonary Function Substudy to the protocol, clarified some aspects of the study conduct and added stent thrombosis as an exploratory endpoint. This amendment was implemented after the start of the study (on 19 December 2007; first patient enrolled on 11 October 2006).

5.3.1.13 Primary Efficacy Objective

The primary efficacy variable was the time to first occurrence of any event from the composite of CV death, MI, and stroke. The primary analysis compared the time from randomization to the first occurrence of any event in the composite endpoint using the Cox proportional hazards model with a factor for treatment group.

Hypothesis testing was at the nominal significance level of 4.97% (2-tailed) in order to account for the planned interim analysis. The end-of-trial (EoT) Visit, withdrawal of consent, or last contact with the patient was treated as censoring events.

The primary analysis was performed on the full analysis set: All patients who have been randomized to study treatment were to be included irrespective of their protocol adherence and continued participation in the study.

In order to address the issue of multiplicity, a prespecified hierarchical test sequence was performed. Once the null hypothesis concerning the primary composite efficacy endpoint is rejected, the secondary composite efficacy endpoints will be tested separately in the order given below:

1. The time to first occurrence of any event from the composite of death from vascular causes, MI and stroke for the subgroup of patients with intent for invasive management at randomization (planned coronary angiography with revascularization if indicated during the index event hospitalization)

2. The time to first occurrence of any event from the composite of all-cause mortality, MI and stroke

3. The time to first occurrence of any event from the composite of death from vascular causes, MI (including silent MI by ECG), stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA and other arterial thrombotic events

4. The time to first occurrence of each component of the primary composite efficacy endpoint individually in the order of MI, death from vascular causes and stroke

5. The time to occurrence of all-cause mortality

Statistical hypothesis testing was continued until the first statistically non-significant treatment difference was observed.

The confirmatory analysis also included a formal interim analysis of the primary composite efficacy endpoint after approximately 1200 events (2/3rds of the total target number of 1780 events) had been observed. Multiplicity between the interim and final analyses was controlled using Peto-Haybittle group sequential boundaries corresponding to critical p-values of 0.001 and 0.0497, respectively. The overall significance level was preserved at 5%.

5.3.1.14 Primary Safety Objective

An analysis of the time from first dose of study medication to each of the following endpoints was performed:
*   Total, non-CABG, non-procedure-related, coronary procedure-related and non-coronary procedure-related major bleeding events
*   Total, non-CABG, non-procedure-related, coronary procedure-related and non-coronary procedure-related minor bleeding events
*   Combined major and minor bleeding events for each of the categories.

The treatment groups were to be compared using the Cox proportional hazards model with a factor for treatment group. The secondary safety endpoints are the combined major and minor bleeding events across different categories as well as different categories of major and minor bleeding events separately. Exploration of potential risk factors for bleeding events, including subgroups and use of concomitant antithrombotic therapy, were performed.

MedDRA was used for the coding and classification of AEs and SAEs in the database. AEs were summarized by system organ class and preferred term using MedDRA. Summaries were presented by treatment group using descriptive statistics. Specific more detailed analyses of dyspnea and bradycardia events were performed. All AEs relating to bleeding summarized separately.

Transfusions of blood products and safety laboratory parameters will be compared between the 2 treatment groups using descriptive statistics for the actual and change from baseline values, where appropriate. Descriptive analyses of the bleeding events related to CABG and other procedures will be performed including the effect of timing of interruption of study medication.

5.3.1.15 Other Objectives

CABG surgery and PCI
The relationship between treatment, CABG/PCI and the primary efficacy and safety endpoints were investigated using models appropriate for bivariate outcomes.

Holter monitoring
The incidence of Holter detected episodes of ventricular pauses ≥ 3 seconds was to be compared between groups using 95% confidence intervals for both the initial and 1 month recordings. All other Holter variables were to be summarized descriptively. Assessments of the relationships of episodes between the two Holters and between Holter episodes and clinical events also were to be made.

Pharmacokinetics
Descriptive analysis of the plasma concentration data of AZD6140 and its active metabolite AR-C124910XX were performed. Population PK parameters for AZD6140 and its active metabolite AR-C124910XX were derived to investigate the pharmacokinetics of AZD6140 and its active metabolite AR-C124910XX; to evaluate covariate effects on the PK parameters; and to evaluate the relationship between exposure (concentrations or PK parameters of AZD6140 and AR-C124910XX) and safety and efficacy responses. A separate population PK analysis plan detailed methods for these analyses.

Health Economics
In addition to the descriptive analyses as part of the main protocol secondary health economic analyses were to be carried out based on a separate health economic analyses plan combining the resource use and clinical study data with country specific unit and/or episode based cost data.

5.3.1.16 PLATO Study Schedule

Table 4. Study Schedule

Assessment	Visit 1 Enrol-ment	Visit 1 Random-isation	Visit 1 Dis-charge	Visit 2 1 month ±10 d	Visit 3 3 m ±10d	Visit 4 6 m ±10d	Visit 5 9 m ±10 d	Visit 6 End of Treatment (EoT) Visit 12 months ±10d	Follow-up Visit EoT Visit + 1 month ±10d
Signed informed consent	✓								
Signed informed consent for genetic research (in 9000 patients where applicable)	✓								
Inclusion & exclusion	✓								
Relevant medical & surgical history, smoking history, family history of cardiac disease	✓								
Demography	✓								
Vital signs, physical examination, Killip class (V1 only), weight, height (V1 only)	✓							✓	
Access IVRS/IWRS	✓		✓	✓	✓	✓	✓		
EQ-5D, NYHA (V6 only)			✓			✓		✓	
Myocardial necrosis biomarkers[a] (Local lab)	✓[a]								
12-lead ECG[b]	✓		✓[c]	✓				✓	
Holter ECG monitoring & diary[d]		✓		✓					
Clinical chemistry & haematology		✓		✓[e]	✓[e]	✓[e]		✓[e]	✓[e]
Blood core substudy[f]		✓	✓[c]	✓		✓			
Urine and/or blood pregnancy test	✓					✓[g]		✓[g]	
Myocardial necrosis biomarkers (Central lab)		✓[h]							
PK blood sample[i]			✓[c]	✓					
Dispense investigational product		✓	✓	✓	✓	✓	✓		
Return investigational product				✓	✓	✓	✓	✓	
Compliance/ drug accountability			✓	✓	✓	✓	✓	✓	
Medications	✓[j]	✓[j]	✓[j]	✓[j]	✓[j]	✓[j]	✓[j]	✓[j]	✓[j]
AEs, SAEs & endpoints	✓	✓	✓	✓	✓	✓	✓	✓	✓
Post-study antiplatelet therapy								✓	✓

a. Myocardial necrosis biomarkers measured for index event (local laboratory) and any subsequent suspected ACS or coronary revascularization procedure.
b. For eligibility ECG, for silent MI.
c. Discharge or 4 days post-enrolment, whichever is sooner.
d. In 2500 patients Holter monitoring should continue for up to 7 days. The Holter monitoring should be repeated for the same patients at Visit 2.
e. Clinical chemistry and hematology samples for all patients at Visit 1 and repeat measurements at Visit 2, Visit 4, Visit 6 and Follow-up Visit until DSMB indicates that this testing is no longer required.
f. Blood core substudy samples for all patients at Visit 1 (randomization) and then repeat measurements in 4000 patients at Visit 1 (discharge/day 4), Visit 2 and Visit 4.
g. For females of child bearing potential a urine pregnancy test should be repeated every 6 months.
h. Troponin I.
i. PK sample first 9000 patients only.
j. All medications will be recorded from 7 days prior to enrolment to hospital discharge and peri-event for any suspected endpoints, SAEs, discontinuations for AE or AZD6140 dose changes. Current medications will be recorded at visits 2, 4, End of treatment and Follow up.
Source: Sponsor, Study Protocol dated 10 April 2006, page 33-34.

6 Review of Efficacy

6.1 Indication

The sponsor has proposed the following Indications and Usage statement in the draft label:

> *BRILINTA is a selective and reversible P2Y12 ADP-receptor antagonist indicated to:*
>
> *Reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be:*
> * *managed medically*
> * *managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG.*
>
> *BRILINTA as compared to clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes.*
>
> *BRILINTA as compared to clopidogrel has also been shown separately to reduce the rate of:*
> * *CV death*
> * *MI*

6.1.1 Methods

The phase 3 pivotal study supporting the efficacy of ticagrelor was entitled, PLATO, a randomized, double-blind, parallel group, efficacy and safety study of ticagrelor compared with clopidogrel for prevention of vascular events in patients with non-ST or ST elevation acute coronary syndromes (ACS)

The design of this study was discussed in detail in Section 5.3.

6.1.2 Demographics

Table 5 presents key demographic data in PLATO, excluding cases for which information is not available or is unknown.

Table 5. PLATO: Baseline Demographics and Characteristics

Characteristic	Statistic / Category	Ticagrelor 90mg bid N = 9333	Clopidogrel 75mg qD N = 9291
Age (years)	Mean	62.1	62.3
	Median	62.0	62.0
Age Group	≥ 65 Years	4022 (43.1%)	3957 (42.6%)
	≥ 75 Years	1396 (15.0%)	1482 (16.0%)
Sex	Male	6678 (71.6%)	6658 (71.7%)
	Female	2655 (28.4%)	2633 (28.3%)
Race (self-reported)	Caucasian	8566 (91.8%)	8511 (91.6%)
	Black	115 (1.2%)	114 (1.2%)
	Oriental	542 (5.8%)	554 (6.0%)
	Other	109 (1.2%)	112 (1.2%)
	Unknown	1 (0.0%)	0 (0.0%)
Weight (kg)	Mean	80.6	80.3
	Median	80.0	80.0
Weight Group	≥ 60 kg	8653 (92.7%)	8603 (92.6%)
	≥ 80 kg	4788 (51.3%)	4725 (50.9%)
Gender-specific median weight group	Male ≥ 82kg; Female ≥ 71kg	4806 (51.5%)	4761 (51.2%)
Waist Circumference(cm)	Mean	98.5	98.6
	Median	98.0	98.0
BMI (kg/m2)	Mean	27.9	27.8
	Median	27.4	27.3
	≥ 30 kg/m^2	2650 (28.4%)	2528 (27.2%)
Troponin I	Positive	7525 (80.6%)	7564 (81.4%)
	Negative	1525 (16.3%)	1443 (15.5%)
	Unknown	283 (3.0%)	284 (3.1%)
Smoking Status	Non-smoker	3592 (38.5%)	3664 (39.5%)
	Ex-smoker	2373 (25.4%)	2303 (24.8%)
	Habitual smoker	3360 (36.0%)	3318 (35.7%)
Proton Pump Inhibitor at Rand.	No	6133 (65.7%)	6116 (65.8%)
	Yes	3200 (34.3%)	3175 (34.2%)

Source: Reproduced from sponsor, Clinical Study Report, p. 790,Table 11.1.3.1.1

Table 6 presents relevant medical history of the PLATO study population. Characteristics are generally as expected for the ACS study population and appear to be well-balanced between treatment groups.

Table 6. PLATO: Relevant Past Medical History

Past Medical History	Ticagrelor 90 mg bid N = 9333	Clopidogrel 75 mg qD N = 9291
Angina Pectoris	4220 (45.2%)	4138 (44.5%)
Myocardial Infarction	1900 (20.4%)	1924 (20.7%)
Coronary Artery Disease	2565 (27.5%)	2561 (27.6%)
Percutaneous Coronary Intervention (PCI)	1272 (13.6%)	1220 (13.1%)
Coronary Artery Bypass (CABG)	532 (5.7%)	574 (6.2%)
Transient Ischemic Attack (TIA)	246 (2.6%)	253 (2.7%)
Non-hemorrhagic Stroke	353 (3.8%)	369 (4.0%)
Carotid Stenosis (≥50%)	166 (1.8%)	210 (2.3%)
Percutaneous Cerebrovascular Revascularization	12 (0.1%)	34 (0.4%)
Surgical Cerebrovascular Revascularization	45 (0.5%)	52 (0.6%)
Peripheral Arterial Disease	566 (6.1%)	578 (6.2%)
Hypertension	6139 (65.8%)	6044 (65.1%)
Dyslipidemia Including Hypercholesterolemia	4347 (46.6%)	4342 (46.7%)
Diabetes Mellitus	2326 (24.9%)	2336 (25.1%)
Type 1	110 (1.2%)	99 (1.1%)
Type 2	2215 (23.7%)	2236 (24.1%)
Family History of Coronary Heart Disease	3028 (32.4%)	2921 (31.4%)
Congestive Heart Failure	513 (5.5%)	537 (5.8%)
Permanent Pacemaker	81 (0.9%)	75 (0.8%)
Gastrointestinal Bleeding	136 (1.5%)	129 (1.4%)
Asthma	267 (2.9%)	265 (2.9%)
Chronic Obstructive Pulmonary Disease	555 (5.9%)	530 (5.7%)
Chronic Renal Disease	379 (4.1%)	406 (4.4%)

Source: Reproduced from sponsor, Clinical Study Report, page 2585, Table 11.1.3.8.1

Table 7 presents medications taken prior to randomization with ≥ 5% prevalence in either group. The medications taken tend to reflect the baseline disease burden of the population as presented in prior tables.

Table 7. PLATO: Medication Taken Prior to Randomization

	Ticagrelor 90 mg bid N = 9333	Clopidogrel 75 mg qD N = 9291
Patients with at least one medication	6912 (74.1%)	6872 (74.0%)
BETA BLOCKING AGENTS SELECTIVE	3415 (36.6%)	3355 (36.1%)
HMG COA REDUCTASE INHIBITORS	3296 (35.3%)	3305 (35.6%)
ORGANIC NITRATES	3008 (32.2%)	2941 (31.7%)
ACE INHIBITORS PLAIN	2862 (30.7%)	2824 (30.4%)
PROTON PUMP INHIBITORS	1306 (14.0%)	1285 (13.8%)
DIHYDROPYRIDINE DERIVATIVES	1149 (12.3%)	1245 (13.4%)
SULFONAMIDES PLAIN	967 (10.4%)	996 (10.7%)
BENZODIAZEPINE DERIVATIVES	916 (9.8%)	901 (9.7%)
BIGUANIDES	789 (8.5%)	778 (8.4%)
SULFONAMIDES UREA DERIVATIVES	712 (7.6%)	687 (7.4%)
ANGIOTENSIN II ANTAGONISTS PLAIN	610 (6.5%)	600 (6.5%)
NATURAL OPIUM ALKALOIDS	496 (5.3%)	485 (5.2%)
INSULINS AND ANALOGUES FOR INJECTION FAST ACTING	489 (5.2%)	492 (5.3%)

Source: Reproduced from sponsor, CSR p. 2612, Table 11.1.4.1.1

6.1.3 Subject Disposition

In total, 18,758 patients enrolled into the study from 43 countries worldwide. The first patient enrolled on October 11, 2006 and the last patient completed the study on February 27, 2009.

6.1.4 Study Close-Out and Censoring

PLATO was an event driven study in which the sponsor projected at what point the study would end based on fulfillment of endpoint events. Based on the projections of number of events in the database, the Executive Committee terminated study enrollment on July 18, 2008. This was the date of the last patient randomized. Consequently, because every patient needed to participate for at least a minimum of 6 months, per DSMB recommendation, the study could not end before January 18, 2009.

Sponsor stated the following (communication dated April 12, 2010):

> "In July 2008, it was realized that with about 14,000 patients in-study, all needing both an End of Treatment [EoT] visit and a 30-day follow-up visit, an orderly completion process for the remaining patients was required. It wasn't realistic to bring all patients in simultaneously (especially near the holiday season). Likewise, because ACS patients need to be individually counseled about whether to transition to open-label clopidogrel before stopping study drug, patients had to finish the trial with an actual visit while they

were still on therapy. As patients approached the end of study, we used their regularly scheduled visits to make this transition."

In effect, patients were phased out uniformly over a 3-month period starting on October 18, 2008. After this date, subjects were to go to their next scheduled visit, which would then become their End of Treatment visit.

However, it would also be possible for a subject to become lost to follow-up or to miss their rescheduled End of Treatment visit as described above. In these situations, the question arises of when one should censor the subjects (because a subject could present with an outcome event at any time, even before they are determined to have been LTFU). A third possible scenario occurs when an investigator did not treat the next scheduled visit after October 18, 2008 as the de facto End of Treatment visit and the subject received additional treatment beyond the scheduled EoT period.

These three scenarios can summarized as below:

Scenario #1. Completers.
Those subjects who made it to their last scheduled visit (End of Treatment) and were censored on that date. After PLATO was fully enrolled (18 July 2008), patients were phased out of the study over a 3-month period starting 18 October 2008 as the patients completed their 6-, 9- or 12-month end-of-treatment visits.

Scenario #2: Projected by randomization date.
Patients who discontinued the study early, but did not withdraw consent, were censored 30 days after the date when their End of Treatment visit should have occurred. This visit was projected as follows:
- For patients randomized prior to 18 January 2008, the End of Treatment visit was the randomization date + 12 months
- For patients randomized between 19 January 2008 and 18 April 2008, the End of Treatment visit was the randomization date + 9 months
- For patients randomized between 19 April 2008 and 18 July 2008, the End of Treatment visit was the randomization date + 6 months.

Scenario #3: Projected by last dispense date
If a patient's recommended End of Treatment visit was at 6 or 9 months after randomization, but a 90-day supply of study drug was dispensed by the site at that visit (for unclear reason); and if the patient did not return for the anticipated subsequent End of Treatment visit; then the patient was censored for efficacy events 90 days after the date that drug was last dispensed. This censoring rule programmed to include any event that occurred within 90 days after any dispense.

Hence, censoring rules were adopted that allowed events to be counted when discovered following the last patient contact. For example, deaths could be discovered during vital status checks, which would be submitted for adjudication, and investigation of deaths could lead to discovery of MI and strokes. Also, additional events that had occurred during the treatment period could be reported later, during a 30-day post treatment visit.

Finally, patients were censored when they withdrew consent.

Sponsor has tabulated the number of subjects in the ITT population that fall into each of the above categories (see Table 8).

Table 8. Number of subjects in each category

Subject Category	Ticagrelor	Clopidogrel	Total
Completers	6863	6731	13594
Projected by randomisation date	722	713	1435
Projected by last dispense date	1078	1118	2196[a]
Withdrawal of consent	273	231	504
Death	397	498	895

[a] The 2196 patients projected by dispense date includes any patients who completed their regular final visit less than 90 days after their previous dispense visit.

Source: Sponsor. Communication dated 12-Apr-2010

A plot of the cumulative censor events over time (Figure 2) illustrates the 6, 9 and 12 month study windows. Also noticeable are the censor event "upticks" (in green circles) that occur at the end of the expected study window closure. Presumably this represents those subjects who are being censored at their projected end of treatment visit date rather than actual EoT visit (category #2) above. Censor events in category #3, would be dispersed throughout the study period and would not be clustered at any particular timepoint.

Figure 2. PLATO censor distribution

Censor Distribution
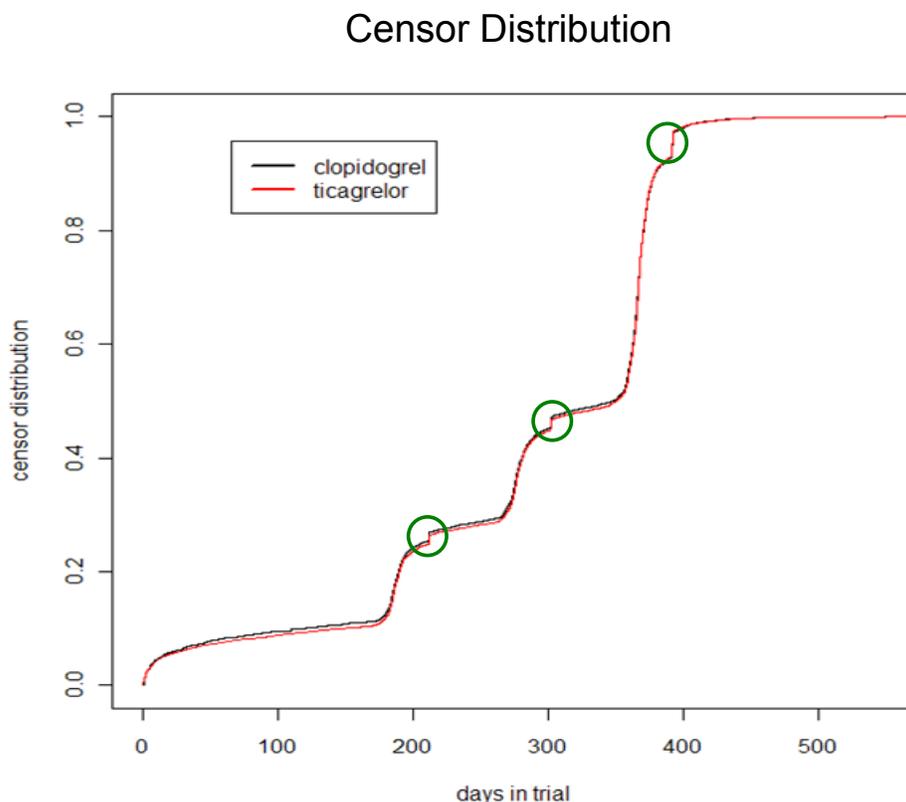
Source: **Jialu Zhang, Statistician**

Refer to **Section 8.3** for an analysis of potential bias this censoring approach had on study outcome (considered unlikely).

6.1.5 Screening Failures

The target patient population in the PLATO study was patients who had experienced an ACS event within the previous 24 hours.

There were 862 global sites that participated in the study. Complete screening logs were retrieved for 680 sites and statements or notes to file were received from 92 additional sites explaining why logs were not kept. In addition, some countries provided an overview of their specific process or explanation regarding why screening logs were not kept in their respective countries.

The following is a summary of the major issues regarding the inclusion of patients for the PLATO trial as documented on the screening logs retrieved.

- A lack of documented evidence of ACS. Many patients presented with possible cardiac ischemic symptoms but had negative enzymes and/or lack of ECG changes indicative of non-ST or ST segment elevation ACS and therefore did not meet entry criteria.
- The 24-hour enrolment timeframe was exceeded. ACS patients were often presented at another hospital and then were transferred to the research hospital.
- Due to the seriousness of the medical condition and the short time frame for consideration of study participation, many subjects did not agree to be consented for the investigational study.
- Exclusionary medications administered prior to randomization. Some high-risk patients received fibrinolytic therapy if timely PCI was not available. Per the inclusion criteria, the patient must be off of fibrinolytic therapy for 24 hours.

6.1.6 Randomized Subjects

Post the enrollment (consent) period, patients had to be randomized prior to any intervention, with the exception of coronary angiography. If the angiography was performed prior to randomization, study procedures had to be completed prior to the intervention (PCI).

The time constraint while transferring a STEMI patient from the emergency room or ambulance to the catheterization laboratory, including information to the patient about the upcoming emergency coronary intervention, many times preclude study personnel from enrolling a patient prior to the procedure, which was a requirement in PLATO.

Nevertheless, according to the sponsor, many hospitals managed to recruit STEMI patients because of a more flexible way of working, which may be reflected by the varying numbers of STEMI patients randomized between countries.

The PLATO study randomized almost all enrolled patients (99.3%). "No index event of non-ST or ST elevation ACS" (14.9% of patients enrolled but not randomized) was the primary reason for not randomizing patients.

A total of 18,758 patients enrolled (informed consent received) in the study and 134 (0.7%) of these patients were not randomized, and excluded from the full analysis set, as shown in Table 9.

Table 9. Reasons Subjects Not Randomized (All Countries)

ALL COUNTRIES	N (%)
Subjects Enrolled (Informed consent received)	18,758
Subjects Randomized	18,624 (99.3%)
Subjects Not Randomized	**134 (0.7%)**
No index event of non-ST or ST segment elevation ACS	20 (14.9%)
No signed informed consent form	2 (1.5%)
Age not at least 18 years	1 (0.7%)
Contraindication	11 (8.2%)
PCI after index event and before first dose	2 (1.5%)
Oral anticoagulation therapy	1 (0.7%)
Increased risk of bradycardic events	1 (0.7%)
Other condition	12 (9.0%)
Previous enrolment or randomization	2 (1.5%)
Reason Missing	82 (61.2%)

Source: Reproduced from Sponsor, CSR page 420, Table 11.1.1.1

The U.S. had the highest number of subjects who were enrolled but not randomized (n=48). Reasons for subjects in the U.S. population not being randomized are provided in Table 10.

Table 10. Reason Subjects Not Randomized (U.S.)

United States	N (%)
Subjects Enrolled (Informed consent received)	1,461
Subjects Randomized	1,413 (96.7%)
Subjects Not Randomized	48 (3.3%)
No index event of non-ST or ST segment elevation ACS	9 (18.8%)
No signed informed consent form	1 (2.1%)
Contraindication	7 (14.6%)
PCI after index event and before first dose	2 (4.2%)
Oral anticoagulation therapy	1 (2.1%)
Increased risk of bradycardic events	1 (2.1%)
Other condition	9 (18.8%)
Reason Missing	18 (37.5%)

Source: Reproduced from Sponsor, CSR page 420, Table 11.1.1.1

In the PLATO study, most of the patients not randomized to the study were excluded during the screening process (pre-consent) as evidenced by the low rate of enrolled but not randomized patients (134 patients out of 18,624).

6.1.7 Received Treatments

The full analysis set included all patients who signed informed consent and were randomized to study treatment, irrespective of their protocol adherence and continued adherence to the study.

The safety analysis set included all patients who signed informed consent and took ≥1 dose of study drug, as shown in Figure 3. Safety analyses assigned patients to treatment group according to study drug actually received.

Figure 3. Patient disposition on study drug
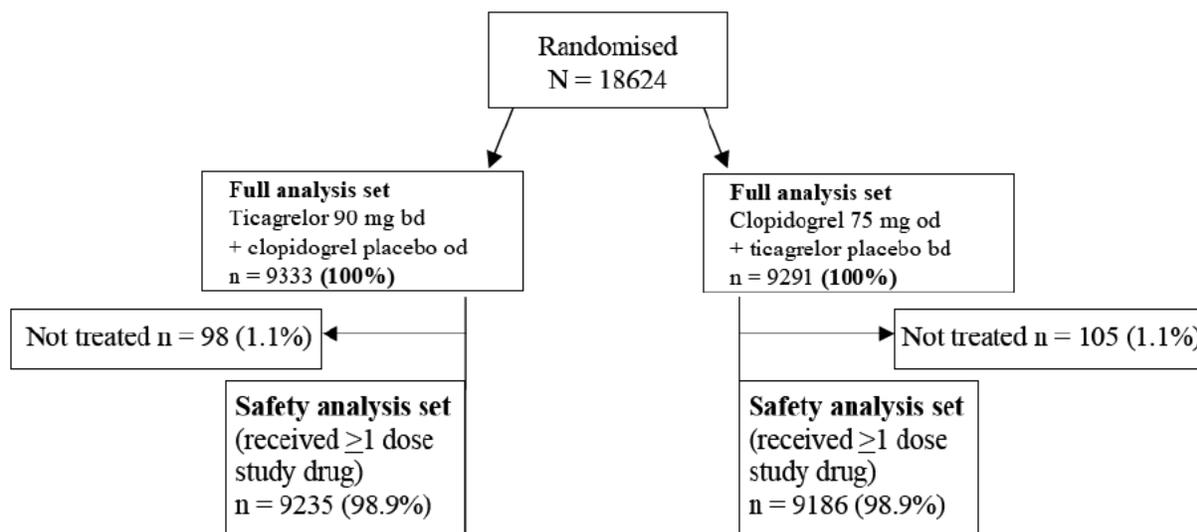
Source: Sponsor, Clinical Study Report, page 96, Figure. 7

In PLATO, the overall mean exposure to study drug was 248 days, with a median exposure of 277 days. Table 11 presents the exposure to investigational product over time.

Table 11. Exposure to Investigational Product (FULL)

Exposure (Days)	Ticagrelor N = 9,333	Clopidogrel N = 9,291	TOTAL N = 18,624
None	98 (1.1%)	105 (1.1%)	203 (1.1%)
>0	9235 (98.9%)	9186 (98.9%)	18421 (98.9%)
>30	7985 (85.6%)	8006 (86.2%)	15991 (85.9%)
>90	7470 (80.0%)	7547 (81.2%)	15017 (80.6%)
>180	6762 (72.5%)	6915 (74.4%)	13677 (73.4%)
>270	5082 (54.5%)	5159 (55.5%)	10241 (55.0%)
>360	3138 (33.6%)	3184 (34.3%)	6322 (33.9%)

Source: Sponsor, Clinical Study Report, Page 3448, Table 11.3.1.1

6.1.8 Discontinued Subjects

Of the 562 patients who prematurely withdrew participation in the study (307 ticagrelor and 255 clopidogrel), nearly half of patients in each treatment group terminated the study within the first 24 hours (n=147 ticagrelor and n=120 clopidogrel patients). An additional 99 patients (62 ticagrelor and 37 clopidogrel) terminated participation by Visit 2 (1 month ±10 days) and an additional 64 patients (36 ticagrelor and 28 clopidogrel) terminated participation by Visit 3 (3 months ± 10 days). The remainder terminated participation at other Visits.

Table 12. Time to Permanent Premature Withdrawal from Study

	Ticagrelor 90mg bid	Clopidogrel 75 mg qD	Total
Number of Patients	307	255	562
Visit 1 (enrolment within 24 hours)	147 (47.9%)	120 (47.1%)	267 (47.5%)
Visit 2 (1 month ± 10 days)	62 (20.2%)	37 (14.5%)	99 (17.6%)
Visit 3 (3 months ± 10 days)	36 (11.7%)	28 (11.0%)	64 (11.4%)
Visit 4 (6 months ±10 days)	12 (3.9%)	18 (7.1%)	30 (5.3%)
Visit 5 (9 months ± 10 days)	8 (2.6%)	7 (2.7%)	15 (2.7%)
Visit 6 (12 months ± 10 days)	3 (1.0%)	5 (2.0%)	8 (1.4%)
Follow-up (+1 month ±10 days)	39 (12.7%)	40 (15.7%)	79 (14.1%)

Source: Sponsor, Clinical Study Report, p. 616, Table 11.1.1.5.1

Table 13 presents the sponsor's analysis of discontinued subjects, however the very low rates of "lost to follow-up" appear due to the assessment of vital status in subjects who did not make their final study visits. This is further discussed in Section 6.1.11 (and Table 15).

Table 13. Discontinued Subjects, Full Analysis Set

	Ticagrelor	Clopidogrel
Consented and randomized (n)	9333	9291
Premature withdrawal from the study	307 (3.3%)	255 (2.7%)
Incorrectly randomized	7 (0.1%)[a]	2 (0.0%)[a]
Patient withdrew informed consent	296 (3.2%)	249 (2.7%)
Reason unknown	2 (0.0%)	4 (0.0%)
Lost to follow-up at end of study period	2 (0.0%)[b]	0 (0.0%)[b]

[a] Incorrectly randomized: These patients were permanently prematurely withdrawn from the study at the discretion of the investigator because they were found not to meet inclusion and/or exclusion criteria.
[b] Per the termination module of the CRFs completed by sites, study termination due to lost to follow-up is noted for 2 ticagrelor patients.
Source: Reproduced from sponsor, Clinical Study Report, page 90, Fig. 5

If patient withdrew consent before the planned end of the study, efficacy events would be counted towards efficacy only if they occurred prior to withdrawal of consent. Any *deaths* discovered by vital-status contact up to the last scheduled visit date are counted in the "all known deaths" analysis. However, if they follow withdrawal of consent they are not adjudicated and are not included in the efficacy analysis. There is no post-study observational period (PSOP) visit as the patient has not consented to make additional visits.

From the PLATO datasets provided by the sponsor, this reviewer (R. Fiorentino) identified subjects who were noted to have the following events:

1. Subjects defined within the Full Analysis dataset, *and*
2. Subjects that did not have a primary outcome event, *and*
3. Were documented to have Prematurely Discontinued from the Study (variable TMSTFL in ADEMOG.xpt), *and*
4. Had a main reason for premature discontinuation from study (variable TMSTREA) as 'Subject withdrawal of Informed Consent' or 'Subject lost to follow-up at end of study period (up to 12 months after randomization)' (ADEMOG.xpt), *and*
5. Had cardiac or neurological adverse events labeled under SOC variable (CARD or NERV)

Of 253 subjects identified by this method, approximately 33 subjects were subjectively reviewed to identify potential events that may have been missed as adjudicated primary events. 11 subjects in ticagrelor and 19 in clopidogrel arm.

A number of the adverse events reviewed did not have incident CRFs provided and no additional adjudication was possible (CRFs were not provided for all AEs). The majority of events that did have CRFs did not suggest that a primary event may have occurred due to the nature of the AE.

Table 14. Subjects that Discontinued Treatment of Study Drug: Safety Analysis

	Ticagrelor	Clopidogrel
Received ≥ 1 dose study drug (n)	9235	9186
Premature permanent discontinuation of study drug[a]	2186 (23.7%)	1999 (21.8%)
Adverse event	690 (7.5%)	556 (6.1%)
Inclusion/exclusion criteria not met [b]	22 (0.2%)	16 (0.2%)
Patient not willing to continue treatment [c]	946 (10.2%)	859 (9.4%)
Severe non-compliance to protocol	41 (0.4%)	47 (0.5%)
Other	479 (5.2%)	518 (5.6%)
Reason unknown	4 (0.0%)	1 (0.0%)

[a] Patients with premature permanent discontinuation of study drug continued to have assessment visits every 3 months up to the end of study to record endpoint events and SAEs, and completed the study, with the exception of the lost to follow-up patients
[b] Patients stayed on study treatment if the investigator decided there was a need for dual antiplatelet therapy
[c] Includes patients who withdrew informed consent.
bd = twice daily dosing; CRFs = case report forms; od = once daily dosing; SAEs = serious adverse events
Source: Reproduced from Sponsor, Clinical Study Report, page 96, Fig. 7

When contrasting Table 13 and Table 14, it should be noted that a subject could have discontinued study drug, but not actually withdraw from study.

6.1.9 Lost to follow-up

Prior to database lock, lost to follow-up status was captured in the CRF modules in three different ways during the PLATO study:

1. **Study termination CRF module (TERM).** Investigators attributed a reason for premature *discontinuation of study*. Subject lost to follow-up was an option in the main reasons for premature discontinuation of study. Lost to follow-up status (not returning for a scheduled visit) reflects the investigator's knowledge of the patient at the time the form was completed.

   Two patients in the ticagrelor group did not complete the study and did not prematurely withdraw from the study (per the study termination CRF page). These 2 patients failed to return for required study visits and vital status remained unknown at the time the form was completed. These 2 patients were recorded by the investigator as "subject lost to follow-up" on the study termination CRF page.

2. **Investigational products CRF module (DOS).** Investigators attributed a reason for premature *permanent discontinuation of study drug* in the CRF modules. Subject lost to follow-up was an option in the main reasons for premature permanent discontinuation of study drug. Lost to follow-up status (not returning for a scheduled visit) reflects the investigator's knowledge of the patient at the time the form was completed.

Six patients (4 in the ticagrelor group and 2 in the clopidogrel group) did prematurely permanently discontinue study drug (per the withdrawal of investigational products CRF module), but did not concurrently withdraw from the study. These 6 patients also failed to return for required study visits and vital status remained unknown at the time the form was completed. These 6 patients were recorded by the investigator as "subject lost to follow-up" on the withdrawal of investigational products CRF page.

3. **Final status CRF module (CONTACT).** This form was completed if a patient *refused to attend a clinical visit and whether the patient had withdrawn consent or not.* This information can be sought because vital status is a matter of public record. Investigators recorded the patient's final status as alive, dead or unknown. The patient's status was recorded as "unknown" if there was no contact or source of information for a patient. Inclusion in the 'last contact' was done at any time after a patient completed the study. This is somewhat different from other studies, where the trial closed on a certain date, at which 'last contact' applied to all patients.

   Contact attempts included telephone contact, primary physician contact and medical record searches. The status for 2 patients in the ticagrelor group and 3 patients in the clopidogrel group was unknown per the final status (CONTACT) CRF module.

Post database lock lost to follow-up patients

Following the last patient out of the study and database lock, attempts were made to contact patients whose vital status at the end of the study period was unknown. In total 5 patients could not be contacted, 3 in the ticagrelor group (E1019005, E1704019 and E2714012) and 2 in the clopidogrel group (E1002004 and E2410013).

6.1.10 Excluded From Analysis

The primary efficacy analysis population was the ITT population as defined in previous sections.

40 subjects with enrollment codes (subject IDs) are excluded from this population in all analysis datasets, with 21 in the ticagrelor arm and 19 in the clopidogrel arm.

The main reasons for not being included in the ITT population were failure to obtain informed consent (4 subjects by this reviewer's count) and duplicate or erroneous enrollment code for an already enrolled subject (e.g., error for the remainder).

6.1.11 Completed Study

Of the randomized patients, the sponsor counts 18,062 subjects as having completed the study. Subjects were considered to have completed the study if they had a final visit, died, or were followed-up/alive (vital status collected when contacted, but patient did not continue participation in the study).

The proportion of patients who completed the study was similar between the treatment groups. Death was an endpoint in the study and therefore subjects who died completed the study.

Table 15 presents study completion rates by treatment arm according to the sponsor's analysis.

Table 15. Subject Disposition: Completed Study

	Ticagrelor 90mg bid N=9333	**Clopidogrel 75mg qD N = 9291**
Total completed Study	N= 9026	N=9036
Final visit	**7645 (81.9%)**	**7542 (81.2%)**
Death	414 (4.4%)	517 (5.6%)
Follow-up / Alive	967 (10.4%)	977 (10.5%)

Source: Sponsor, Figure 5, page 90 of Clinical Study Report

A separate analysis showed that 86% of ticagrelor and 87% of clopidogrel subjects had adequate clinical follow-up or died. Of those who had *inadequate* follow-up, 78% of ticagrelor and 79% of clopidogrel subjects had vital status assessments (not tabulated).

A sensitivity analysis of the impact that inadequate cardiovascular-event follow-up had on the study outcome is presented in Section 8.3. The results of this analysis were similar to the original analysis.

6.1.12 Protocol Deviations

Sponsor has defined "important" protocol deviations as the following:

- Failed Inc. Criteria - Evidence of ACS
- Failed Inc. Criteria - Age < 18 yrs.
- Failed Inc. Criteria - Consent form
- Failed any of the Exclusion Criteria
- Failed any of the Inclusion Criteria
- Randomized but not Treated
- MIs-Randomized at Visit 1
- Tablet Compliance Less Than 80%
- Capsule Compliance Less Than 80%
- Disallowed Medications

The "important" protocol deviations listed above that had non-zero events are presented in Table 16.

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Table 16. Subjects with "Important" Protocol Deviations – Full analysis dataset

Category	Ticagrelor 90 mg bid N=9,333	Clopidogrel 75 mg qd N=9,291	Total N=18,624
Total number of deviations	287	302	589
Patients with at least 1 deviation	286 (3.1%)	301 (3.2%)	587 (3.2%)
Failed any of the inclusion criteria	219 (2.3%)	228 (2.5%)	447 (2.4%)
Failed inclusion criteria - consent form	1 (0.0%)	1 (0.0%)	2 (0.0%)
Failed any of the exclusion criteria	67 (0.7%)	73 (0.8%)	140 (0.8%)

If a patient failed inclusion criteria, only the first reason was captured in the eCRF. Patients who failed inclusion criteria could also have had 1 or more deviation captured.
Source: Sponsor, CSR, p.106, Table 8.

6.1.4 Analysis of Primary Endpoint

The primary efficacy variable was the time to first occurrence of any event from the composite of death from vascular causes (CV death), MI and stroke.

Refer to Section 8.1 for detailed PLATO endpoints definitions.

As presented in Table 17, ticagrelor was superior in the prevention of thrombotic events (RRR 16%, absolute risk reduction [ARR] 1.9%) of the composite efficacy endpoint (CV death, MI, and stroke) over 12 months in patients with ACS events (UA, NSTEMI and STEMI) compared to clopidogrel (hazard ratio [HR] 0.84; p=0.0003).

Table 17. PLATO Primary Composite Endpoint and Component Endpoints

ENDPOINT	Ticagrelor 90 mg bd N = 9333		Clopidogrel 75 mg qd N = 9291			
	Patients with Events	KM %	Patients with Events	KM %	Hazard Ratio (95% CI)	p-value
PRIMARY: Composite of CV Death/MI (excl. silent MI) /Stroke	864 (9.3%)	9.8%	1014 (10.9%)	11.7%	0.84 (0.77, 0.92)	0.0003
MI (excl. silent MI)	504 (5.4%)	5.8%	593 (6.4%)	6.9%	0.84 (0.75, 0.95)	0.0045
CV Death	353 (3.8%)	4.0%	442 (4.8%)	5.1%	0.79 (0.69, 0.91)	0.0013
Stroke	125 (1.3%)	1.5%	106 (1.1%)	1.3%	1.17 (0.91, 1.52)	0.2249

Hazard ratio and p-value calculated from Cox proportional hazards model with study treatment as only explanatory variable. Kaplan-Meier percentage calculated at 12 months. For patients with multiple events the analysis uses the time to the earliest event: each patient is counted only once in each row.
* Percentages are calculated using different denominators for intent to invasively manage patients.
Source: Sponsor, CSR p. 3361, Table 11.2.1

The reduction in primary events was driven primarily by reductions in the rates of myocardial infarction and cardiovascular death. Strokes were numerically higher in the ticagrelor arm but did not reach statistical significance.

As illustrated in Figure 4, the Kaplan-Meier curves for ticagrelor and clopidogrel continue to diverge out to one year, suggesting the relative benefit of ticagrelor continues to accrue over time.

Figure 4. KM plot of primary clinical endpoint
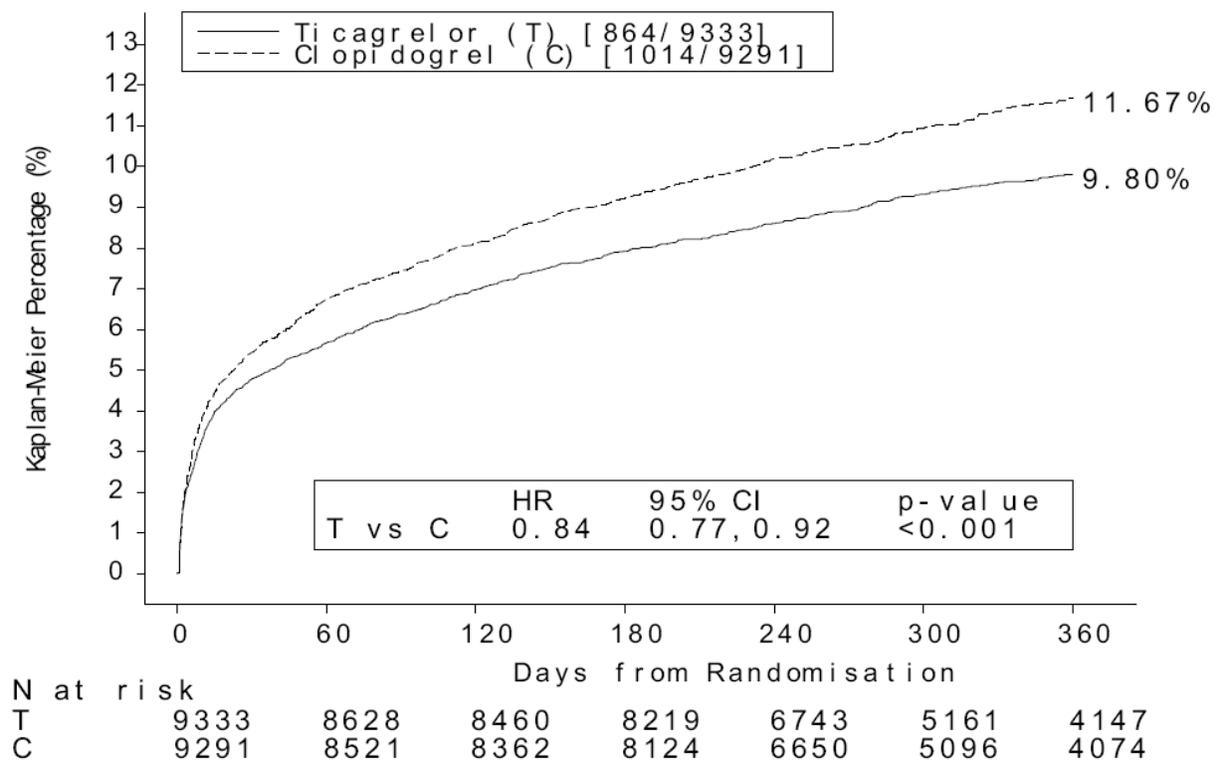
Source: Sponsor, CSR p. 3400, Figure 11.2.1

6.1.4.1 Primary Endpoint Landmark Analyses

A landmark analysis at 30 days demonstrated that approximately half of all primary events occurred before this timepoint and suggesting an early benefit to ticagrelor compared to clopidogrel. Table 18 shows that this difference trended towards statistical significance.

Table 18. 30-day Landmark Analysis: Primary Endpoint

Primary Endpoint	Time Interval	Ticagrelor 90 mg bd N=9333			Clopidogrel 75 mg od N=9291			Hazard Ratio (95% CI)	p-value
		n	Patients with Events	KM %	n	Patients with Events	KM %		
Composite of CV Death, MI (excl. silent MI), Stroke	1- 30 days	9333	443 (4.7%)	4.8%	9291	502 (5.4%)	5.4%	0.88 (0.77,1.00)	0.0446
	31-360 days	8763	413 (4.7%)	5.3%	8688	510 (5.9%)	6.6%	0.80 (0.70,0.91)	0.0008

Only patients who are event free in the first period (days 1-30) are included in the second period (days 31-360).
Source: Reproduced from sponsor, CSR p. 3374, Table 11.2.5

Figure 5 shows the early separation of the time to reach primary endpoint, occurring within the first few days following randomization.

Figure 5. Primary Endpoint KM Curve: 0 to 30 days
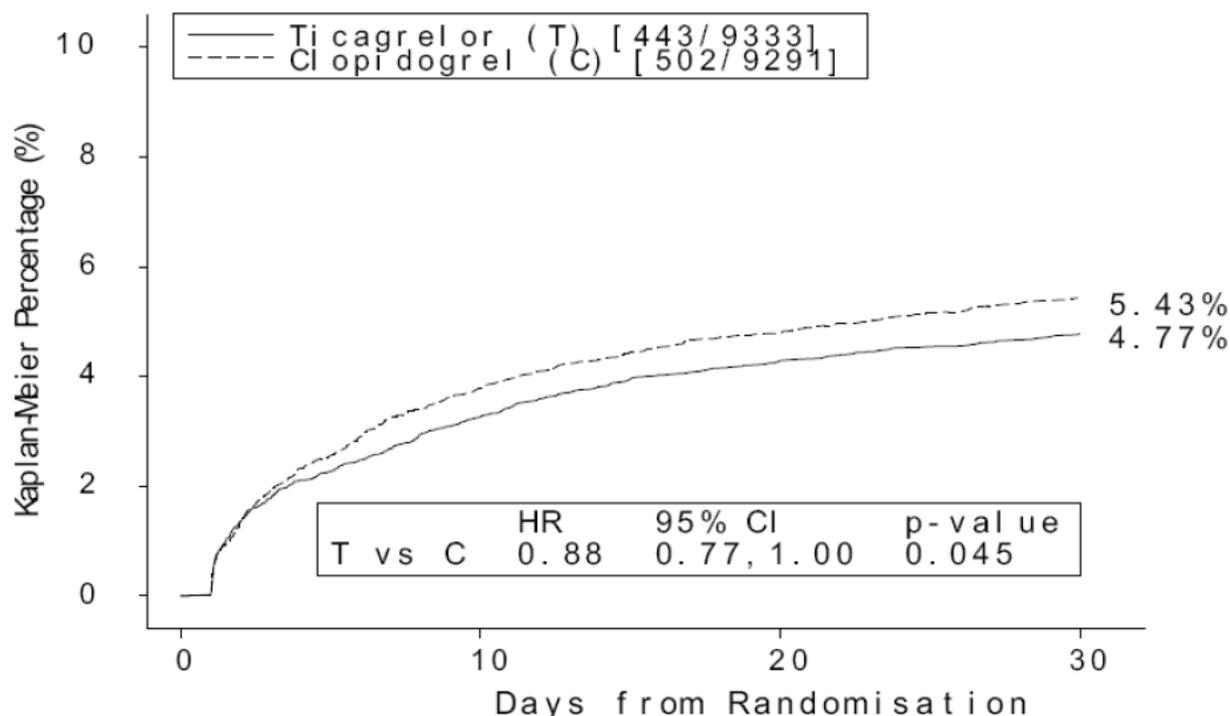
Source: Sponsor, CSR, p. 3421, Fig. 11.2.16

In those patients free of events and still in the trial during the first 30 days, the KM curves again continue to separate out to the remainder of follow-up, as shown in Figure 6.

Figure 6. Primary Endpoint KM Curve: 31 to 360 days
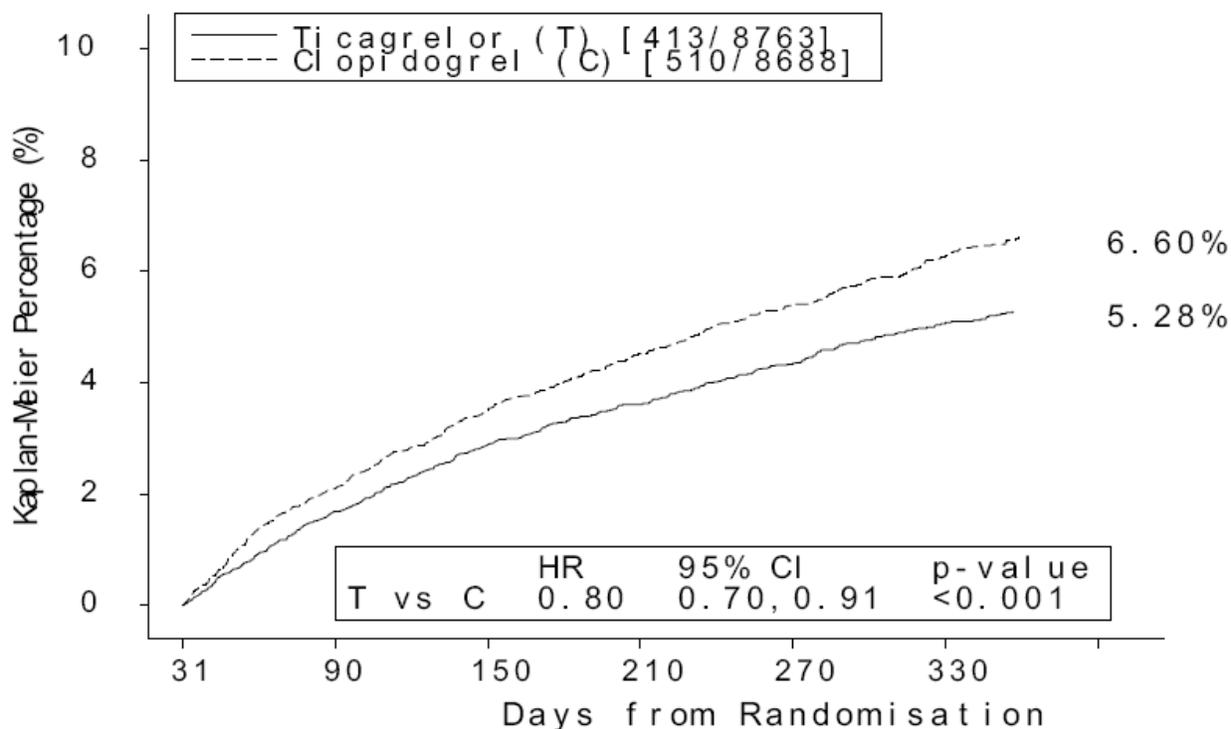
Source: Sponsor, CSR p. 3421, Fig. 11.2.16

6.1.4.2 Forest Plots: Primary Endpoint

Figure 7 provides the sponsor's forest plot of hazard ratios and event rates across multiple subgroups. Generally the HR plots tend to fall along the overall treatment difference reference line at 0.84. Some of the subgroups presented are discussed in later sections of this review, most notably the disparate outcomes across the four pre-specified geographic regions.

Figure 7. Hazard Ration and Rates of Primary Endpoint by Subgroup (forest plot)

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
Overall Treatment Effect					
Primary Endpoint		18624	9.8	11.7	0.84 (0.77, 0.92)
Age Group					
<65 Years		10643	7.2	8.5	0.85 (0.74, 0.97)
>=65 Years		7979	13.2	16.0	0.83 (0.74, 0.94)
<75 Years		15744	8.6	10.4	0.82 (0.74, 0.91)
>=75 Years		2878	16.8	18.3	0.94 (0.78, 1.12)
Sex					
Male		13336	9.2	11.1	0.85 (0.76, 0.95)
Female		5288	11.2	13.2	0.83 (0.71, 0.97)
Race					
Caucasian		17077	9.5	11.2	0.85 (0.77, 0.94)
Black		229	13.0	19.6	0.63 (0.32, 1.23)
Oriental		1096	12.5	14.8	0.87 (0.62, 1.21)
Other		221	14.4	21.4	0.63 (0.33, 1.21)
BMI Group					
<30 kg/m2		13354	10.1	11.9	0.86 (0.77, 0.95)
>=30 kg/m2		5178	8.9	10.8	0.83 (0.69, 0.99)
Median Weight (gender)					
males <82kg / females <71kg		9001	11.4	12.5	0.93 (0.82, 1.05)
males >=82kg / females >=71kg		9567	8.2	10.8	0.76 (0.67, 0.87)

0.5   1.0   2.0

Ticagrelor (Ti.) better   Clopidogrel (Cl.) better

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
Region					
Asia/Australia		1714	11.4	14.8	0.80 (0.61, 1.04)
Cent/Sth America		1237	15.2	17.9	0.86 (0.65, 1.13)
Euro./Mid E./Afr.		13859	8.8	11.0	0.80 (0.72, 0.90)
North America		1814	11.9	9.6	1.25 (0.93, 1.67)
Diabetes Mellitus					
No		13962	8.4	10.2	0.83 (0.74, 0.92)
Yes		4662	14.1	16.2	0.88 (0.76, 1.03)
Planned Treatment Approach					
Invasive		13408	8.9	10.6	0.84 (0.75, 0.94)
Medically managed		5216	12.0	14.3	0.85 (0.73, 1.00)
CYP3A Inhibitor (rand.)					
No		16717	9.7	11.6	0.84 (0.77, 0.93)
Yes		1907	10.4	12.1	0.85 (0.65, 1.12)
Glycoprotein IIb/IIIa (Index)					
No		13562	9.7	11.9	0.82 (0.74, 0.92)
Yes		5062	10.0	11.1	0.90 (0.76, 1.07)
ACE Inhibitor use (rand.)					
No		8102	9.4	10.6	0.90 (0.78, 1.03)
Yes		10522	10.1	12.5	0.81 (0.72, 0.91)
Final Diagnosis					
Unstable angina		3112	8.6	9.1	0.96 (0.75, 1.22)
NSTEMI		7955	11.4	13.9	0.83 (0.73, 0.94)
STEMI		7026	8.5	10.1	0.84 (0.72, 0.98)
Other		489	9.1	14.7	0.58 (0.34, 1.00)

0.5   1.0   2.0

Ticagrelor (Ti.) better   Clopidogrel (Cl.) better

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
Hx of PCI					
No		16132	9.1	11.2	0.82 (0.74, 0.90)
Yes		2492	14.1	14.6	0.98 (0.79, 1.22)
Hx of CABG					
No		17518	9.2	11.0	0.84 (0.77, 0.93)
Yes		1106	19.5	21.7	0.88 (0.67, 1.15)
Index Event to Study Med					
< 12 hours		9556	8.2	10.4	0.79 (0.69, 0.90)
>= 12 hours		8854	11.4	12.9	0.90 (0.79, 1.01)
NSTEMI TIMI Risk Score					
0-2		730	4.2	4.1	1.11 (0.53, 2.31)
3-4		5488	8.2	10.9	0.77 (0.64, 0.92)
5-7		4849	14.4	15.6	0.92 (0.79, 1.07)
STEMI TIMI Risk Score					
0-2		3889	4.7	6.2	0.76 (0.58, 1.01)
3-6		2884	12.6	13.7	0.91 (0.74, 1.12)
>6		253	19.6	30.1	0.62 (0.37, 1.06)
Weight Group					
<60 kg		1312	13.1	17.3	0.75 (0.56, 0.99)
>=60 kg		17256	9.5	11.2	0.86 (0.78, 0.94)
<80 kg		9055	11.4	12.8	0.90 (0.79, 1.01)
>=80 kg		9513	8.3	10.5	0.79 (0.69, 0.90)

0.5   1.0   2.0

← Ticagrelor (Ti.) better   Clopidogrel (Cl.) better →

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
Waist Circ.					
<100 cm		9627	9.6	11.1	0.88 (0.77, 1.00)
>=100 cm		7978	9.7	12.1	0.79 (0.69, 0.91)
Unknown		1019	12.6	13.4	0.95 (0.66, 1.35)
Lipid-Lowering use (rand.)					
No		3768	11.0	11.2	1.02 (0.83, 1.24)
Yes		14856	9.5	11.8	0.80 (0.73, 0.89)
Beta Blocker use (rand.)					
No		4564	9.0	11.6	0.79 (0.65, 0.95)
Yes		14060	10.1	11.7	0.86 (0.78, 0.96)
First Troponin I					
Positive		15089	10.3	12.3	0.85 (0.77, 0.94)
Negative		2968	7.0	7.0	1.00 (0.75, 1.32)
Antiplatelet Therapy					
None		12147	8.2	10.0	0.82 (0.73, 0.93)
Clopidogrel		289	18.7	17.1	1.26 (0.70, 2.28)
ASA		5024	11.8	14.0	0.84 (0.71, 0.98)
Clopidogrel+ASA		1108	15.0	18.0	0.88 (0.65, 1.19)
Other		56	24.4	13.9	1.93 (0.55, 6.85)

0.5   1.0   2.0

← Ticagrelor (Ti.) better   Clopidogrel (Cl.) better →

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
ASA at Rand.					
No		927	11.6	13.8	0.87 (0.60, 1.27)
Yes		17697	9.7	11.6	0.84 (0.77, 0.93)
Clopidogrel loading dose					
300 to 375 mg		7449	9.2	12.0	0.77 (0.65, 0.91)
600 to 675 mg		3104	7.2	9.1	0.79 (0.61, 1.03)
Other		2036	10.1	11.6	0.84 (0.63, 1.13)
Continuing on clopidogrel		1004	17.6	17.9	1.09 (0.80, 1.48)
No clopidogrel >75mg		5031	9.9	10.9	0.77 (0.41, 1.44)
Previous MI					
No		14800	8.6	10.2	0.85 (0.76, 0.94)
Yes		3824	14.6	17.4	0.84 (0.71, 0.99)

0.5   1.0   2.0

← Ticagrelor (Ti.) better   Clopidogrel (Cl.) better →

Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti.	KM % at Month 12 Cl.	HR (95% CI)
Heparin use					
No		6696	10.4	12.6	0.84 (0.73, 0.98)
Yes		11928	9.5	11.1	0.85 (0.75, 0.95)
Angiotensin II (rand.)					
No		16981	9.6	11.6	0.83 (0.76, 0.92)
Yes		1643	11.8	12.8	0.96 (0.72, 1.28)
Ca-Channel Blocker (rand.)					
No		15888	9.6	11.3	0.86 (0.78, 0.95)
Yes		2736	10.8	13.8	0.76 (0.61, 0.95)
Hx of TIA/Non-Haem. Stroke					
No		17462	9.2	11.1	0.84 (0.76, 0.93)
Yes		1152	19.0	20.8	0.87 (0.66, 1.13)
PPI use (rand.)					
No		12249	9.2	11.0	0.83 (0.74, 0.93)
Yes		6375	11.0	12.9	0.86 (0.75, 1.00)

0.5   1.0   2.0

← Ticagrelor (Ti.) better   Clopidogrel (Cl.) better →

Source: Sponsor, CSR, pp.3414-9, Fig. 11.2.15

6.1.4.3 Index ACS Event: STEMI, NSTEMI, and UA

Table 19 tabulates outcomes according to the index event of STEMI, NSTEMI, UA or "Other" as captured by the investigator on the CRF.

Table 19. Primary Endpoint by Index ACS Event

	N subjects	Clopidogrel # Events/n, (365 day KM%)	Ticagrelor # Events/n, (365 day KM%)	HR (95% CI)
STEMI	7,026	337/3530 (10.1%)	281/3496 (8.49%)	0.84 (0.72, 0.98)
NSTEMI	7,955	510/3950 (13.9%)	432/4005 (11.5%)	0.83 (0.73, 0.94)
UA	3,112	132/1563 (9.07%)	124/1549 (8.62%)	0.96 (0.75, 1.22)
Other*	489	32/230 (14.7%)	22/259 (9.08%)	0.59 (0.34, 1.02)

* As indicated on CRF (includes non-ACS terms, e.g., "CAD", "myocarditis", "pericarditis", PE, etc.)
Source: R. Fiorentino, Clinical Reviewer

Analysis by index event appears to suggest that the overall superiority of ticagrelor was driven primarily by the STEMI and NSTEMI subgroups, with only a small numerical difference in the UA subgroup. The hazard ratios in the STEMI and NSTEMI subgroups were comparable.

6.1.4.4 Planned Invasive Strategy vs. Medical Management

PLATO allowed for subjects to be either invasively (PCI) or medical managed at the discretion of the investigators. Since PCI occurred post-randomization in PLATO, the effectiveness of ticagrelor was assessed in the subgroup of patients with intent for invasive management at randomization.

Table 20 presents primary outcomes by planned strategy and treatment group. Although the medically managed subgroup has higher event rates in general, the treatment benefit was similar to the planned invasive groups.

**Table 20. Invasive Strategy vs. Medical Management**

Planned Strategy	# subjects	Clopidogrel # events/n (KM% 365d)	Ticagrelor # events/n (KM% 365d)	HR (95% CI)
Invasive Mgmt	13,408	668/6676 (10.7%)	569/6732 (9.02%)	0.84 (0.75, 0.94)
Medical Mgmt	5,216	346/2615 (14.3%)	295/2601 (12.1%)	0.85 (0.73, 1.00)

Source: R. Fiorentino, Clinical Reviewer

Figure 8 presents the Kaplan-Meier curves of each strategy by treatment group. Of note is the higher rate of rise in primary events for the Invasive group that diminishes after approximately 30 days, whereas the planned medical-management has a more prolonged curve.

Also notable in Figure 8 is a continued separation of curves out to one year, which is most pronounced in the planned medical-management subgroup.

Figure 8. KM Curve: Planned Invasive vs. Medical Management

Primary Endpoint
Planned Invasive vs. Medical Management
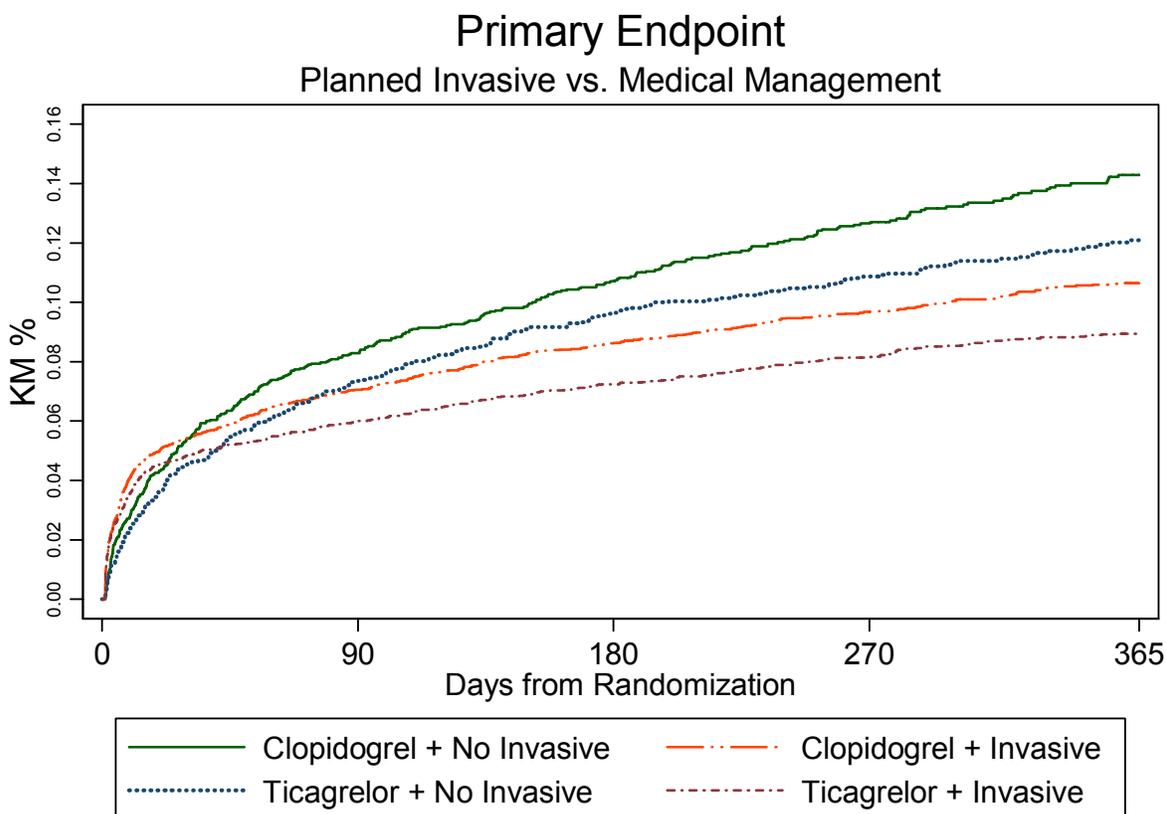
Source: R. Fiorentino, Clinical Reviewer

Finally, as presented in Table 21, an analysis of the primary outcome according to PCI subgroup showed a preserved treatment benefit regardless of early or any PCI subgroup.

Table 21. Primary Outcome by Actual Invasive Strategy (PCI subgroup)

	N	Clopidogrel events/n	Ticagrelor events/n	Cox HR (95%CI)
Early PCI*				
Yes	9,254	407/4625	349/4629	0.85 (0.74, 0.99)
No	9,364	607/4666	515/4698	0.84 (0.75, 0.94)
Any PCI (w/o prior event)				
Yes	11,855	545/5931	484/5924	0.89 (0.78, 1.00)
No	6,763	469/3360	380/3403	0.80 (0.70, 0.91)

*subjects that were intended to invasively manage, who had a PCI within the time period from 24 hours prior to randomization and 24 hours after randomization (36 hours if time of PCI not given and set to 12:00 by default) and who did not have a prior primary endpoint.
Source: R. Fiorentino, Clinical Reviewer

6.1.4.5 Planned Treatment Approach vs. Index ACS Event

In general, treatment benefit was similar among STEMI and NSTEMI subjects irrespective of planned treatment approach. Subjects with unstable angina had essentially equivocal benefit from ticagrelor across treatment approaches (Table 22).

Table 22. Primary Endpoint: Planned Treatment Approach at Randomization *vs.* Index ACS event

HR (95%CI) events / N	STEMI	NSTEMI	UA
Medical Mgmt	0.73 (0.46, 1.16) 75/451	0.85 (0.70, 1.02) 416/2910	0.97 (0.69, 1.37) 132/1726
Invasive Mgmt	0.86 (0.72, 1.01) 543/6575	0.82 (0.70, 0.97) 526/5045	0.95 (0.67, 1.35) 124/1386

HR from Cox prop. Haz model
Source: R. Fiorentino, Clinical Reviewer

6.1.4.6 Timing of PCI

An exploratory analysis examined the primary endpoint following PCI in a subset of patients with planned invasive management who actually received PCI within (±) 24 hours of randomization (early PCI).

According to this analysis, 9,254 subjects are documented to have had an early PCI in PLATO, representing approximately half of all subjects enrolled. The primary endpoint in those who had an early PCI was similar to the overall PLATO results, HR=0.85, 95%CI (0.74, 0.99). This

benefit was primarily driven by a reduction in MIs: Ticagrelor 4.7% vs. Clopidogrel 5.9% [HR=0.74, 95%CI (0.62, 0.89)].

Figure 9 presents the K-M curve for the primary endpoint in this subgroup. Almost half of the MIs occurred within only a few days of randomization and PCI.

Figure 9. Kaplan-Meier plot of primary clinical endpoint events for patients intended to have invasive management who received PCI within 24 hours
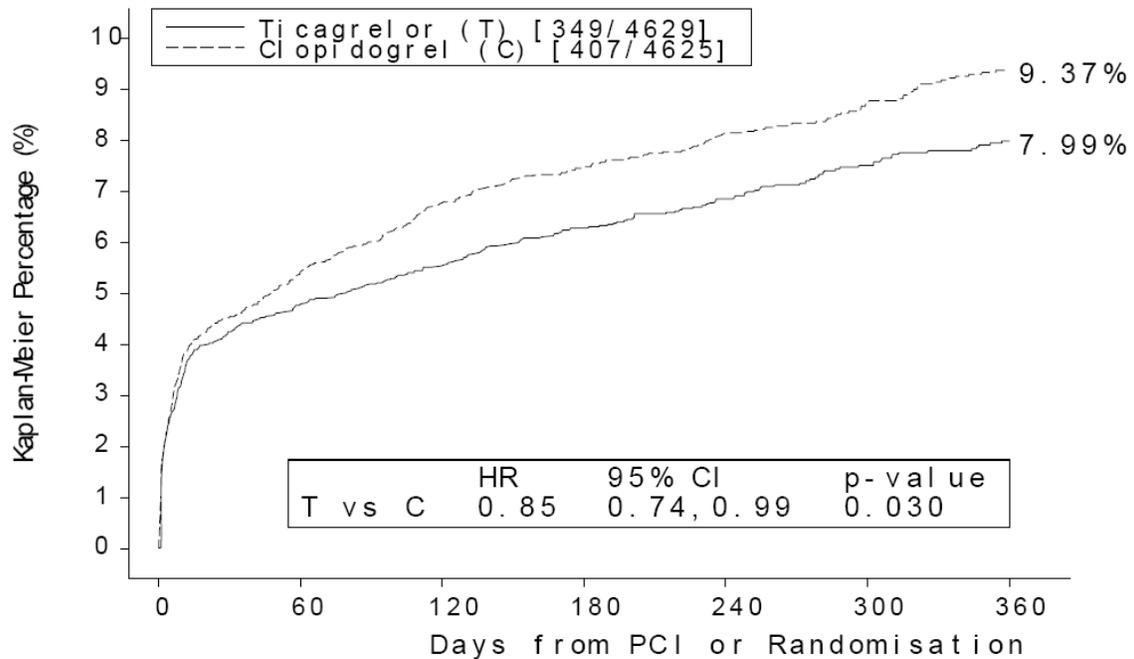

Source: Sponsor, CSR, p. 151, Fig. 15

Figure 10 and Figure 11 illustrate the frequency of primary events in the early PCI subgroup, with a large fraction of events occurring very early following randomization.

Figure 10. Early PCI: Time to Primary Event
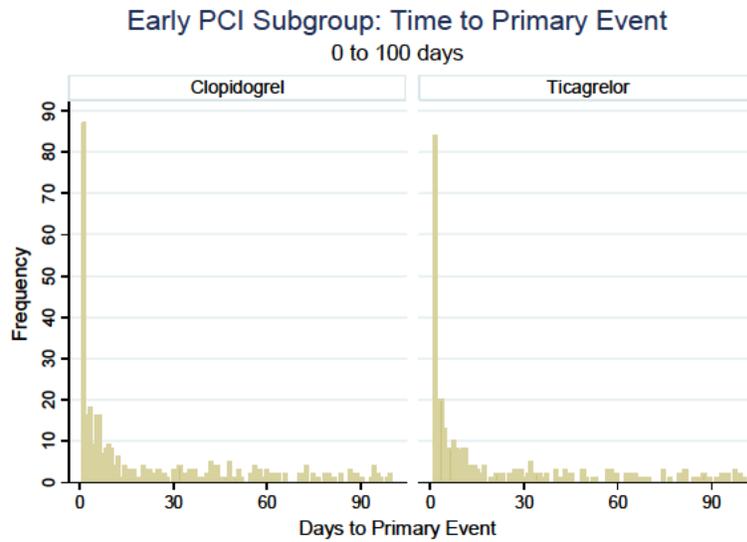
Source: R. Fiorentino, Clinical Reviewer

Figure 11. Early PCI: Time to Primary Event (first 24hrs)
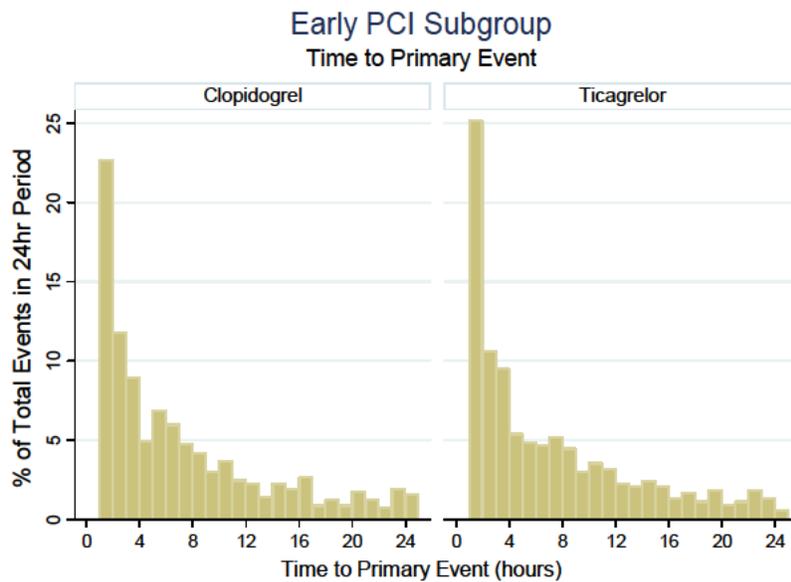
Source: R. Fiorentino, Clinical Reviewer

Time to 1st PCI

Because the type of index ACS event (STEMI, NSTEMI, UA) can determine the urgency of revascularization, an analysis of the time to PCI by index event was performed according to these subgroups.

Histograms plotting the time to 1st PCI were created on subjects who had either STEMI, NSTEMI or UA as the index event (Figure 12, Figure 13, Figure 14).

From these figures, it can be seen that STEMI subjects tended to undergo PCI early and frequently, as would be expected for a population with an indication for primary PCI. Both NSTEMI and UA also had an early spike of PCI but also showed delays in PCI procedures. The multimodal time course of PCIs in NSTEMI and UA subjects is notable in the figures; a clear explanation for this observation is not readily apparent.

Figure 12. STEMI Index Event: Time to 1st PCI
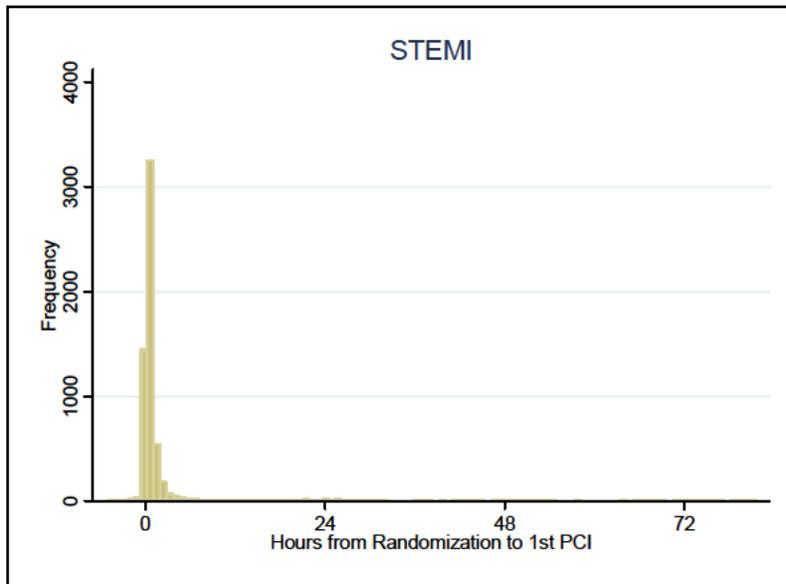
Source: R. Fiorentino, Clinical Reviewer

Figure 13. NSTEMI Index Event: Time to 1st PCI
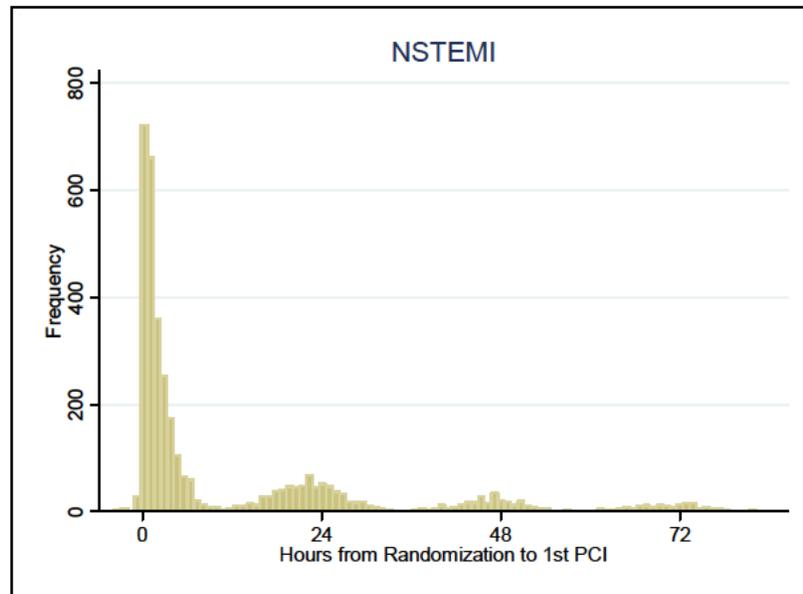
Source: R. Fiorentino, Clinical Reviewer

Figure 14. UA Index Event: Time to 1st PCI
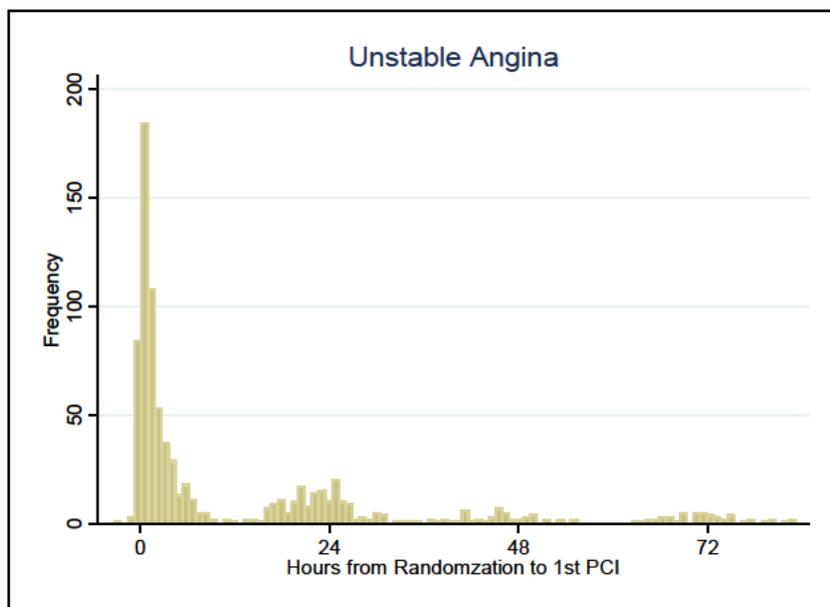
Source: R. Fiorentino, Clinical Reviewer

6.1.4.7 Primary Outcome by Renal Function (eGFR)

Table 23 presents the primary study outcome according to estimated GFR (Cockcroft-Gault) subgroups.

Table 23. Primary Outcome by eGFR

eGFR (C-G)	N	Ticagrelor # events/n (KM%*)	Clopidogrel # events/n (KM%*)	Haz. Ratio	95%CI
<15	16	6/8 (75%)	1/8 (20%)	12.0	1.38, 104
<30	262	39/119 (36%)	50/143 (40%)	0.97	0.64, 1.47
<60	3,847	308/1887 (18%)	390/1960 (22%)	0.80	0.69, 0.93
<90	11,558	650/5770 (12%)	757/5788 (14%)	0.86	0.77, 0.95

*365 day KM%
Source: R. Fiorentino, Clinical Reviewer

Overall, there were higher rates of primary outcome events in subjects with worsened renal failure. However the relatively small number of subjects with severe kidney disease (GFR<30) makes determination of an adverse trend in this group a challenge.

6.1.4.8 Primary Outcome by History of Hepatic Disorder

The demographic dataset contained a variable indicating a history of hepatic disorders (Standardized MedDRA term) derived from the baseline medical history query.

Table 24 presents a tabulation of the primary outcome according to documented history of hepatic disorders. Although limited by a small sample size, no apparent difference in outcome was observed in the subgroup of subjects with hepatic disorders as defined.

Table 24. Primary Outcome by History of Hepatic Disorder

History	Ticagrelor # events/n (KM%*)	Clopidogrel # events/n (KM%*)	Haz. Ratio (95%CI)
Hepatic Disorder	17/197 (9.2%)	24/218 (11.5%)	0.79 (0.42, 1.47)
No hepatic disorder	847/9136 (9.9%)	990/9073 (11.7%)	0.85 (0.77, 0.93)

*365 day KM%
Source: R. Fiorentino, Clinical Reviewer

6.1.5 Analysis of Secondary Endpoints

6.1.5.1 Hierarchical analysis

A closed hierarchical testing procedure was used to evaluate efficacy across multiple secondary endpoints.

Table 25 presents the hypothesis testing conclusions for the secondary efficacy endpoints under the pre-specified hierarchical testing sequence (top to bottom of table).

Table 25. Clinical Endpoints: Hierarchical Analysis

Endpoint	Ticagrelor 90 mg bd N = 9333		Clopidogrel 75 mg od N = 9291		HR (95%CI)	p-value	Significant?
	Patients with Events	KM%	Patients with Event	KM%			
PRIMARY ENDPOINT							
Composite of CV Death/MI (excl. silent MI) /Stroke	864 (9.3%)	9.8%	1014 (10.9%)	11.7%	0.84 (0.77, 0.92)	0.0003	Yes
SECONDARY ENDPOINTS							
Composite of CV Death/MI (excl. silent MI) /Stroke - Intent to Invasively Manage*	569 (8.5%)	8.9%	668 (10.0%)	10.6%	0.84 (0.75, 0.94)	0.0025	Yes
Composite of All Cause Mortality/MI (excl. silent MI)/Stroke	901 (9.7%)	10.2%	1065 (11.5%)	12.3%	0.84 (0.77, 0.92)	0.0001	Yes
Composite of CV Death/Total MI/Stroke/ Severe Recurrent Cardiac Ischemia/ Recurrent Cardiac Ischemia/Transient Ischemic Attack/Other Arterial Thrombotic Events	1290 (3.8%)	14.6%	1456 (15.7%)	16.7%	0.88 (0.81, 0.95)	0.0006	Yes
MI (excl. silent MI)	504 (5.4%)	5.8%	593 (6.4%)	6.9%	0.84 (0.75, 0.95)	0.0045	Yes
CV Death	353 (3.8%)	4.0%	442 (4.8%)	5.1%	0.79 (0.69, 0.91)	0.0013	Yes
Stroke	125 (1.3%)	1.5%	106 (1.1%)	1.3%	1.17 (0.91, 1.52)	0.2249	No
All Cause Mortality	399 (4.3%)	4.5%	506 (5.4%)	5.9%	0.78 (0.69, 0.89)	0.0003	No

Hazard ratio and p-value calculated from Cox proportional hazards model with study treatment as only explanatory variable.
Kaplan-Meier percentage calculated at 12 months.
Formal statistical testing performed in sequence presented above until first non-significant result observed.
For patients with multiple events the analysis uses the time to the earliest event: each patient is counted only once in each row.
A single event may be counted in more than one row.
* Percentages are calculated using different denominators for intent to invasively manage patients.
Source: Sponsor, CSR, p.3361, Table 11.2.1

Because ticagrelor was not superior to clopidogrel on the endpoint of stroke, subsequent hierarchical testing of all-cause mortality would not be considered statistically valid.

6.1.5.2 Myocardial Infarction

Clinical MIs and periprocedural MIs detected by biomarkers were included in the primary variable, as adjudicated by the ICAC. Due to absence of symptoms, the exact timing of silent MIs detected by ECG alone usually cannot be determined. For these reasons, the primary efficacy variable time to event analysis does not include silent MIs.

An MI "trigger program" identified potential MIs by CK-MB or troponin in the electronic data capture system and were sent to be adjudicated by the ICAC, and when confirmed were included in the primary efficacy analysis with other MIs.

Table 26 presents MIs according to whether they were identified by investigator or by biomarkers. Notably, approximately 15-20% of all adjudicated MIs were initially detected through the cardiac enzyme biomarker trigger program.

Table 26. MI: Investigator reported and biomarker identified MIs

	Total Events		First Event	
	Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od N = 9291	Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od N = 9291
All MI (excl. silent MI)	566	667	504 (5.4%)	593 (6.4%)
MI detected by Investigator	452	546	395 (4.2%)	482 (5.2%)
MI detected from cardiac enzyme biomarkers	114	121	114 (1.2%)	121 (1.3%)

Cumulative event rates shown.
Source: Reproduced from sponsor, CSR page 3380, Table 11.2.7.5

Because the rates of biomarker identified MIs were similar between the two arms, investigator detected MIs primarily drove the overall benefit for MI.

Table 27 presents MIs by index ACS event and treatment arm. As for the primary composite endpoint, the relative reduction in MIs with ticagrelor was most pronounced in the STEMI and (to a lesser extent) the NSTEMI group, with little benefit observed in UA.

Table 27. MI Endpoint by ACS index event type

Index Event	N subjects	Ticagrelor # Events/n (KM%)	Clopidogrel # Events/n (KM%)	HR (95%CI)
STEMI	7,026	136/3496 (4.2%)	184/3530 (5.7%)	0.74 (0.59, 0.93)
NSTEMI	7,955	288/4005 (7.9%)	324/3950 (8.9%)	0.87 (0.74, 1.02)
UA	3,112	76/1549 (5.2%)	75/1563 (5.1%)	1.02 (0.75, 1.42)
OVERALL*	18,624	504/9333 (5.9%)	593/9291 (6.9%)	0.84 (0.75, 0.95)

365 day KM% shown
* Includes "unknown" ACS event type (not shown)
Source: R. Fiorentino, Clinical Reviewer

Although influenced by sample size, a more significant reduction in MIs in the ticagrelor arm was seen in the Planned Invasive subgroup, as shown in Table 28.

Table 28. MI Endpoint by Planned Treatment Approach at Randomization

Planned Treatment Approach at Randomization	N subjects	Ticagrelor # Events/n (KM%)	Clopidogrel # Events/n (KM%)	HR (95%CI)
Medical Mgmt	5,216	176/2601 (7.3%)	187/2615 (7.8%)	0.94 (0.77, 1.15)
Invasive Mgmt	13,408	328/6732 (5.3%)	406/6676 (6.6%)	0.80 (0.69, 0.92)

365 day KM% shown
Source: R. Fiorentino, Clinical Reviewer

Table 29 presents a *post-hoc* exploratory evaluation of MIs outcome across six categories from a combined analysis of MIs as tabulated in Table 27 and Table 28, according to Planned Treatment approach and Index ACS event type.

Table 29. MIs: Planned Treatment Approach vs. Index ACS Event

HR (95%CI) n/N	STEMI	NSTEMI	UA
Medical Mgmt	0.99 (0.53, 1.85) 39/451	0.87 (0.68, 1.11) 248/2910	1.25 (0.78, 2.01) 70/1726
Invasive Mgmt	0.71 (0.56, 0.91) 281/6575	0.87 (0.71, 1.07) 364/5045	0.88 (0.57, 1.36) 81/1386

HR from Cox prop. Haz model
Source: R. Fiorentino, Clinical Reviewer

Of the six subgroups shown above (Table 29) the greatest comparative benefit for ticagrelor was observed in subjects with STEMIs who had planned invasive management.

MI Subtypes

The ICAC classified clinical endpoints of MI subtypes according to a modification of the scheme proposed by Thygesen (et al 2007) in order to provide information on the clinical setting (e.g.,

spontaneous, associated with stent thrombosis, and post-procedural) in which MIs tended to occur during the study.

As presented in Table 30, the most notable difference between the two arms is a numerical reduction in the proportion of MIs attributable to stent thromboses. An analysis of a more rigorously defined and adjudicated stent thrombosis is provided in Section 6.1.5.5.

Table 30. MI Subtypes

	Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od N = 9291
Total number of MIs	603	682
Type 5 (CABG MI): Any peri-CABG MI	45 (7.5%)	38 (5.6%)
Type 4b: Any MI that is adjudicated as associated with stent thrombosis	80 (13.3%)	113 (16.6%)
Type 4a: Any peri-PCI MI	100 (16.6%)	124 (18.2%)
Type 3: Any MI not covered in types 4-5, accompanied by death	18 (3.0%)	15 (2.2%)
Types 1 and 2: Any MI not covered by definitions 3-5	360 (59.7%)	392 (57.5%)

Source: Sponsor, CSR p. 3377, Table 11.2.7.2

Silent MIs

For completeness, silent MIs are included in a secondary composite endpoint and are also presented separately. In addition, sensitivity analysis of the primary efficacy variable including silent MI was performed.

59 subjects had silent MIs identified and submitted for adjudication. Of these, 11 were adjudicated as silent MIs, with the remainder adjudicated as "No Event."

Table 31. Adjudicated Silent MIs

	Ticagrelor N=9333 Events, (%)	Clopidogrel N=9291 Events, (%)	HR (95%CI)
Silent MI	5 (0.1%)	6 (0.1%)	0.83 (0.25, 2.72)

Source: Sponsor, CSR, p.3367, Table 11.2.3.1

6.1.5.3 Strokes

Figure 15 presents the KM failure plot for strokes. Notably, the KM curves appear to separate (numerically) within the first month after randomization.

Figure 15. KM Time to First Stroke

Time to First Stroke
KM Failure
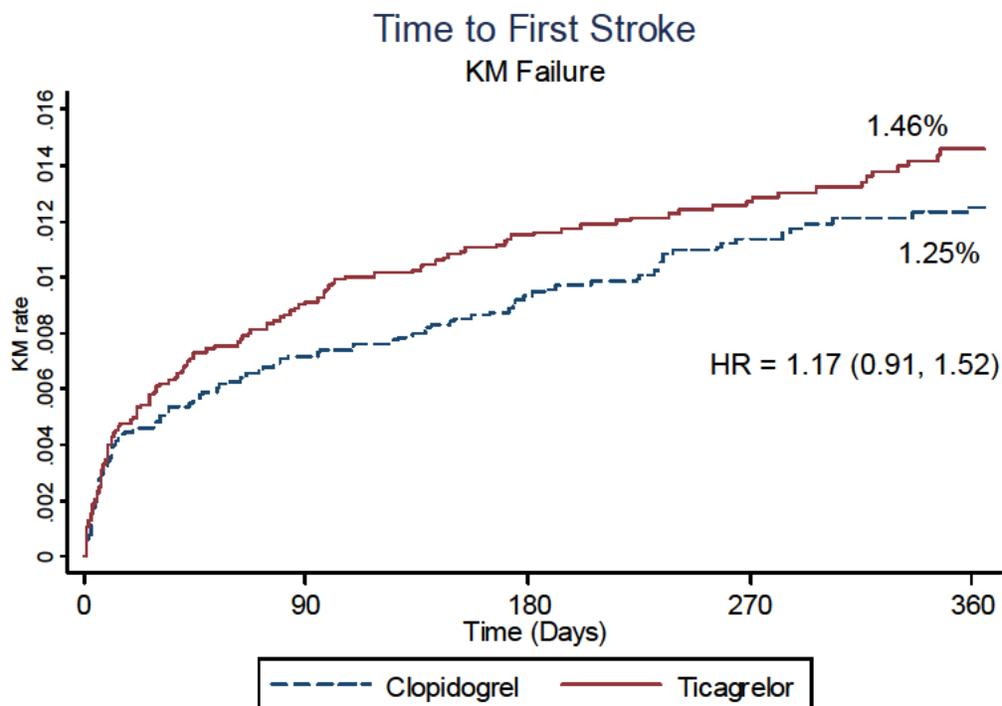
K-M percentages calculated at 365 days
Source: R. Fiorentino, Clinical Reviewer

A total of 195 non-hemorrhagic stroke events were reported (ticagrelor, n=100 vs. clopidogrel, n=95) in PLATO. A total of 36 hemorrhagic strokes were reported (ticagrelor, n=23 vs. clopidogrel, n=13). Unknown/no imaging performed was reported for 10 ticagrelor vs. 2 clopidogrel patients.

Table 32 presents hemorrhagic and non-hemorrhagic strokes and demonstrates that the numerically increased overall rate of strokes in the ticagrelor arm was driven primarily by increased hemorrhagic strokes (23 vs. 13).

Table 32. Stroke Subtypes

	Total Events		First Event	
	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od N = 9291
Non-hemorrhagic	100	95	96 (1.0%)	91 (1.0%)
Hemorrhagic	23	13	23 (0.2%)	13 (0.1%)
Unknown/ No Imaging Performed	10	2	10 (0.1%)	2 (0.0%)

Source: Sponsor, CSR p. 3391, Table 11.2.14.1

As noted by the sponsor, there were a total of 73 "fatal" strokes (46 ticagrelor vs. 27 clopidogrel subjects) defined as strokes in subjects who died during the study period.

In general, there were too few subjects with a prior history of stroke or TIA to make definitive conclusions regarding efficacy in this subgroup. Time to first stroke stratified by prior history of stroke or TIA is presented in Table 33.

Table 33. Time to First Stroke by Prior History

	N Subjects	Ticagrelor n/N	Clopidogrel n/N	HR (95% CI)
Prior Stroke				
Yes	722	7/353	14/369	0.51 (0.20, 1.25)
No	17,892	118/8973	92/8919	1.28 (0.97, 1.68)
Prior TIA				
Yes	499	13/246	5/253	2.52 (0.90, 7.06)
No	18,115	112/9080	101/9035	1.10 (0.84, 1.45)

Source: R. Fiorentino, Clinical Reviewer

6.1.5.4 Deaths

The ticagrelor arm had significantly lower rates of CV deaths compared to clopidogrel. This difference is illustrated in Figure 16, where the KM curves numerically begin to separate within the first 30 days from randomization and continue their separation thereafter.

Figure 16. KM plot: CV Death
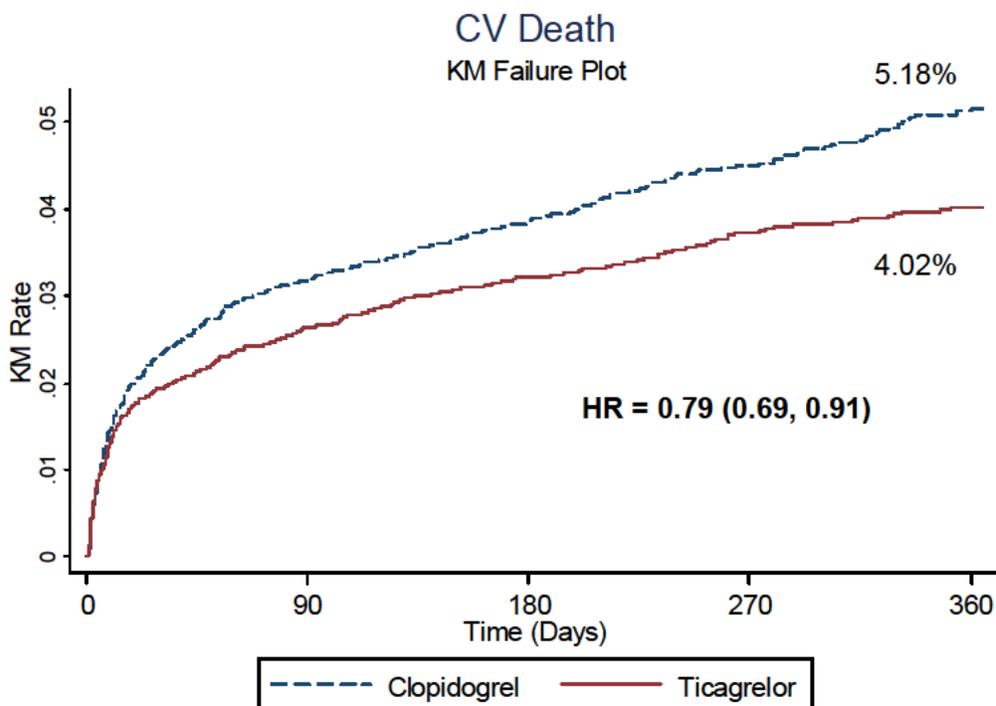
KM% at 365 days
Source: R. Fiorentino, Clinical Reviewer

Table 34 presents CV deaths by index event subgroups. Numerical reductions in CV death were observed across all index event subtypes. Numerically, the NSTEMI population appeared to gain the largest relative reduction in CV death.

Table 34. CV Death by Index ACS Event

Index Event	N subjects	Ticagrelor # Events (KM%)	Clopidogrel # Events (KM%)	HR (95%CI)
STEMI	7,026	140/3496 (4.17%)	164/3530 (4.97%)	0.86 (0.69, 1.08)
NSTEMI	7,955	146/4005 (3.90%)	191/3950 (5.31%)	0.75 (0.61, 0.93)
UA	3,112	46/1549 (3.28%)	60/1563 (4.29%)	0.78 (0.53, 1.14)
OVERALL*	18,624	353/9333 (4.02%)	442/9291 (5.18%)	0.79 (0.69, 0.91)

365 day KM% shown; HR from Cox prop. Haz. model
* Includes "unknown" ACS event type (not shown)
Source: R. Fiorentino, Clinical Reviewer

Treatment benefit with respect to CV death also appeared similar in both planned invasive treatment strategy [305/5216; HR = 0.82 (0.68, 0.97)] and medical management [490/13408; HR=0.76 (0.61, 0.96)], as chosen by the investigator at the time of randomization.

In contrast, there was no statistical difference in non-CV death rates, which were low in both treatment arms and presented in Figure 17.

Figure 17. KM Plot: Non-CV Death

non CV Death
KM Failure Plot
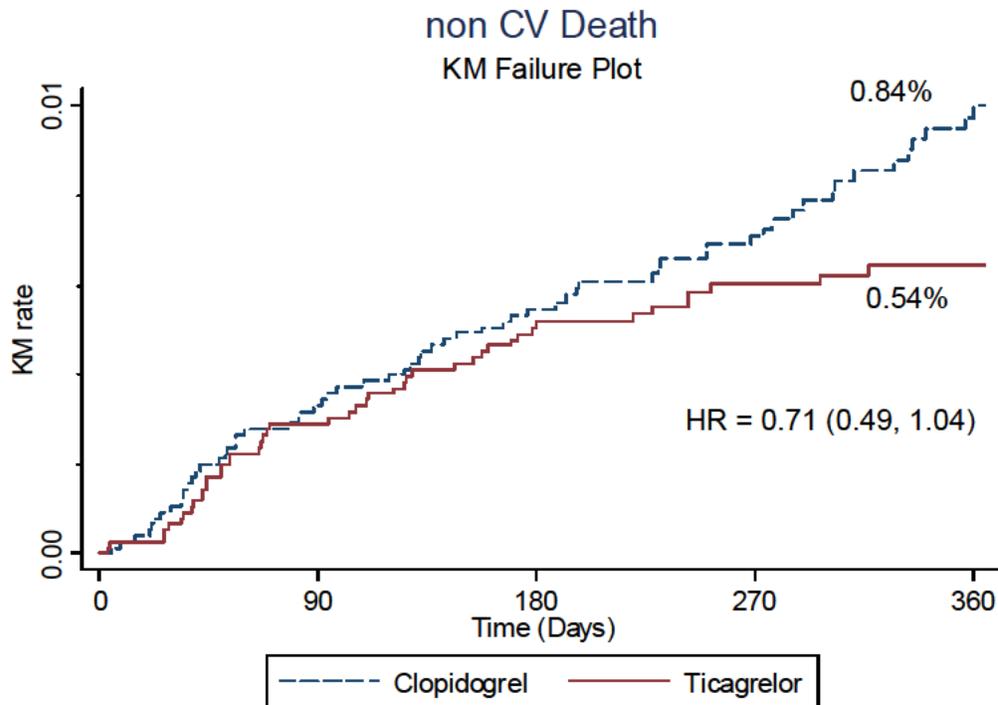
KM% rates estimated at 365 days
Source: R. Fiorentino, Clinical Reviewer

Based on this analysis, the predominant contributor to the lower all-cause death rate observed in the ticagrelor arm was CV death. Otherwise, non-CV death rates were low (<1%) across all index ACS event subtypes, as presented in Table 35.

Table 35. Non-CV Death by Index ACS Event

Index Event	N subjects	Ticagrelor # Events/n (KM%)	Clopidogrel # Events/n (KM%)	HR (95%CI)
STEMI	7,026	9/3496 (0.30%)	22/3530 (0.78%)	0.41 (0.19, 0.90)
NSTEMI	7,955	31/4005 (0.84%)	28/3950 (0.84%)	1.09 (0.65, 1.81)
UA	3,112	5/1549 (0.35%)	10/1563 (0.84%)	0.51 (0.17, 1.48)
OVERALL*	18,624	46/9333 (0.54%)	64/9291 (0.84%)	0.71 (0.49, 1.04)

365 day KM% presented; HR derived from Cox prop. Haz. model
* Includes "unknown" ACS event type (not shown)
Source: R. Fiorentino, Clinical Reviewer

6.1.5.5 Stent Thrombosis

Protocol Amendment 3 (dated December 19, 2007) added cases of stent thrombosis as events for adjudication by the ICAC so that an *exploratory analysis* examining the frequency of stent thrombosis could be performed. This required, per the protocol, that suspected cases of stent thrombosis would be adjudicated, both retrospectively (from start of the study until the amendment became effective) and prospectively (thereafter until end of the study). After Protocol Amendment 3, events which fell into the category of ischemic cardiac event and death had to be adjudicated again for the presence or absence of stent thrombosis.

The definition proposed by the Academic Research Consortium (ARC) was used by ICAC for classification of definite, probable and possible stent thromboses (Cutlip, Windecker et al. 2007). See Section 8.1 for a detailed presentation of the definitions of stent thrombosis.

According to the sponsor (communication dated June 3, 2010), ST events were identified in two ways:

1. Stent thrombosis was identified by ICAC as a component of the adjudication process for the clinical events of death and suspected ischemic cardiac event. A "stent thrombosis" query was included on the adjudication form for events identified as death, myocardial infarction, severe recurrent ischemia and recurrent ischemia. The ICAC did not adjudicate the stent thrombosis data as a separate endpoint event, but as part of a death or ischemic cardiac event as defined in the June 2008 ICAC Charter.

2. Asymptomatic stent thrombosis identified by the site investigator and not considered to be a part of a suspected endpoint event was reported by the site as an AE or SAE and was not sent to ICAC for adjudication.

The ICAC did not review actual angiograms. The adjudicators reviewed angiogram reports, which were included with the endpoint package source documentation. Stent thromboses were not confirmed by an angiographic core lab.

In the statistical analysis of stent thromboses, time-at-risk was calculated from the date of first stent insertion in the study to the date of the first thrombosis event. For patients entering the study with a history of PCI, the time was calculated from the date of randomization to the time of the first thrombosis event.

As presented in Table 36, the ICAC charter required specific documentation to make a determination of stent thrombosis:

Table 36. Documentation Required by ICAC for Adjudication of Stent Thrombosis

REQUIRED eCRF DATA	REQUIRED SOURCE DOCUMENTATION
- Index Event hospitalization information - All cardiac biomarker measurements (all CK-MB, Troponin I & T) - Cardiac Ischemic Event - All other hospitalization forms (if applicable) - Procedures and Operations (Cardiac Cath & PCI) - Death Form	- Discharge Summary and/or Investigator Assessment and Narrative Form. These documents collectively, should provide a complete and concise event history (subject presentation treatments, disposition) /comprehensive summary of the event. - ECGs: (date and time the ECG was performed must be on each ECG submitted) - Enrolment Visit - Pre-Discharge (discharge after ACS event if event occurs in separate hospitalization) 1 Month - Peri-endpoint event (ECGs showing changes described in the discharge summary, investigator narrative or reported by site) - Angiography Report **(If done)** - Reports from any/all the revascularizations that were performed related to the event - Investigator Assessment and Narrative Form if death at home - Autopsy report **(if done)**

Source: ICAC Charter, Appendix E, p. 28

Table 37 presents the results of the stent thrombosis adjudication.

Table 37. Time to First Adjudicated Stent Thrombosis

| Characteristic | Ticagrelor N = 9333 | | Clopidogrel N=9291 | | | |
	Patients with Events	KM %	Patients with Events	KM %	HR (95%CI)	p-value*
Patients with a History of PCI / Receiving any Stent during the study	6182		6196			
Definite Stent Thrombosis	73 (1.2%)	1.2%	107 (1.7%)	1.8%	0.68 (0.51, 0.92)	0.0123
Definite or Probable Stent Thrombosis	121 (2.0%)	2.0%	160 (2.6%)	2.7%	0.76 (0.60, 0.96)	0.0215
Definite, Probable or Possible Stent Thrombosis	159 (2.6%)	2.7%	205 (3.3%)	3.5%	0.78 (0.63, 0.96)	0.0168
Patients Receiving any Stent during the study	5640		5649			
Definite Stent Thrombosis	71 (1.3%)	1.3%	106 (1.9%)	1.9%	0.67 (0.50, 0.91)	0.0091
Definite or Probable Stent Thrombosis	118 (2.1%)	2.2%	158 (2.8%)	2.9%	0.75 (0.59, 0.95)	0.0167
Definite, Probable or Possible Stent Thrombosis	155 (2.8%)	2.9%	202 (3.6%)	3.8%	0.77 (0.62, 0.95)	0.0131
Patients Receiving a Drug-Eluting Stent during the study	1719		1757			
Definite Stent Thrombosis	20 (1.2%)	1.3%	28 (1.6%)	1.7%	0.73 (0.41, 1.29)	0.2784
Definite or Probable Stent Thrombosis	37 (2.2%)	2.3%	42 (2.4%)	2.5%	0.90 (0.58, 1.40)	0.6381
Definite, Probable or Possible Stent Thrombosis	47 (2.7%)	3.0%	62 (3.5%)	3.7%	0.77 (0.53, 1.13)	0.1838
Patients Receiving a Bare Metal Stent during the study	3921		3892			
Definite Stent Thrombosis	51 (1.3%)	1.3%	78 (2.0%)	2.1%	0.65 (0.46, 0.92)	0.0163
Definite or Probable Stent Thrombosis	81 (2.1%)	2.1%	116 (3.0%)	3.0%	0.69 (0.52, 0.92)	0.0112
Definite, Probable or Possible Stent Thrombosis	108 (2.8%)	2.9%	140 (3.6%)	3.8%	0.76 (0.59, 0.98)	0.0361

* p-value does not represent the results of pre-specified hypothesis testing and is therefore descriptive in nature
Source: Reproduced from Sponsor, CSR, p. 3375, Table 11.2.6

The principal exploratory analysis was performed in those subjects with either a history of PCI (prior stent) or who received any stent during the study. Because of the exploratory nature of this analysis and the presentation of multiple endpoints, the relevance of the p-values is uncertain. However, there was a clear numerical trend toward lower stent thromboses rates in the ticagrelor arm, of all classifications, across subgroups.

Table 38 presents MIs adjudicated as associated with stent thromboses. As expected, a relatively small proportion of the total MIs were attributable to stent thromboses. Of those that were, subjects in the ticagrelor arm had numerically lower rates of stent thromboses associated MIs compared to clopidogrel.

Table 38. MIs Adjudicated as Associated with Stent Thrombosis (MI Type 4b)

	Ticagrelor N = 9333	Clopidogrel N = 9291
Total MIs	13.3% (80/603)	16.6% (113/682)
Patients with Events (1st MI)	13.4% (71/529)	16.4% (99/604)

Source: Reproduced from sponsor, CSR Tables 11.2.7.1 and 11.2.7.2

A separate analysis by this reviewer also evaluated the number of investigator-reported stent thromboses submitted as serious adverse events (SAEs). A total of 110 stent thrombosis events were identified in 97 subjects. The results of this analysis are presented in Table 39, which estimates the rate of stent thrombosis submitted as SAEs, independent of the adjudication process.

Table 39. Stent Thromboses Reported as Serious Adverse Events

	Total Events	Subjects with Events	As a proportion of subjects w/ prior PCI or stent placement	Difference (95% CI)*
Clopidogrel (n=9291)	68	60	60 / 6196 (0.97%)	.37%
Ticagrelor (n=9333)	42	37	37 / 6182 (0.60%)	(0.06%, 0.68%)

* derived from a 2-sample test of proportions for descriptive purposes only
Source: R. Fiorentino, Clinical Reviewer

There was a numerically lower frequency and (estimated) cumulative rate of stent thromboses, reported as SAEs in the ticagrelor arm, compared to clopidogrel. These estimated rates are lower when contrasted against the adjudicated ST events but were derived without using a survival analysis. However, the trend towards a lower number of stent thromboses in the ticagrelor arm remains apparent.

Further analyses were performed by this reviewer to investigate the time course of stent thrombosis. Figure 18 presents the results graphically.

Figure 18. Time to Stent Thrombosis
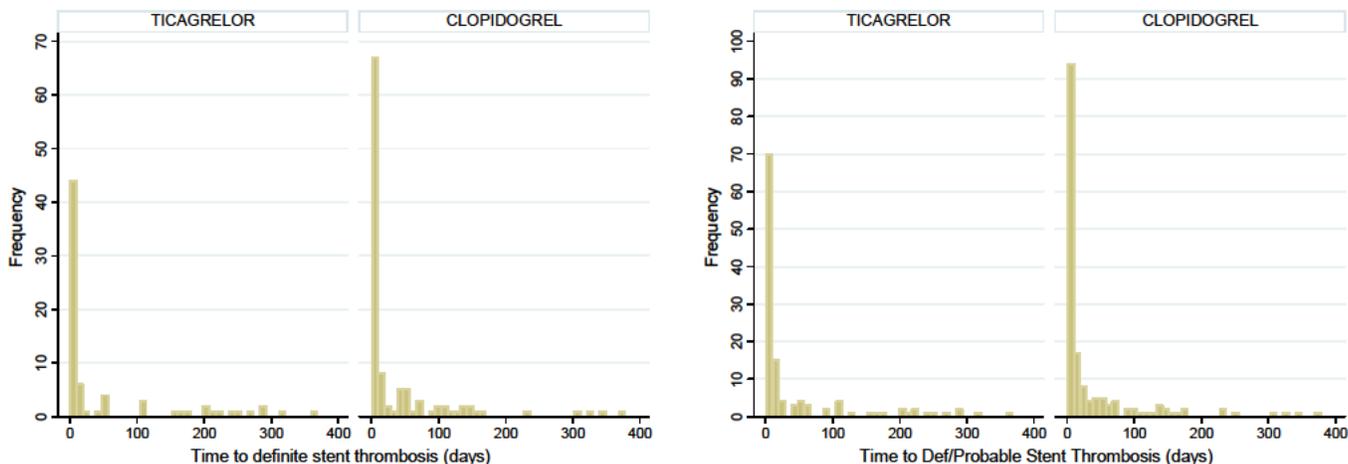
Source: R. Fiorentino, Clinical Reviewer

The apparent lower numbers of stent thromboses in the ticagrelor arm appears to be primarily explained by a substantially lower number of ST events very early subsequent to randomization, with a somewhat less pronounced decrease attributable to later timepoints. This would be expected as a result of acute stent thromboses (within 24hrs) following PCI.

Table 40 presents the frequency of stent thrombosis according to the timing of event for those subjects who had an in-study PCI. The numbers differ somewhat from those in Figure 18, which includes subjects who enroll in the study with prior stent implantation.

Table 40. Stent Thrombosis by ARC Definitions*

ARC Classification	Ticagrelor N=9333	Clopidogrel N=9291
Acute Stent Thrombosis (0-24 hours after implantation)	16	13
Subacute (>24 hours to 30 days)	37	62
Late (>30 days to 1 year)	18	30
Very Late (>1 year)	0	1

* Only patients with a prior in-study PCI
Source: Reproduced from sponsor, submission date 21 June 2010, p. 10, Table 6.15.1

Because the inclusion of an exploratory analysis of stent thrombosis was implemented mid-trial, the adjudicated ST events were identified both retrospectively and prospectively. A tabulation of the number of ST occurring before and after the date of the protocol amendment is presented in Table 41.

Table 41. Adjudicated stent thrombosis events occurring before and after Dec 19, 2007 (protocol amendment 3)

	Randomized treatment		
	Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291	Total[a]
All stent thrombosis events	195 (100%)	255 (100%)	450 (100%)
Occurring prior to 19 December 2007	80 (41.03%)	100 (39.22%)	180 (40%)
Occurring on or after 19 December 2007	115 (58.97%)	155 (60.78%)	270 (60%)

[a] For detailed subject listings, please refer to Appendix B, which provides a listing of stent thrombosis prior to and after 17 December 2007.

Source: Sponsor, submission dated June 4, 2010

Notable is the similar number of stent thrombosis events occurring in both arms, with a somewhat higher number of events occurring after the relevant protocol amendment and later in the study.

Table 42 and Table 43 present stent thromboses time-to-event analyses of stent thrombosis events for subjects randomized before and after the implementation of protocol Amendment 3.

Table 42. Adjudicated Stent Thrombosis For Subjects Randomized Before December 19, 2007 observed up to December 18, 2007

	Randomised Treatment				
	Ticagrelor 90 mg bd N = 4868		Clopidogrel 75 mg od N = 4859		
Characteristic	Patients with Events	KM %	Patients with Events	KM %	Hazard Ratio (95% CI)
Patients with a History of PCI / Receiving any Stent during the study	3252		3263		
Definite Stent Thrombosis	35 (1.1%)	1.3%	43 (1.3%)	1.5%	0.82 (0.53, 1.29)
Definite or Probable Stent Thrombosis	56 (1.7%)	2.0%	66 (2.0%)	2.5%	0.86 (0.60, 1.22)
Definite, Probable or Possible Stent Thrombosis	69 (2.1%)	2.9%	80 (2.5%)	6.2%	0.87 (0.63, 1.20)
Patients Receiving any Stent during the study	2965		2970		
Definite Stent Thrombosis	34 (1.1%)	1.4%	42 (1.4%)	1.6%	0.82 (0.52, 1.28)
Definite or Probable Stent Thrombosis	55 (1.9%)	2.2%	65 (2.2%)	2.7%	0.85 (0.60, 1.22)
Definite, Probable or Possible Stent Thrombosis	68 (2.3%)	3.2%	79 (2.7%)	6.7%	0.87 (0.63, 1.20)
Patients Receiving a Drug-Eluting Stent during the study	880		909		
Definite Stent Thrombosis	7 (0.8%)	1.1%	7 (0.8%)	0.8%	
Definite or Probable Stent Thrombosis	15 (1.7%)	2.1%	17 (1.9%)	2.5%	0.91 (0.46, 1.83)
Definite, Probable or Possible Stent Thrombosis	19 (2.2%)	4.1%	24 (2.6%)	3.7%	0.82 (0.45, 1.49)
Patients Receiving a Bare Metal Stent during the study	2085		2061		
Definite Stent Thrombosis	27 (1.3%)	1.5%	35 (1.7%)	2.0%	0.77 (0.47, 1.27)
Definite or Probable Stent Thrombosis	40 (1.9%)	2.2%	48 (2.3%)	2.8%	0.83 (0.55, 1.26)
Definite, Probable or Possible Stent Thrombosis	49 (2.4%)	2.9%	55 (2.7%)	8.7%	0.89 (0.60, 1.30)

Source: Sponsor, submission dated June 21, 2010, Table 6.10.1

Table 43. Adjudicated Stent Thrombosis For Subjects Randomized On or After December 19, 2007

	Randomised Treatment				
	Ticagrelor 90 mg bd N = 4465		Clopidogrel 75 mg od N = 4432		
Characteristic	Patients with Events	KM %	Patients with Events	KM %	Hazard Ratio (95% CI)
Patients with a History of PCI / Receiving any Stent during the study	2930		2933		
Definite Stent Thrombosis	29 (1.0%)	1.0%	57 (1.9%)	2.4%	0.51 (0.33, 0.80)
Definite or Probable Stent Thrombosis	55 (1.9%)	1.9%	84 (2.9%)	3.3%	0.66 (0.47, 0.92)
Definite, Probable or Possible Stent Thrombosis	67 (2.3%)	2.4%	95 (3.2%)	3.7%	0.71 (0.52, 0.97)
Patients Receiving any Stent during the study	2675		2679		
Definite Stent Thrombosis	28 (1.0%)	1.1%	57 (2.1%)	2.6%	0.49 (0.31, 0.77)
Definite or Probable Stent Thrombosis	53 (2.0%)	2.1%	83 (3.1%)	3.6%	0.64 (0.45, 0.90)
Definite, Probable or Possible Stent Thrombosis	65 (2.4%)	2.5%	93 (3.5%)	4.0%	0.70 (0.51, 0.96)
Patients Receiving a Drug-Eluting Stent during the study	839		848		
Definite Stent Thrombosis	10 (1.2%)	1.3%	20 (2.4%)	3.3%	0.50 (0.23, 1.07)
Definite or Probable Stent Thrombosis	18 (2.2%)	2.2%	24 (2.8%)	3.7%	0.75 (0.41, 1.39)
Definite, Probable or Possible Stent Thrombosis	20 (2.4%)	2.5%	28 (3.3%)	4.2%	0.72 (0.40, 1.28)
Patients Receiving a Bare Metal Stent during the study	1836		1831		
Definite Stent Thrombosis	18 (1.0%)	1.0%	37 (2.0%)	2.3%	0.49 (0.28, 0.85)
Definite or Probable Stent Thrombosis	35 (1.9%)	2.0%	59 (3.2%)	3.6%	0.59 (0.39, 0.90)
Definite, Probable or Possible Stent Thrombosis	45 (2.5%)	2.6%	65 (3.5%)	3.9%	0.69 (0.47, 1.01)

Source: Sponsor, submission dated June 21, 2010, Table 6.10.2

In general, the data does appear to suggest relatively lower rates of stent thrombosis in the ticagrelor arm, including lower rates of stent related MIs. However, I have a number of concerns regarding the data. First, this was intended to be a non-prespecified exploratory analysis and fundamentally the findings should remain exploratory in nature. Second, the current ARC definitions of definite stent thrombosis require either angiographic or pathological confirmation. However the adjudication committee (ICAC) did not review actual angiograms and relied on reported stent thromboses observed during angiography (e.g., 2nd hand accounts) or in hospital summaries (where autopsy not available). Stent thromboses could not always be independently confirmed by the ICAC and there was no angiographic core lab used in PLATO. Finally, I am not convinced that the observed reduction in stent thrombosis in ticagrelor is not the result of a sampling (or ascertainment) bias. This is possible given that having any cardiac event may increase the likelihood of a stent thrombosis being detected and adjudicated. Since we know ticagrelor reduces MIs and subsequently the creation of a cardiac ischemic event (CIE) or cardiovascular AE report, one might expect a lower frequency of suspected stent thrombosis when retrospectively evaluating them (even if the true difference in ST were zero). To put it another way, if there were fewer cardiac ischemic events (CIE) in the ticagrelor arm, one would also discover, retrospectively, fewer cases of stent thrombosis, since CIE reports represented the source data.

6.1.6 Subpopulations

6.1.6.1 Age

An analysis of primary endpoint by age group (Table 44) suggested a potentially attenuated benefit observed in the elderly, ≥75 year-old subgroup [HR=0.94, 95%CI: (0.78, 1.12)].

Table 44. Primary Endpoint by Age Group

Age Group	# subjects	Ticagrelor 12m KM% (n/N)	Clopidogrel 12m KM% (n/N)	HR (95% CI)
<65 Years	10,643	7.2% (360/5310)	8.5% (427/5333)	0.85 (0.74, 0.97)
≥65 Years	7,979	13.2% (504/4023)	16.0% (587/3958)	0.83 (0.74, 0.94)
<75 Years	15,744	8.6% (641/7936)	10.4% (763/7808)	0.82 (0.74, 0.91)
≥75 Years	2,880	16.8% (223/1397)	18.3% (251/1483)	0.94 (0.78, 1.12)

Source: Reproduced from Sponsor, CSR Fig. 16; other tabulation by R. Fiorentino

Notable is the trend towards more events in the elderly. The relationship between advancing age and primary outcome is potentially confounded by other baseline and disease characteristic.

6.1.6.2 Sex

An analysis of the primary clinical endpoint by sex demonstrated similar hazard ratios in both male and female subjects but with numerically higher event rates in female subjects.

Table 45. Primary Endpoint by Sex

	# subjects	Ticagrelor 12m KM% (n/N)	Clopidogrel 12m KM% (n/N)	HR (95% CI)
Male	13,336	9.2% (586/6678)	11.1% (686/6658)	0.85 (0.76, 0.95)
Female	5,288	11.2% (278/2655)	13.2% (328/2633)	0.83 (0.71, 0.97)

Source: Reproduced from sponsor, CSR Fig. 16; other tabulation by R. Fiorentino

6.1.6.3 Race

The relatively small number of non-Caucasian subjects makes definitive conclusions regarding effectiveness in these subgroups a challenge. Regardless, a numerical benefit of ticagrelor compared to clopidogrel was preserved across racial subgroups. However, non-Caucasian racial subgroups were observed to have, in general, numerically higher primary event rates overall (Table 46).

Table 46. Primary Endpoint by Patient-reported Ethnicity

Ethnicity*	# subjects	Ticagrelor (12m KM%)	Clopidogrel (12m KM%)	HR (95% CI)
"Caucasian"	17,077	9.5% (769/8566)	11.2% (893/8511)	0.85 (0.77, 0.94)
"Black"	229	13.0% (14/115)	19.6% (21/114)	0.63 (0.32, 1.23)
"Oriental"	1,096	12.5% (66/542)	14.8% (77/554)	0.87 (0.62, 1.21)
Other	221	14.4% (15/109)	21.4% (23/112)	0.63 (0.33, 1.21)

*Ethnicity was patient-reported.
Source: Sponsor, CSR Fig. 16; additional tabulation by R. Fiorentino

6.1.6.4 Weight & Body Mass Index (BMI)

BMI was a prespecified subgroup in PLATO. Table 47 demonstrates that although the majority of subjects had BMIs <30kg/m², the hazard ratios were similar across groups.

Table 47. Primary Endpoint by BMI Subgroups

BMI	# subjects	Ticagrelor (12m KM%)	Clopidogrel (12m KM%)	HR (95% CI)
< 30 kg/m²	13,354	10.1% (636/6641)	11.9% (747/6713)	0.86 (0.77, 0.95)
≥ 30 kg/m²	5,178	8.9% (228/2692)	10.8% (267/2578)	0.83 (0.69, 0.99)

Source: Sponsor, CSR Fig. 16.

Body weight by gender-specific median was not a prespecified subgroup, but was evaluated by the sponsor on an exploratory basis. Lower event rates were observed in subjects who were above their gender-specific median weights. Table 48 presents the primary endpoint across each of these two subgroups, suggesting that the relative benefit of ticagrelor may have been driven primarily by males and females above their gender-specific median weight.

Table 48. Primary Endpoint by Gender-Specific Median Weight Groups

Median Weight Group by Sex	# subjects	Ticagrelor (12m KM%)	Clopidogrel (12m KM%)	HR (95% CI)
Males <82kg / Females <71kg	9,001	11.4%	12.5%	0.93 (0.82, 1.05)
Males ≥82kg / Females ≥71kg	9,567	8.2%	10.8%	0.76 (0.67, 0.87)

Source: Sponsor, CSR Fig. 16.

Furthermore, assessment of an interaction between randomized treatment and these subgroups produced a p-value of 0.0378 (per sponsor). This suggests the possibility of a greater comparative benefit with ticagrelor in patients who are above their gender-specific median weight group, although the clinical significance of this finding, including its explanation, is not readily apparent

6.1.6.5 Age-by-Weight Group

Table 49 presents primary outcome hazard ratios (and 95%CI) according to eight categories of age and weight groups.

Table 49. Primary Endpoint by Age/Weight Group

HR (95%CI)		Age Group (years)			
		<65	≥65	<75	≥75
Weight Group (kg)	<60	0.75 (0.46, 1.23) 64/575	0.74 (0.52, 1.05) 125/737	0.78 (0.54, 1.12) 115/969	0.75 (0.47, 1.20) 74/343
	60 - 80	0.91 (0.74, 1.12) 350/4464	0.95 (0.81, 1.11) 609/4,390	0.90 (0.78, 1.05) 686/7,139	1.03 (0.81, 1.31) 273/1,715
	>80	0.81 (0.66, 0.99) 373/5,604	0.71 (0.57, 0.87) 357/2,854	0.75 (0.64, 0.88) 603/7,636	0.90 (0.64, 1.28) 127/822

Source: R. Fiorentino, Clinical Reviewer

Treatment benefit does appear to trend adversely across any specific age/weight subgroup.

6.1.6.6 Prior PCI or CABG

Table 50 presents the primary endpoint results by history of PCI or CABG. A relatively small number of subjects had a PCI or CABG prior to enrollment into PLATO, which limits the conclusions that can be drawn from the data.

Table 50. Primary Endpoint by History of PCI or CABG

	N subjects	Ticagrelor	Clopidogrel	HR (95% CI)
Prior PCI	2,492	166 / 1272	162 / 1220	0.98 (0.79, 1.22)
No Prior PCI	16,132	698 / 8061	852 / 8071	0.82 (0.74, 0.90)
Prior CABG	1,106	97 / 532	115 / 574	0.88 (0.67, 1.15)
No Prior CABG	17,518	767 / 8801	899 / 8717	0.84 (0.77, 0.93)

Source: R. Fiorentino, Clinical Reviewer

It is not clear why a Prior PCI subgroup would lack a diminished relative benefit from ticagrelor or if there are other variables that may confound this finding.

6.1.6.7 Concomitant Medication Use

6.1.6.7.1 General Overview

As presented in Table 51, medication use post-randomization was generally typical of the ACS study population, including a high prevalence of lipid lowering agents, beta blockers and ACE inhibitors.

Table 51. Selected Non-Antithrombotic Medication taken Post Randomization

	Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od N = 9291
Patients with at least one medication	9305 (99.7%)	9261 (99.7%)
Lipid lowering agents	8726 (93.5%)	8677 (93.4%)
Beta blockers	8066 (86.4%)	8058 (86.7%)
ACE Inhibitors	7423 (79.5%)	7344 (79.0%)
Nitrates	6968 (74.7%)	6896 (74.2%)
Proton pump inhibitors	4814 (51.6%)	4710 (50.7%)
Calcium channel blockers	2291 (24.5%)	2289 (24.6%)
Antihypertensives, Other	1958 (21.0%)	1976 (21.3%)
Angiotensin Receptor blockers	1598 (17.1%)	1596 (17.2%)

Includes medications taken at any time after randomization date
Source: CSR, p. 3341, Table 11.1.4.16.2

6.1.6.7.2 Clopidogrel Use Prior to Enrollment

Approximately 30% of patients received an additional 300 mg or greater loading dose of clopidogrel, reflecting medical practice for ACS treatment. In some instances, such as before PCI, it is recommended that ACS patients receive a 600 mg loading dose of clopidogrel. In PLATO, both treatment groups could have received a clopidogrel loading dose, including open label administration.

Table 52 presents primary study outcome according to documented history of prior clopidogrel use or "naïve" status. Although limited by a relatively small sample size in the prior clopidogrel group, relative benefit of ticagrelor in this subgroup was attenuated.

Table 52. Primary Endpoint by Prior Clopidogrel Use

	N	Ticagrelor	Clopidogrel	HR (95%CI)
Clopidogrel "Naïve"	17,227	757 / 8625	903 / 8602	0.83 (0.75, 0.92)
Prior clopidogrel	1,397	107 / 708	111 / 689	0.95 (0.73, 1.24)

Naïve: Pre-Index event antiplatelet therapy recorded as: None, ASA only, or "Other"
Source: R. Fiorentino, Clinical Reviewer

Figure 19 presents study-drug and open-label clopidogrel use over the course of the study. Over time, this figure indicates the numbers of patients taking study drug without open-label clopidogrel (solid filled) and with open-label clopidogrel (double-hatched), patients not taking study drug or open-label clopidogrel (clear) and those just taking open-label clopidogrel (single-hatched).

On the day of the index event (Day 0), patients were randomized (0 to 24 hours post index event) and patients started study drug with or without prior open-label clopidogrel (per protocol). From Day 1 onwards, the majority of patients took study drug and no open-label clopidogrel, per the CSP.

Figure 19. Study-drug and open-label clopidogrel use over course of study
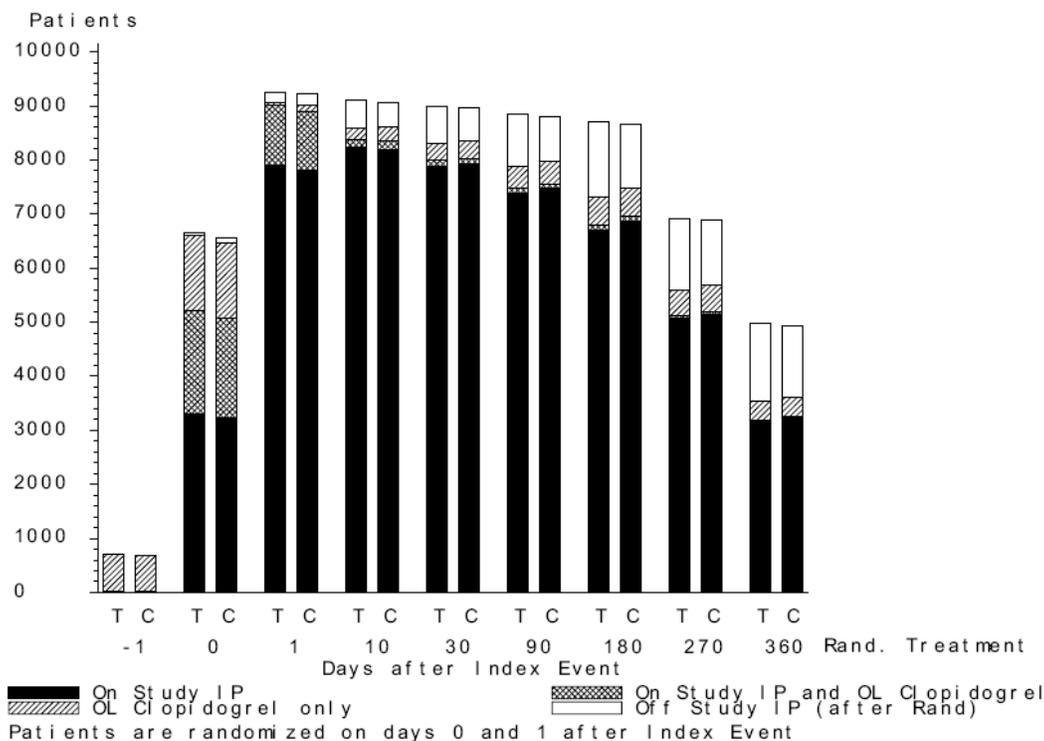
Source: Sponsor, CSR, p. 98, Fig. 8

Table 53 presents open label clopidogrel exposure prior to the first PCI procedure. Open label clopidogrel use prior to PCI was fairly common, however, the doses appear to be well-balanced between treatment arms.

Table 53. Clopidogrel Exposure at Time of First PCI

	Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291
Patients receiving PCI	4736	4736
Clopidogrel OL drug received[a]	2306 (48.7%)	2333 (49.3%)
75 to 275 mg	324 (6.8%)	326 (6.9%)
300 to 575 mg	992 (20.9%)	1056 (22.3%)
600 to 675 mg	972 (20.5%)	936 (19.8%)
>675 mg	18 (0.4%)	15 (0.3%)

[a] Includes medication taken at any time between randomization date (which could include medication prior to actual time of randomization) and first PCI procedure, inclusive; OL=open label
Source: R. Fiorentino, Clinical Reviewer

In addition, investigators were permitted to administer, at their discretion, an extra *blinded* 300 mg or 600 mg clopidogrel loading dose, depending on timing and if patients were undergoing PCI. PLATO did not exclude these patients from the study or from the analyses.

Table 54 presents the primary outcome according to clopidogrel loading dose. Note that it includes clopidogrel loading doses in those subjects randomized to clopidogrel (and had blinded clopidogrel loading).

Of note is the higher event rates in the low dose (300-375mg) compared to the high dose (600-675mg) clopidogrel subgroups. However, a similar hazard ration favoring ticagrelor was observed in both groups.

Table 54. Primary Outcome by Clopidogrel Loading Dose Category

	Group	Ticagrelor 90 mg bd N = 9333			Clopidogrel 75 mg od N = 9291			
		n	Subjects with Events	KM %	n	Subjects with Events	KM%	HR (95%CI)
Clopidogrel* Loading Dose	300 to 375 mg	1921	167 (8.7%)	9.2%	5528	620 (11.2%)	12%	0.77 (0.65, 0.91)
	600 to 675 mg	1282	87 (6.8%)	7.2%	1822	156 (8.6%)	9.1%	0.79 (0.61, 1.03)
	Other (≥75mg)	697	65 (9.3%)	10.1%	1339	147 (11.0%)	11.6%	0.84 (0.63, 1.13)
	Continuing on clopidogrel	496	84 (16.9%)	17.6%	508	81 (15.9%)	17.9%	1.09 (0.80, 1.48)
	No clopidogrel (>75mg)	4937	461 (9.3%)	9.9%	94	10 (10.6%)	10.9%	0.77 (0.41, 1.44)

Clopidogrel Loading Dose: This variable indicates, the different categories of Clopidogrel loading doses based on the dosing amount taken in 24 hr timeline between index event and Rand+24hr
Source: Sponsor, CSR p. 3363, Table 11.2.2

6.1.6.7.3 Proton Pump Inhibitor (PPI) Use

As presented previously in Table 51, the proportion of subjects using PPIs was balanced between treatment groups.

This reviewer performed an analysis of subjects identified in the submitted datasets who were recorded to have taken a PPI (anytime) during the trial. Overall outcomes did not differ between subjects who had and who had not taken PPIs, as shown in Table 55.

Table 55. Primary Outcome by PPI Use

	N	HR(95%CI)
No PPI	8,911	0.84 (0.72, 0.97)
PPI	9,690	0.85 (0.76, 0.95)

Source: R. Fiorentino, Clinical Reviewer

Furthermore, there was so significant interaction observed between treatment and PPI use with respect to the primary study outcome (p=0.897).

Omeprazole

The FDA released a public health advisory in November 2009 stating that omeprazole (a PPI) can, "reduce the anti-blood clotting effect of by almost half" when these two medicines are taken by the same patient.

An exploratory analysis was performed on 3,435 subjects identified in the primary medication use dataset who were recorded to have taken omeprazole. The use of omeprazole was derived from the variable that listed a drug name, which included both generic names as well as domestic and foreign brand names.

18.1% of subjects in the clopidogrel arm and 18.7% in the ticagrelor arm were identified as having taken omeprazole (including brand names).

Based on this analysis, the primary outcome did not clearly differ between subjects identified as having had taken omeprazole or not, as presented in Table 56.

Table 56. Primary Outcome by Omeprazole Use

	N	HR(95%CI)
No omeprazole	15,195	0.82 (0.74, 0.91)
Omeprazole	3,429	0.91 (0.76, 1.09)

Source: R. Fiorentino, Clinical Reviewer

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

The rationale for the current ticagrelor 90mg twice daily dosing regimen is discussed in Section 8.2 and was based on data collected from phase 2 studies.

As PLATO only investigated one dosing regimen, 90mg bid, no other determination of the efficacy of alternative ticagrelor dosing can be made in the general ACS population.

That being said, ticagrelor exposure is increased with the concomitant use of some medications, including moderate or strong CYP3A inhibitors, such as diltiazem and ketoconazole, respectively. Within PLATO, only a small subset of subjects, n=264, were documented to have taken strong CYP3A inhibitors. Outcomes in these subjects remained comparable to the overall results, with HR=0.67 (95%CI: 0.37, 1.20). However the clinical relevance of concomitant drug-induced increased exposure to ticagrelor remains unclear.

Similarly, subjects noted to be <80% compliant with study drug (n=1,104) had similar outcomes compared to those documented to be compliant, as presented in Table 66. Primary Study Outcome by Compliance.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not relevant to proposed indication.

6.1.9 Additional Efficacy Issues/Analyses

6.1.9.1 Regional Differences

Region was prospectively defined in PLATO as, 1) Europe, Middle East and Africa, 2) North America, 3) Asia and Australia, and 4) Central and South America. In a prespecified analyses of 31 baseline factors, significant interactions were observed for region (p=0.0453). The HR point estimate for the primary endpoint numerically favored clopidogrel in the NA region and favored ticagrelor in each of the other 3 regions.

Further evaluation indicated that the observation was driven primarily by results in the US compared with the non-US countries. The HR point estimate for the primary endpoint within the US was 1.27 (95%CI: 0.92, 1.75) compared to 0.81 (95%CI: 0.74, 0.90) for the non-US region.

Figure 20 presents a forest plot that highlights the regional differences originally observed in PLATO.

Figure 20. Forrest Plot: Region
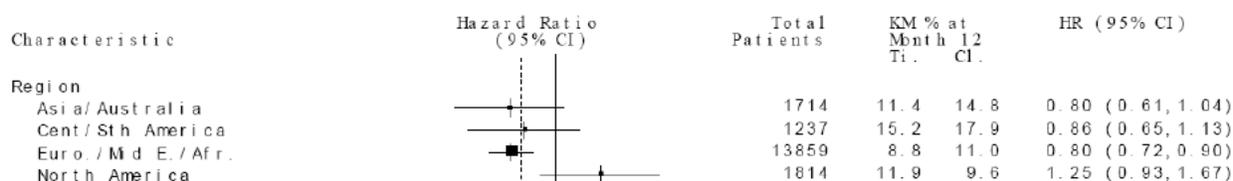
Source: Sponsor, CSR Fig. 16, page 159

In order to gain further insight into the regional differences, this reviewer re-classified the sponsor's regional definitions into 6 different categories, USA, Eastern Europe, Western Europe, Asia, Latin America and "Other" (Canada, Israel, South Africa and Australia). Table 57 presents the results across these regions as well as cumulative event rates for each of the .

Table 57. Cumulative Outcome Events Rates by FDA-defined Regions

Reclassified FDA Region	Primary Endpoint HR (Cox)	Arm	Primary Endpoint	MI (exc. Silent)	CV Death	Stroke
USA N=1413	1.27 (0.92, 1.75)	TIC n=707	84 (12%)	64 (9%)	24 (3%)	7 (1%)
		CLOP n=706	67 (9%)	47 (7%)	19 (3%)	4 (1%)
E. Europe N=7645	0.76 (0.65, 0.88)	TIC n=3820	299 (8%)	162 (4%)	150 (4%)	41 (1%)
		CLOP n=3825	394 (10%)	242 (6%)	173 (5%)	38 (1%)
W. Europe N=5429	0.84 (0.71, 1.00)	TIC n=2725	240 (9%)	157 (6%)	60 (2%)	40 (1%)
		CLOP n=2704	281 (10%)	169 (6%)	101 (4%)	36 (1%)
Asia N=1631	0.77 (0.58, 1.01)	TIC n=819	90 (11%)	37 (5%)	56 (7%)	13 (2%)
		CLOP n=812	114 (14%)	45 (6%)	75 (9%)	10 (1%)
L. America N=1237	0.86 (0.65, 1.13)	TIC n=621	91 (15%)	48 (8%)	43 (7%)	15 (2%)
		CLOP n=616	104 (17%)	52 (8%)	57 (9%)	13 (2%)
Other N=1269	1.11 (0.77, 1.60)	TIC n=641	60 (9%)	36 (6%)	20 (3%)	9 (1%)
		CLOP n=628	54 (9%)	38 (6%)	17 (3%)	5 (1%)

Other = Canada, Israel, South Africa, Australia; TIC=ticagrelor, CLOP=clopidogrel
Source: R. Fiorentino, Clinical Reviewer

The USA clearly has a numerically higher hazard ratio in favor of clopidogrel; albeit not statistically significant. Due to their relatively large sample size and point estimate, Eastern

Europe, and to a lesser extent, Western Europe, appear to make the greatest contribution to the overall outcome.

Of note, excluding Eastern Europe from the primary outcome analysis gives an overall HR=0.90, 95%CI (0.80, 1.01), p=0.07, n=10,979.

Similarly, excluding both Eastern Europe *and the US* gives an overall HR=0.86, 95%CI (0.76, 0.97), p=0.013, n=9,566.

6.1.9.2 US vs. non-US Outcomes

Table 58 compares the outcomes observed in the US alone with the non-US subgroup. Although the US results include a HR=1.0, the 95% confidence intervals in the US and non-US populations do exclude one other.

Table 58. Outcomes by US and non-US

	Ticagrelor	Clopidogrel	HR (95% CI)	P-value
Overall N=18,624	864/9333 (9.8%)	1014/9291 (11.7%)	0.84 (0.77, 0.93)	p<0.0001
Non-US n=17,211	780/8626 (9.6%)	947/8585 (11.8%)	0.81 (0.74, 0.90)	p<0.0001
US n=1,413	84/707 (12.6%)	67/706 (10.1%)	1.27 (0.92, 1.75)	P=0.146

Source: R. Fiorentino, Clinical Reviewer

Figure 21 presents a Kaplan-Meier failure plot in which the US results are overlaid on the non-US plot.

Figure 21. Kaplan-Meier plot of adjudicated primary endpoints by treatment in the US versus non-US
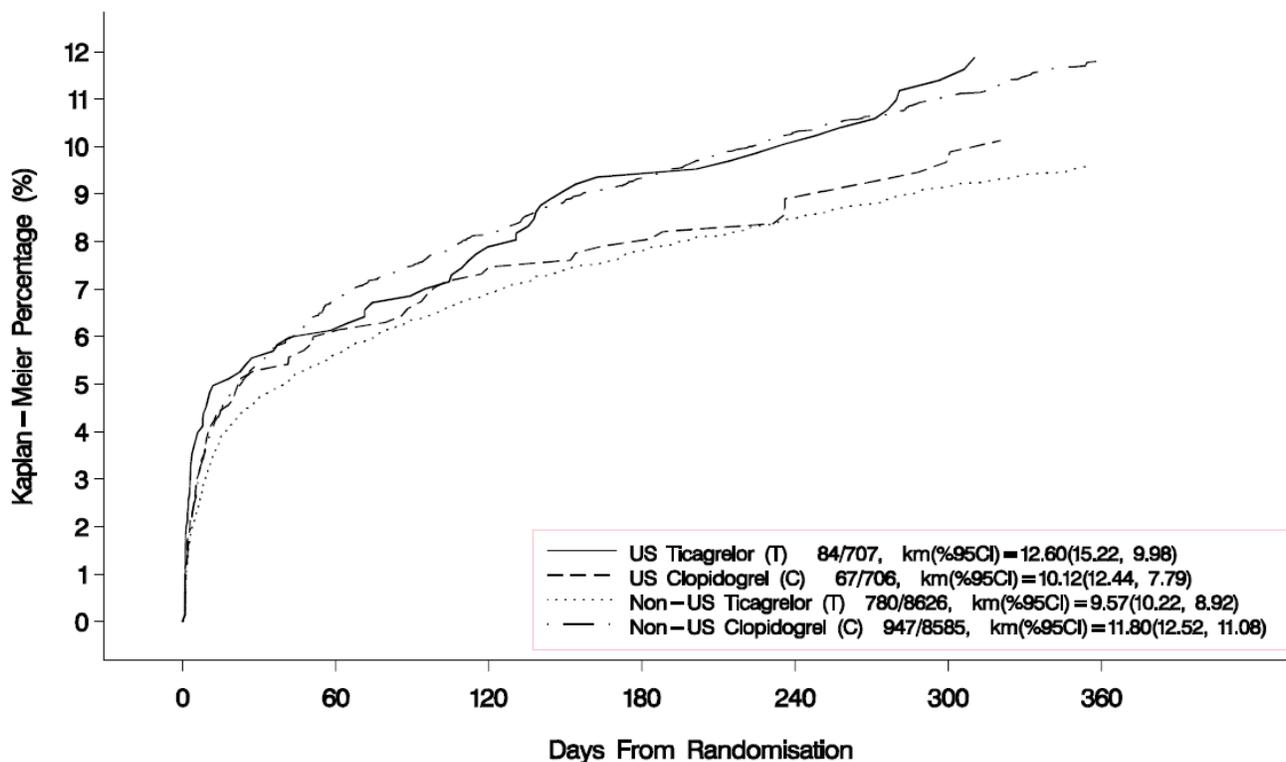
PATIENTS AT RISK

US(T)	707	644	627	602	512	405	306
US(C)	706	644	634	623	532	413	322
Non−US(T)	8626	7984	7833	7617	6231	4756	3841
Non−US(C)	8585	7877	7728	7501	6118	4683	3752

Source: Sponsor, Exploratory Analysis of Treatment Interactions in Plato, p.32, Fig. 4

Because the results obtained in the US were essentially the "reverse" of what had been observed in non-US, the sponsor considered the possible contribution of systematic errors in drug delivery at US sites. This was investigated by evaluation of records, pharmacokinetic analyses, and comparison of rates of dyspnea in the US and non-US populations, a biologic effect that was found in phase 2 studies to be related to ticagrelor exposure. Based on these findings, the sponsor was able to rule out systematic errors in drug delivery at US sites as an explanation for the observed treatment-by-region interaction.

Figure 22 presents K-M failure plots of the primary outcome for each of the six FDA-defined regions. Of note is a large separation occurring early in the Eastern Europe subgroup and continuing to diverge out to 1 year.

Figure 22. K-M Plot: Primary Outcome by FDA-defined Regions
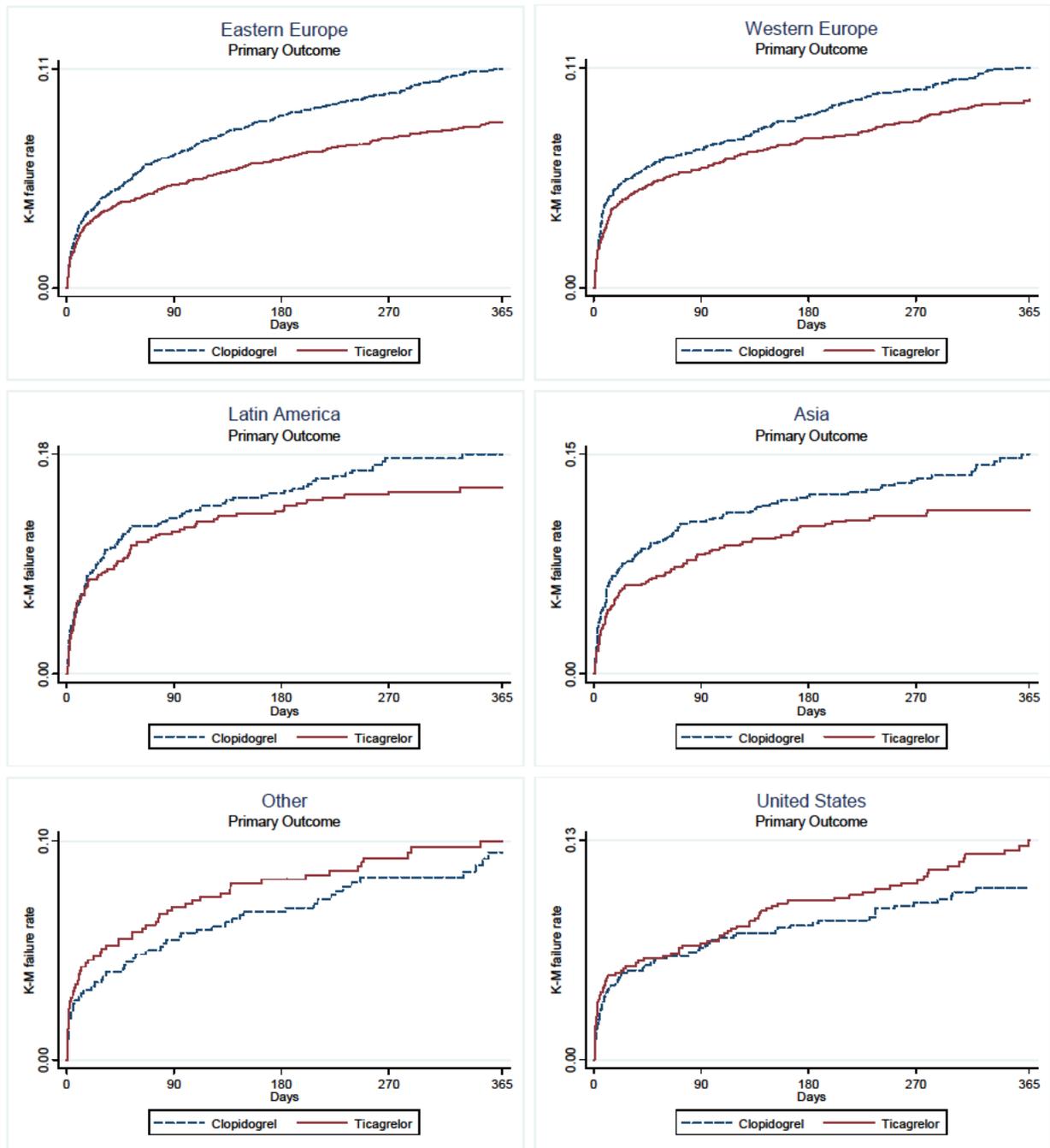
Other = Canada, Israel, South Africa, Australia
Source: R. Fiorentino, Clinical Reviewer

Figure 23 presents a forest plot of all countries in PLATO (excluding Hong Kong). In general, the HR point estimates appear symmetrically distributed around the overall HR of 0.84. Also

notable is the comparatively narrower confidence interval around the US results (near bottom) relative to other countries with HR>1.0.

Figure 23. Forrest Plot: HR by Country

COUNTRY	N	ES (95% CI)	% Weight
Turkey	51	0.25 (0.05, 1.18)	0.27
Singapore	64	0.47 (0.04, 5.20)	0.34
Greece	90	0.57 (0.14, 2.40)	0.48
Hungary	1267	0.59 (0.40, 0.86)	6.81
Indonesia	62	0.60 (0.19, 1.89)	0.33
India	575	0.65 (0.38, 1.09)	3.09
Switzerland	211	0.67 (0.24, 1.87)	1.13
Finland	154	0.67 (0.25, 1.76)	0.83
Netherlands	913	0.67 (0.43, 1.04)	4.91
France	422	0.67 (0.35, 1.30)	2.27
Philippines	78	0.68 (0.30, 1.54)	0.42
Poland	2666	0.69 (0.53, 0.90)	14.33
UK	281	0.74 (0.38, 1.46)	1.51
Brazil	690	0.76 (0.52, 1.10)	3.71
Ukraine	169	0.77 (0.31, 1.90)	0.91
China	416	0.77 (0.42, 1.43)	2.24
Bulgaria	451	0.79 (0.43, 1.47)	2.42
Malaysia	56	0.80 (0.28, 2.30)	0.30
Slovakia	336	0.81 (0.43, 1.51)	1.81
Belgium	170	0.83 (0.28, 2.46)	0.91
Czech Republic	1021	0.84 (0.55, 1.27)	5.49
Portugal	152	0.85 (0.35, 2.04)	0.82
Germany	1156	0.89 (0.62, 1.28)	6.21
Spain	314	0.90 (0.49, 1.68)	1.69
Romania	397	0.91 (0.48, 1.73)	2.13
Italy	625	0.95 (0.52, 1.75)	3.36
Sweden	347	0.95 (0.54, 1.67)	1.86
Thailand	152	0.96 (0.47, 1.97)	0.82
Mexico	137	0.97 (0.44, 2.17)	0.74
South Africa	149	0.99 (0.45, 2.16)	0.80
Argentina	410	1.02 (0.61, 1.68)	2.20
Israel	636	1.03 (0.59, 1.81)	3.42
Austria	143	1.04 (0.30, 3.61)	0.77
Norway	159	1.05 (0.43, 2.59)	0.85
Russia	678	1.06 (0.67, 1.68)	3.64
South Korea	120	1.13 (0.30, 4.20)	0.64
Georgia	519	1.16 (0.56, 2.37)	2.79
Canada	401	1.17 (0.59, 2.31)	2.15
Denmark	382	1.24 (0.60, 2.59)	2.05
USA	1413	1.27 (0.92, 1.75)	7.59
Taiwan	92	1.41 (0.45, 4.46)	0.49
Australia	83	2.45 (0.48, 12.65)	0.45
Overall (I-squared = 0.0%, p = 0.941)		0.87 (0.78, 0.96)	100.00

Excludes Hong Kong; weighted by N
Source: R. Fiorentino, Clinical Reviewer

Figure 24 presents a funnel-plot as a visual aid for illustrating asymmetry of treatment effect in the US subpopulation according to total events per country and observed HR. As an outlier, this plot could suggest that the outcomes in the US might not be due to a randomly driven process due to a power-related (event driven) issue, but instead to possibly a more systematic cause.

Figure 24. Funnel plot by Country
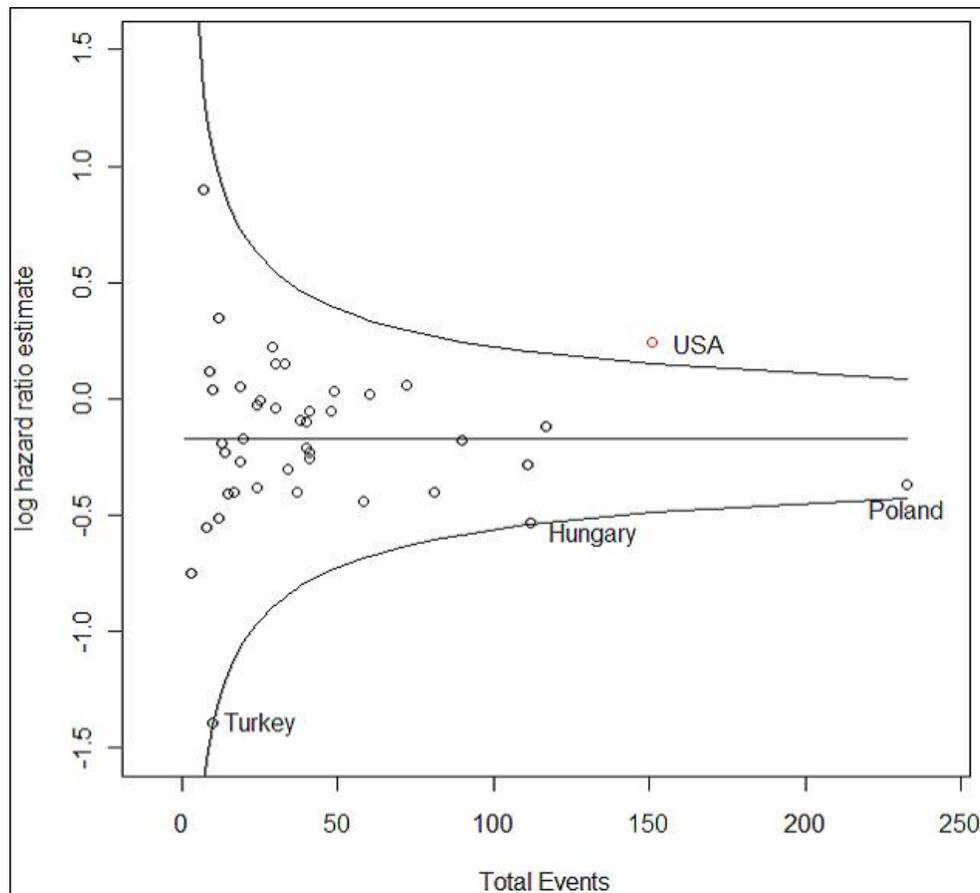
Source: Jialu Zhang, FDA Biostatistician

Table 59 provides a detailed tabulation of primary and secondary study outcomes by US and non-US regions.

Table 59. Adjudicated Endpoints by US and non-US Populations

EVENT	Region	n	Patients with Events	KM%	n	Patients with Events	KM%	Hazard Ratio (95% CI)	p-value	p-value (Int.)
			Ticagrelor 90 mg bd N=9333			Clopidogrel 75 mg od N=9291				
CV DEATH / MI (EXC SILENT) / STROKE	US	707	84 (11.9%)	12.6%	706	67 (9.5%)	10.1%	1.27 (0.92, 1.75)	0.1459	0.0092
	Non-US	8626	780 (9.0%)	9.6%	8585	947 (11.0%)	11.8%	0.81 (0.74, 0.90)	<0.0001	
CV DEATH	US	707	24 (3.4%)	3.7%	706	19 (2.7%)	2.7%	1.26 (0.69, 2.31)	0.4468	0.1190
	Non-US	8626	329 (3.8%)	4.0%	8585	423 (4.9%)	5.3%	0.77 (0.67, 0.89)	0.0005	
MI (EXC SILENT)	US	707	64 (9.1%)	9.6%	706	47 (6.7%)	7.2%	1.38 (0.95, 2.01)	0.0956	0.0065
	Non-US	8626	440 (5.1%)	5.5%	8585	546 (6.4%)	6.9%	0.80 (0.70, 0.90)	0.0004	
STROKE	US	707	7 (1.0%)	1.0%	706	4 (0.6%)	0.6%	1.75 (0.51, 5.97)	0.3730	0.5089
	Non-US	8626	118 (1.4%)	1.5%	8585	102 (1.2%)	1.3%	1.15 (0.88, 1.50)	0.2964	
ALL CAUSE MORTALITY	US	707	28 (4.0%)	4.2%	706	24 (3.4%)	3.6%	1.17 (0.68, 2.01)	0.5812	0.1406
	Non-US	8626	371 (4.3%)	4.6%	8585	482 (5.6%)	6.1%	0.77 (0.67, 0.88)	0.0001	

Source: Sponsor, Exploratory Analysis of Treatment Interactions in Plato, p.107, Table 1.7

Except for strokes, outcomes outside the US consistently favor ticagrelor against clopidogrel. In contrast, for the US subpopulation, the opposite is true. However, a numerical increase in strokes for the ticagrelor arm compared to clopidogrel is observed in both the US and non-US groups.

Within treatment arms, the US had lower rates of CV death, strokes and all-cause mortality, yet numerically higher rates of MI, plus a mixed-picture regarding the primary outcome (higher in ticagrelor, lower in clopidogrel)

Figure 25 presents a Kaplan-Meier plot of the primary outcome in the US. Notable is a late divergence beyond approximately 150 days following randomization.

Figure 25. K-M Curve: US Primary Outcome
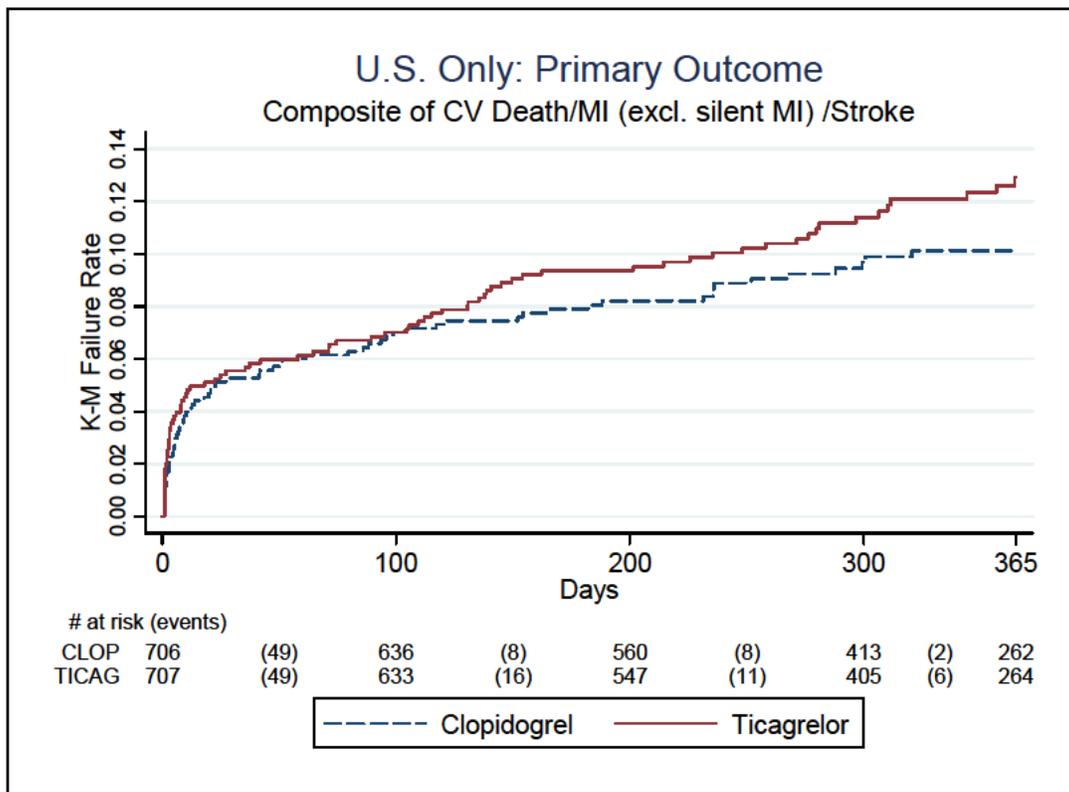
Source: R. Fiorentino, Clinical Reviewer

In contrast, within the US there was an early (non-significant) divergence in MI rates that persisted out to one year (Figure 26).

Figure 26. K-M Curve: U.S. Myocardial Infarctions
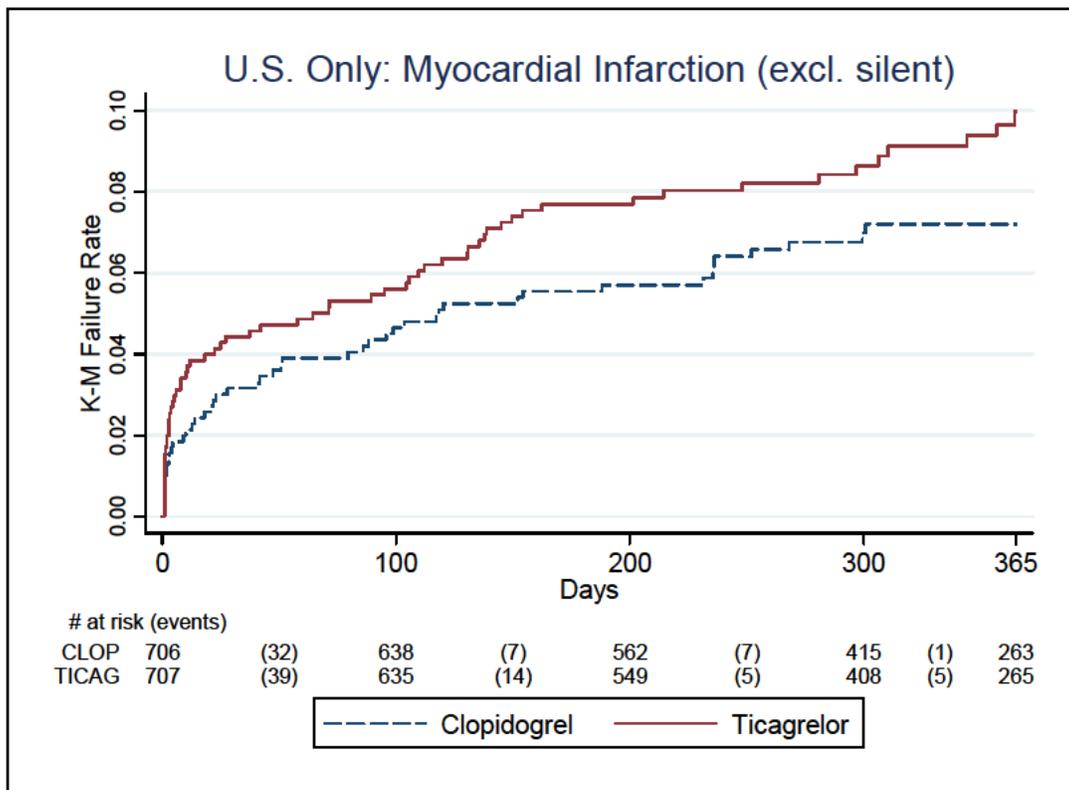
Source: R. Fiorentino, Clinical Reviewer

Further focus on the MI rate in the first 30 days post-randomization is illustrated in Figure 27 and illustrates the higher frequency of events occurring very early in the ticagrelor arm.

Figure 27. K-M Curve 30-day Landmark: U.S. Myocardial Infarctions
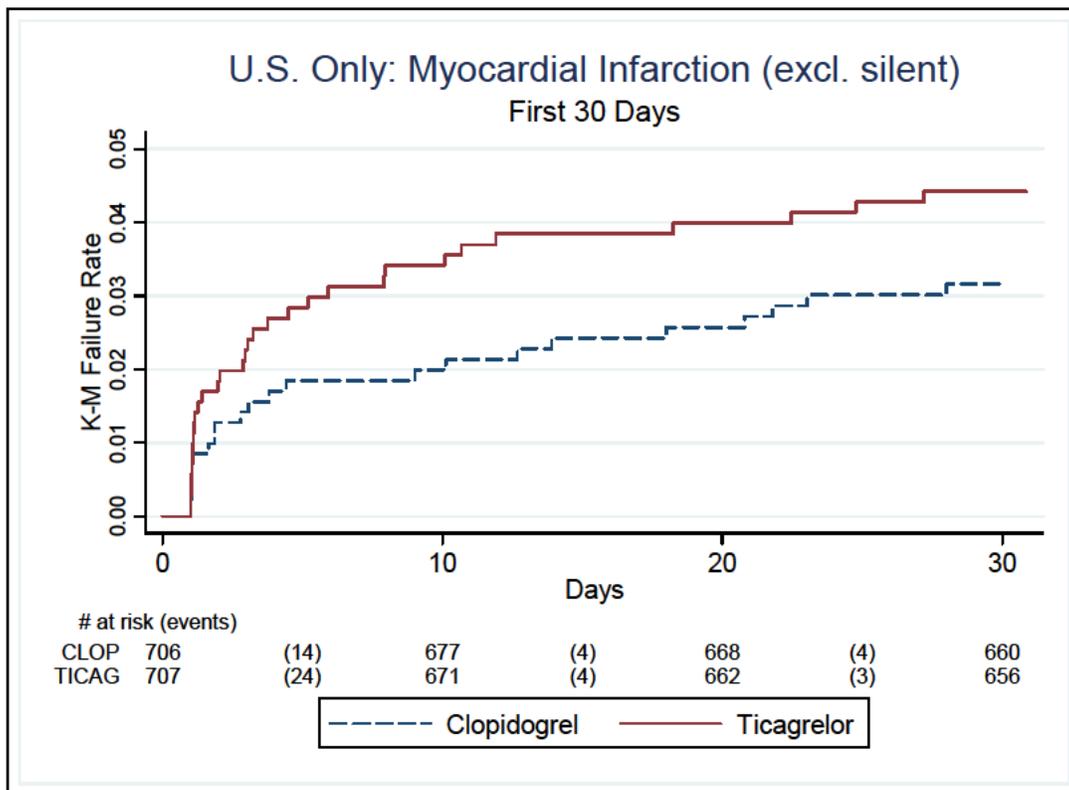
Source: R. Fiorentino, Clinical Reviewer

Figure 28 presents KM plot for CV death in the US. Although there appears an early divergence in the ticagrelor arm, the numbers of events are very small and the difference was non-significant.

Figure 28. K-M Curve: U.S. CV Death
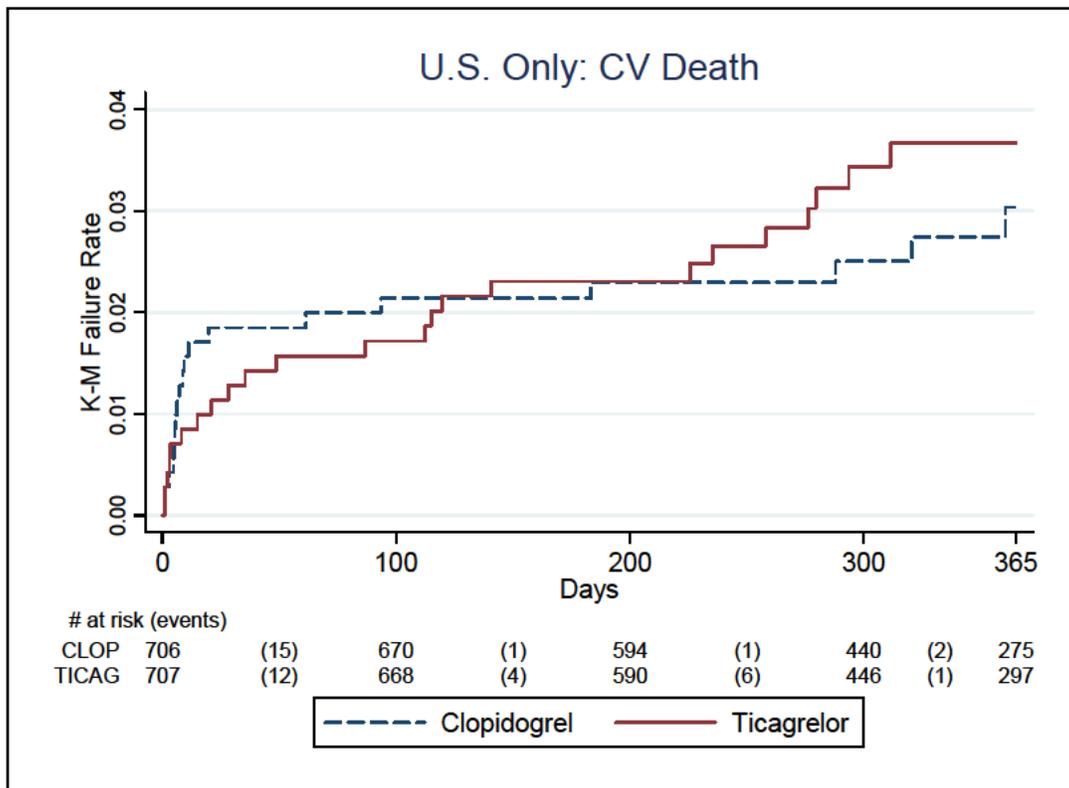
Source: R. Fiorentino, Clinical Reviewer

KM plot of strokes in the US are presented in Figure 29. The numbers of events were small.

Figure 29. K-M Curve: U.S. Strokes
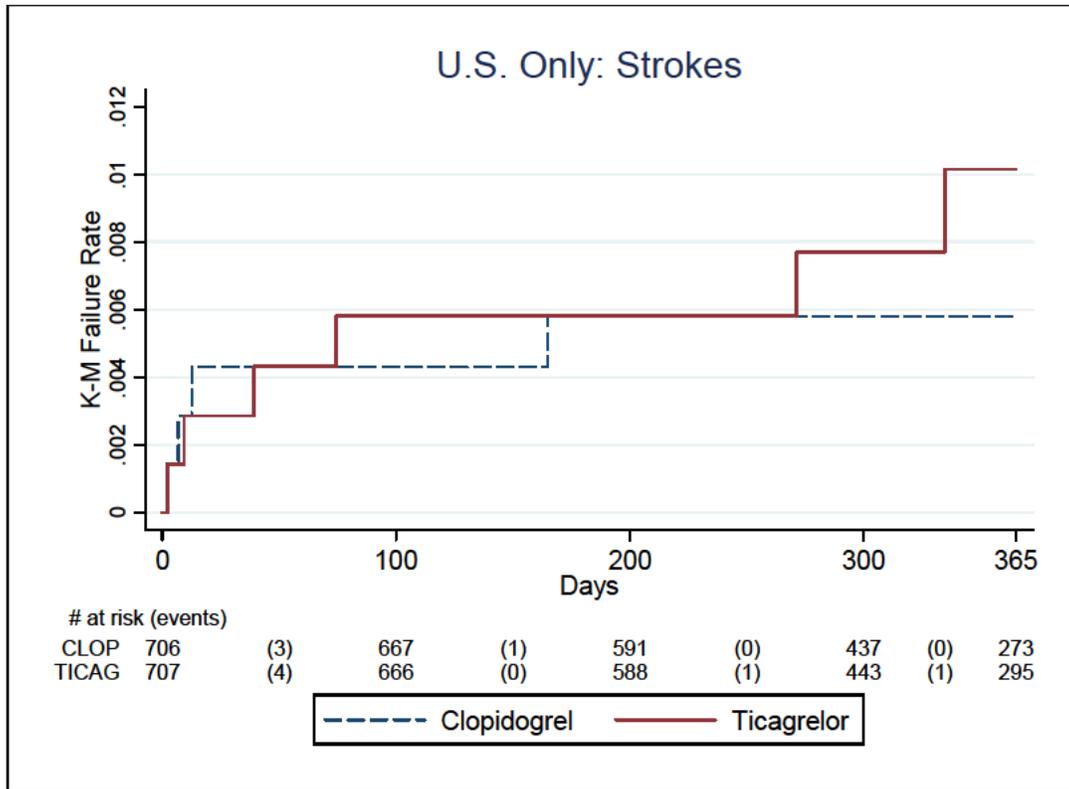
Source: R. Fiorentino, Clinical Reviewer

KM plot of all-cause mortality is presented in Figure 30, and closely follows the CV death failure plot (Figure 28) due to CV death being the primary contributor to overall death in the PLATO population.

Figure 30. K-M Curve: U.S. All-Cause Mortality
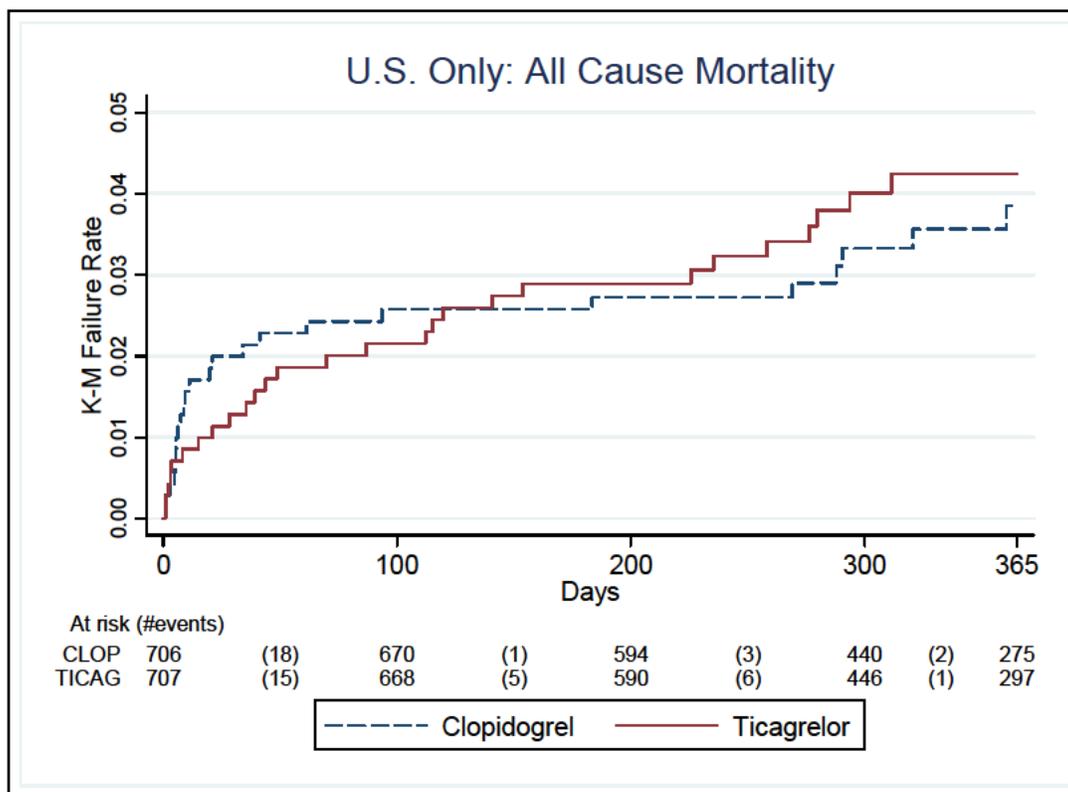
Source: R. Fiorentino, Clinical Reviewer

6.1.9.3 Analysis of US *vs.* non-US Populations

In order to provide insight into a possible explanation for the disparate outcomes observed between the US vs. non-US subgroups, a number of additional analyses were performed.

Table 60 presents the number of key baseline factors that have differences (or pertinent similarities) between the US and non-US study populations. For brevity, the large number of variables that were similar between the two subgroups are not shown.

Table 60. Key Baseline Factors: US vs. non-US

Factor	US (N=1,413)	Non-US (N=17,211)
Mean Age (SD)	61.1 (11.6)	62.3 (11.2)
Male sex, n (%)	1007 (71.3%)	12329 (71.6%)
Race		
Caucasian	1262 (89.3%)	15815 (91.9%)
Black	137 (9.7%)	92 (0.5%)
Oriental	9 (0.6%)	1087 (6.3%)
Habitual Smoker	515 (36.4%)	6163 (35.8%)
Weight, kg		
Mean (SD)	89.2 (20.6)	79.7 (15.3)
Median	88	76.5
Weight ≥ Gender-specific median	980 (69.4%)	8587 (49.9%)
Index event, n (%)		
UA	142 (10.0%)	2970 (17.3%)
NSTEMI	949 (67.2%)	7006 (40.7%)
STEMI	222 (15.7%)	6804 (39.5%)
Pre-index event antiplatelet therapy		
None	744 (52.7%)	11403 (66.3%)
Clopidogrel	35 (2.5%)	254 (1.5%)
ASA	482 (34.1%)	4542 (26.4%)
Clopidogrel + ASA	152 (10.8%)	956 (5.6%)
Clopidogrel Naïve*	1226 (87%)	16,001 (93%)
Diabetes mellitus, n (%)	472 (33.4%)	4190 (24.3%)
Prior PCI, n (%)	415 (29.4%)	2077 (12.1%)
Prior CABG, n (%)	236 (16.7%)	870 (5.1%)
Prior Stroke	49 (3.5%)	673 (3.9%)

*naïve = pre-index event antiplatelet agent documented none, ASA, or "other"
Source: R. Fiorentino, Clinical Reviewer

Although this analysis was *post hoc* in nature, a number of key differences are apparent. Among these are that the US population was heaver (based on both mean and median weights) by approximately 10kg (22lbs). The US also had a higher rate of diabetes, and higher rates of prior PCI and CABG. The prevalence of smokers between the US and non-US were similar.

The US also appeared to have higher use of clopidogrel and/or ASA, reflecting a more prevalent cardiac history. Most importantly, the index event characteristics differed substantially, with the US having a higher proportion of NSTEMI and lower proportion of STEMI subjects in PLATO than non-US subjects.

An analysis of key treatment-related factors also differed between the US and non-US populations, as presented in Table 61.

Table 61. Key Treatment-related Factors: US vs. non-US

Factor	US (N=1,413)	Non-US (N=17,211)
Time ≥12 hrs from index event to first dose of study drug, n (%)	893 (63.2%)	7,961 (46.3%)
Intended invasive management n (%)	1,323 (93.6%)	12,085 (70.2%)
Early PCI (w/in 24hrs)	866 (61.3%)	8,388 (48.8%)
Drug eluting stent, n(%) Ave. # DES implanted	653 (46%) 1.8	3,339 (19.4%) 1.6
Bare Metal stent, n(%) Ave. # BMS implanted	331 (23%) 1.5	7993 (46%) 1.5
GP IIb/IIIa use during index hospitalization, n (%)	709 (50.2%)	4,353 (25.3%)
β-blocker use on day of randomization	1,226 (86.8%)	12,834 (74.6%)
At least 80% compliance	1,210 (85.6%)	16,310 (94.8%)
ASA dose (median) mg* Median Mean	 325 217	 100.0 99
Subjects with median ASA dose* (median) ≥300 mg	618 (44%)	239 (1.4%)

* excludes ASA doses before the first 5 days and following primary event;
includes subjects with available ASA doses (at least 2)
Source: R. Fiorentino, Clinical Reviewer

First, the US had a higher proportion of subjects with ≥12 hours from index event to study drug, reflecting the lower proportion of STEMI subjects who have more urgent treatment demands. However, the US also had higher proportions of intent to invasively manage (with PCI), more early PCI, more frequent use of drug eluting stents (but less frequent BMS) and higher rates of GP IIb/IIIa use during index hospitalization.

These analyses suggest that the US population had different baseline factors at the time of enrollment and subsequently underwent different treatment strategies compared to the general non-US population.

Table 62 and Table 63 provide additional information regarding various treatment-related factors comparing the US to the non-US population. Of specific note is a longer time from index event to investigational product and longer time from hospitalization to PCI, again possibly explained by different baseline characteristics in the US, as discussed previously.

Table 62. Treatment Factor: US vs. non-US

Interval Factor (medians)	US (hours)	Non-US (hours)
Index Event to Randomization	15.3	10.1
Index Event to IP	16.7	10.8
Randomization to IP	0.57	0.32
Index Event to Hospital Admission	2.8	2.8
Total Hospital Days	5 days	9 days

IP = investigational product
Source: R. Fiorentino, Clinical Reviewer

Table 63. Treatment Interval by US vs. non-US: Time to PCI

Interval Factor (median times)	US (hours)	Non-US (hours)
Index Event to PCI	17.6	10.4
Randomization to 1st PCI	1.1	0.97
IP to 1st PCI	0.23	0.65
Randomization to Early PCI (w/in 24hrs)	0.99	0.62
Hospitalization to PCI (approx. "door-to-balloon")	11.07	1.75
Index event to early PCI	16.8	6.58
IP to early PCI	0.20	0.33

IP = Investigational Product
Source: R. Fiorentino, Clinical Reviewer

Table 64 presents the above treatment time intervals according to index presentation. Of note is the similar time intervals for STEMI patients in the US and non-US groups, with variability in times across other index events. The small number of subjects in these subgroups and incompleteness of data may introduce some random variability into these estimates.

Table 64. US vs. non-US: Median Time to Treatment Intervals

Time Interval (hrs where not spec.)	STEMI		NSTEMI		UA	
	non-US	US	non-US	US	non-US	US
Days in Hospital	8	5	9	5	8	6
IE to Rand	4.7	4.3	15.4	16.5	12.9	15.6
IE to IP	5.0	4.7	16.3	18.4	13.8	17.7
IE to EarlyPCI	4.7	4.2	16.8	18.9	14.7	18.6
IE to PCI	5.0	4.2	26.7	19.6	27.8	19.4
IE to Hosp	2.9	2.6	2.9	2.8	2.4	2.5
Rand. To 1st PCI	0.5	0.4	6.9	1.5	17.2	1.5
Rand. To EarlyPCI	0.5	0.4	1.6	1.3	1.3	1.4
Rand. To IP	0.2	0.3	0.4	0.6	0.4	0.7
Hospital Adm. To PCI	1.2	1.3	10.6	14.4	8.6	13.8
IP to 1st PCI	0.3	0.1	6.3	0.3	16.3	0.4
IP to EarlyPCI	0.2	0.1	1.1	0.3	0.8	0.3

IP= Investigational Product, IE = Index Event, Rand. = Randomization
EarlyPCI = ± 24hrs from randomization
All times are medians.
Source: R. Fiorentino, Clinical Reviewer

There were a number of key differences in medication use as documented at the time of randomization between the US and non-US groups, as presented in Table 65. This included higher use of proton pump inhibitors (PPI), β-blockers, glycoprotein IIb/IIIa inhibitors (as noted previously) and lower documented use of ACE inhibitors.

Table 65. Medication Use at the Time of Randomization

	Treatment	PPI	ACE-I	ARB	β-blocker	CCB	GPI	heparin	Lipid lowering agent
Non-US	Clopidogrel	33.8%	57.1%	8.5%	75.0%	14.9%	25.4%	63.9%	79.7%
	Ticagrelor	33.5%	57.3%	8.5%	74.2%	14.4%	25.2%	63.8%	80.1%
	Total	**33.6%**	**57.2%**	**8.5%**	**74.6%**	**14.7%**	**25.3%**	**63.8%**	**79.9%**
US	Clopidogrel	39.2%	47.2%	12.2%	86.8%	15.3%	50.8%	66.9%	78.3%
	Ticagrelor	43.8%	48.4%	13.7%	86.7%	14.3%	49.5%	66.1%	77.9%
	Total	**41.5%**	**47.8%**	**13.0%**	**86.8%**	**14.8%**	**50.2%**	**66.5%**	**78.1%**

Source: R. Fiorentino, Clinical Reviewer

PPI and Omeprazole Use

In this reviewer's analysis, PPI use *documented at anytime during the trial* in the US was approximately 51% compared to 60% non-US subjects. In the US, 57% of subjects in the clopidogrel arm took a PPI, whereas 63% in the ticagrelor arm did so. Also, within the US, the hazard ratio for subjects not documented as having taken a PPI was 1.01 [95%CI(0.57, 1.80), n=568] compared to 1.37 [95%CI(0.93, 2.03), n=843] in those who took a PPI.

The specific use of omeprazole was investigated by searching the medication dataset for use of omeprazole, requiring the determination of both generic and foreign brand names. Although the US had comparable rates of omeprazole use (17%) versus non-US (19%), in the US the estimated omeprazole use was slightly higher in the ticagrelor arm (19.0% vs. 15.6%). Further, although a numerical difference was notable, the hazard ratio on the primary outcome for subjects in the US who took omeprazole (HR=0.81, 95%CI:0.41, 1.60, n=244) was not statistically different that those subjects who did not (HR=1.40, 95%CI: 0.98, 2.02, n=1169).

Compliance Data

According to the sponsor, at each study visit the investigator assessed the patient's compliance with study medications and recorded it in the eCRF. If the patient reported taking more than 80% of the expected doses of study medication between each visit the investigator regarded the patient as compliant.

In the study overall (US and non-US), there was no clear association between compliance and primary outcomes as presented in Table 66.

Table 66. Primary Study Outcome by Compliance

Compliance ≥80%	N subjects	HR (95%CI)
Yes	17,520	0.84 (0.77, 0.93)
No	1,104	0.83 (0.62, 1.12)

Source: R. Fiorentino, Clinical Reviewer

Similarly, there was no clear relationship observed between compliance rate by country and outcome, as presented in Figure 31.

Figure 31. Primary HR and Compliance rate by Countries
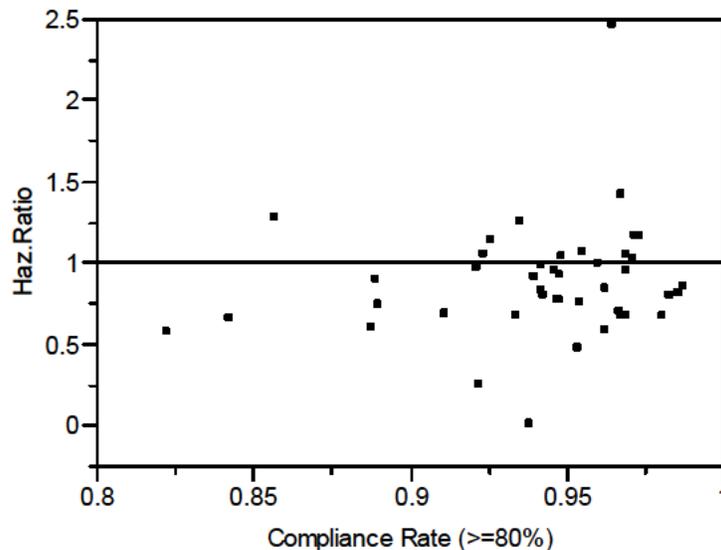
Source: R. Fiorentino, Clinical Reviewer

However, the USA had lower mean compliance rates (Table 67), as recorded by the CRFs and defined as at least 80% compliant with study medication (via sponsor's derivation).

Table 67. Compliance US vs. non-US

	N	≥80% compliant	Mean compliance rate (≥80%)
Non-US	17,211	16,310	94.8%
US	1,413	1,210	85.7%

Source: R. Fiorentino, Clinical Reviewer

Furthermore, although sample sizes are small, poorer compliance in the US was associated, at least numerically, with a greater hazard ratio with respect to the primary endpoint (Table 68). However the relationship between non-compliance and adverse outcomes is potentially confounded by concomitant illnesses or related events.

Table 68. US: Primary Outcomes by Compliance

US (n=1413)	Ticagrelor	Clopidogrel	HR by treatment (95%CI)	p-value
Compliant (n=1210)	68/604	60/606	1.14 (0.81, 1.62)	0.454
Non-compliant (n=203)	16/103	7/100	2.41 (0.99, 5.86)	0.053

Source: R. Fiorentino, Clinical Reviewer

Further exploratory analyses were performed on subgroups that previously had been identified to differ between the US and non-US populations.

Table 69 presents US primary outcome according to index ACS events. Because almost 70% of subjects in the US had NSTEMI as the index ACS event, this subgroup provides the greatest contribution to the overall US outcome. In the US, outcomes were relatively unfavorable in both STEMI and NSTEMI groups, with a numerically trend toward relative benefit in UA subjects.

Table 69. U.S.: Primary Outcome by Index ACS Event

	N	Clopidogrel events/n	Ticagrelor events/n	Cox HR (95%CI)
Unstable Angina	142	9/66	8/76	0.73 (0.28, 1.89)
NSTEMI	949	47/471	60/478	1.29 (0.88, 1.89)
STEMI	222	10/117	14/105	1.56 (0.69, 3.52)
Other*	98	1/51	2/47	2.24 (0.20, 24.7)

* as documented on CRF; 2 subjects with "unknown" index ACS event
Source: R. Fiorentino, Clinical Reviewer

Table 70 presents the primary outcome in the US according to planned invasive strategy and presence or absence of PCI. It should be noted that in this analysis, the event "flag" for having either an early PCI or any PCI excluded subjects who had a primary event before the PCI.

Although this analysis is *post hoc* and limited by small subgroup sample sizes, a trend toward higher hazard ratios was observed in subjects who underwent PCI across three categories: planned invasive strategy, early PCI (+/- 24hrs of randomization) and any PCI (with outcomes potentially highly-correlated across these groups).

Table 70. U.S.: Primary Outcome by Planned and Actual PCI subgroups

U.S. Only	N	Clopidogrel events/n	Ticagrelor events/n	Cox HR (95%CI)
Planned Invasive Strategy				
Yes	1,323	58/664	74/659	**1.30** (0.92, 1.84)
No	90	9/42	10/48	**0.98** (0.40, 2.40)
Early PCI (<24hrs)*				
Yes	866	37/437	54/429	**1.50** (0.99, 2.28)
No	546	30/269	30/277	**0.98** (0.59, 1.62)
PCI*				
Yes	930	41/472	59/458	**1.50** (1.01, 2.24)
No	482	26/234	25/248	**0.91** (0.53, 1.58)

* For subjects who did not have a primary event prior to PCI occurrence
Source: R. Fiorentino, Clinical Reviewer

To further investigate this finding, an analysis was performed to compare primary outcomes in US and Non-US subjects who underwent PCI. Again, the analysis excluded subjects who had primary events before the PCI (due to possible confounding).

Table 71 presents the result of the analysis and demonstrated that the subgroups which did not undergo PCI had more favorable benefit from ticagrelor in PLATO than those who had a PCI, with the divergence being most pronounced in the US. However, because the investigators determined who went to PCI, in part based on clinical findings, the association is potentially confounded by other disease-related variables.

Table 71. US vs. non-US: Primary Events in Subjects with/without PCI

	N	Clopidogrel events/n	Ticagrelor events/n	Cox HR (95%CI)
PCI [1]				
US	930	41/472	59/458	**1.50** (1.01, 2.24)
non-US	10,920	504/5459	425/5466	**0.84** (0.74, 0.95)
Overall	11,850	545/5931	484/5924	**0.89** (0.78, 1.00)
No PCI				
US	482	26/234	25/248	**0.91** (0.53, 1.58)
non-US	6,281	443/3126	355/3155	**0.79** (0.69, 0.91)
Overall	6,763	469/3360	380/3403	**0.80** (0.70, 0.91)

[1] Calculates the number of days from first PCI to the first occurrence of the primary endpoint or censored date if the subject did not experience a primary endpoint for patients with PCI during the study.
Source: R. Fiorentino, Clinical Reviewer

As noted previously, because treatment strategy (PCI vs. no PCI) may depend on the index ACS event type, an analysis of primary outcomes according to index event and PCI was performed to compare outcomes in the US vs. non-US populations.

Table 72 presents the result of this analysis. In the non-US population there was not a clear trend across each subgroup and the US population was limited by the small size in each subgroup. UA represented the subgroup with the most similar outcomes between the US and non-US, but the reason for this is unclear.

Table 72. US vs. non-US: Primary Outcome by Index Event and Treatment Strategy

	UA		NSTEMI		STEMI	
	n/N	HR (95%CI)	n/N	HR (95%CI)	n/N	HR (95%CI)
US						
PCI	T: 4/42	0.66	T: 42/319	1.46	T: 13/88	2.18
	C: 5/39	(0.18, 2.46)	C: 29/314	(0.91, 2.35)	C: 7/101	(0.87, 5.44)
No PCI	T: 4/34	0.83	T: 18/159	1.01	T: 1/17	0.30
	C: 4/27	(0.21, 3.31)	C: 18/157	(0.53, 1.94)	C: 3/16	(0.03, 2.86)
Planned Inv. Treatment	T: 7/67	0.74	T: 51/447	1.32	T: 14/105	1.56
	C: 8/60	(0.27, 2.04)	C:39/438	(0.87, 2.00)	C: 10/117	(0.69, 3.52)
Planned Med. Mgmt	T: 1/9	0.68	T: 9/31	1.25	T: 0/0	n/a
	C: 1/6	(0.04, 11.0)	C: 8/33	(0.48, 3.25)	C: 0/0	
NON-US						
PCI	T: 45/490	1.12	T: 157/1930	0.75	T: 215/3004	0.86
	C: 44/535	(0.74, 1.70)	C: 203/1904	(0.61, 0.92)	C: 248/2986	(0.72, 1.04)
No PCI	T: 71/983	0.90	T: 215/1597	0.81	T: 52/387	0.70
	C: 79/962	(0.65, 1.23)	C: 260/1575	(0.67, 0.97)	C:79/427	(0.50, 1.00)
Planned Inv. Treatment	T: 52/609	0.98	T: 191/2117	0.74	T: 236/3173	0.84
	C: 57/650	(0.67, 1.42)	C: 245/2043	(0.61, 0.90)	C: 283/3180	(0.70, 0.99)
Planned Med. Mgmt	T: 64/864	0.97	T: 181/1410	0.83	T: 31/218	0.73
	C: 66/847	(0.69, 1.37)	C:218/1436	(0.68, 1.01)	C: 44/233	(0.46, 1.16)

Source: R. Fiorentino, Clinical Reviewer

An analysis of the time from index ACS event to investigational product in the US and stratified by index ACS event is presented in Table 73. From this, it is clear that the STEMI population is being enrolled sooner into PLATO, as might be expected for this population. An analysis of subjects who received investigational product above or below their median times according to ACS index event, did not show a clear outcome trend, although the divergence in UA across groups is notable.

Table 73. U.S.: Primary Outcome by Time from Index Event to Investigational Product (IP)

U.S. Only	Median time from Index Event to IP	< Median time (index event to IP)		≥ Median time (index event to IP)	
		n/N	HR(95%CI)	n/N	HR(95%CI)
Unstable Angina	17.7 hrs	T: 6/41	1.22	T: 2/35	0.36
		C: 3/27	(0.30, 4.88)	C:6/39	(0.07, 1.78)
NSTEMI	18.4 hrs	T: 23/232	1.15	T: 37/246	1.40
		C: 20/227	(0.63, 2.10)	C: 27/244	(0.85, 2.30)
STEMI	4.7 hrs	T: 6/47	1.55	T: 8/58	1.53
		C: 5/61	(0.47, 5.08)	C: 5/56	(0.50, 4.69)

IP = Investigational Product, T=ticagrelor, C=clopidogrel
Source: R. Fiorentino, Clinical Reviewer

For comparison,
Table 74 presents the same analysis as above but in the non-US population. Again, at least numerically, the results in the non-US group are more favorable in the ticagrelor arm.

Table 74. Non-US: Primary Outcome by Time from Index Event to Investigational Product (IP)

Non-US	Median time from Index Event to IP	< Median time (index event to IP)		≥ Median time (index event to IP)	
		n/N	HR(95%CI)	n/N	HR(95%CI)
Unstable Angina	13.8 hrs	T: 57/752	1.13	T: 59/721	0.87
		C: 49/718	(0.77, 1.65)	C: 74/779	(0.62, 1.23)
NSTEMI	16.3 hrs	T:167/1763	0.66	T:205/1764	0.92
		C:242/1711	(0.54, 0.80)	C:221/1768	(0.76, 1.11)
STEMI	5.0 hrs	T:104/1670	0.83	T:163/1721	0.81
		C:125/1673	(0.64, 1.08)	C:202/1740	(0.66, 1.00)

IP = Investigational Product, T=ticagrelor, C=clopidogrel
Source: R. Fiorentino, Clinical Reviewer

Finally, because of differences in the dose of concomitant ASA between the US and non-US and observed difference in outcome according to PCI treatment, further investigation was performed to indentify any relationship between these two outcome (Section 6.1.9.4)

6.1.9.4 Investigation of a Possible Aspirin-Treatment Interaction

Overview

It was observed within PLATO that the US subgroup took larger doses of concomitant aspirin during the study. In particular, the US population was virtually the only country to use the 325mg dose of concomitant aspirin (in addition to 81mg) and had an estimated mean aspirin dose of approximately 220 mg daily. During the review of the NDA a number of questions were raised and addressed regarding the definition and derivation of the aspirin doses presented in the original dataset.

The sponsor had provided a revised ASA dataset to the FDA during the review of the NDA that corrected apparent programming errors used to derive the ASA doses. In addition, discussions during an FDA/sponsor meeting on June 7, 2010, focused on the most appropriate analysis methods to be used on the ASA data. This included restricting the definition of ASA doses to include only the ASA data recorded before a primary event, such that changes in doses due to events would not confound the analysis. Similarly, it also seemed practical to provide a derived ASA dose for subjects who discontinued ASA before having a primary event (a small number). Also, because subjects can receive high ASA loading doses at very early timepoints during which treatment strategy may be highly variable and intensive with other medications/interventions, it seemed more robust to include a derivation that restricted the inclusion of ASA doses in this period. Finally, it was also discussed whether only subjects who had two or more recorded doses of ASA would provide more useful data. The rationale for these analysis methods was generally accepted for subsequent analyses, but remains fundamentally arbitrary in nature.

The following definitions of ASA dose were submitted by the sponsor and their respective means of derivations are presented below:

MEDIAN20
- Includes all aspirin during the study drug period for patients who did not have an event
- For patients who had a primary event, it includes all aspirin up to the time of the event
- Excludes patients with less than 5 days of aspirin
- If a patient had 5 doses of aspirin under these rules, all 6 doses would be included in the calculation

MEDIAN24
- Follows the same rules as MEDIAN20, with the exception that it excludes patients with less than 2 days of aspirin.

MEDIAN25
- Follows the same rules as MEDIAN20, with the exception that it excludes patients with no aspirin records.

MEDIAN55
- Excludes the initial (loading) dose
- Counts aspirin up to the minimum of the date of the event or the date of stopping study drug, for patients who had a primary event.

Table 75 presents the median and mean ASA doses in the US compared to the non-US population, according to the definitions above. The median ASA dose by US vs. non-US is consistent across definitions of median ASA dose (325mg vs. 100mg). However the average median ASA dose varies slightly according to the definition used to derive the ASA dose.

Table 75. Mean and Median ASA doses by US vs. non-US

	Median of Median ASA doses	Mean of Original ASA Mean Dose (SD)	Mean of MEDIAN20	Mean of MEDIAN24	Mean of MEDIAN25	Mean of MEDIAN55
US	325	223 (249)	217	219	222	219
Non-US	100	101 (42)	99	101	107	100

Source: R. Fiorentino, Clinical Reviewer

It should be noted that the average of the mean ASA doses differed only slightly from average of the median doses by US vs. non-US.

Figure 32 presents the distribution of median aspirin dose in the US subgroup (as calculated by the total doses of aspirin recorded divided by the number of days on record). Of note is the nearly dichotomous use of ASA 81mg and 325mg in the US.

Figure 32. US: Distribution of Mean Aspirin Use
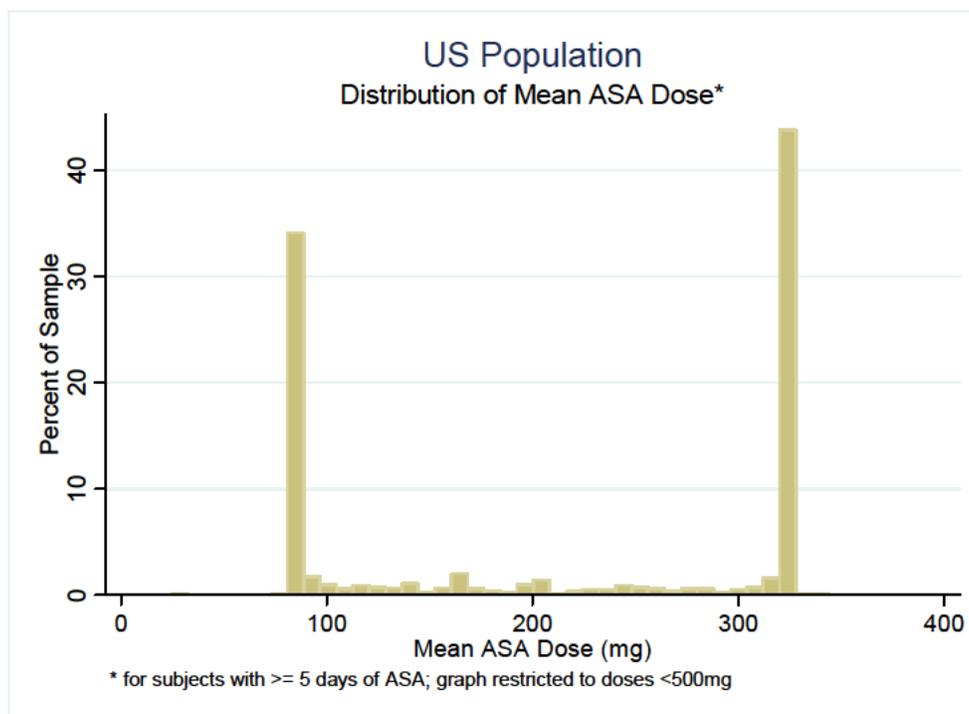
Source: R. Fiorentino, Clinical Reviewer

The distribution of median ASA doses in the US follows a similar pattern (Figure 33).

Figure 33. US: Distribution of Median ASA Dose
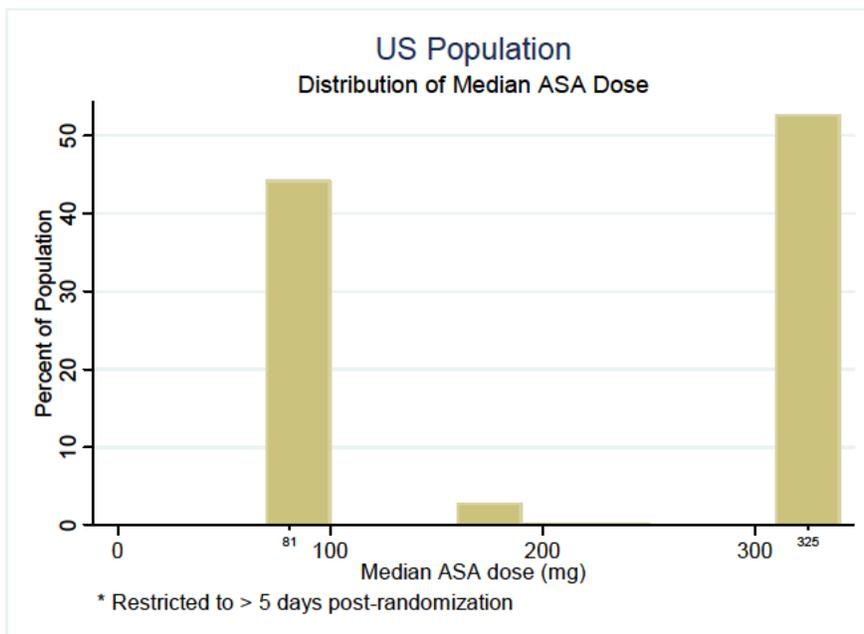
Source: R. Fiorentino, Clinical Reviewer

In contrast, the distribution of mean and median ASA doses in the non-US subgroup are predominantly of the 75mg and 100mg doses (Figure 34 & Figure 35).

Figure 34. Non-US: Distribution of Mean ASA Dose
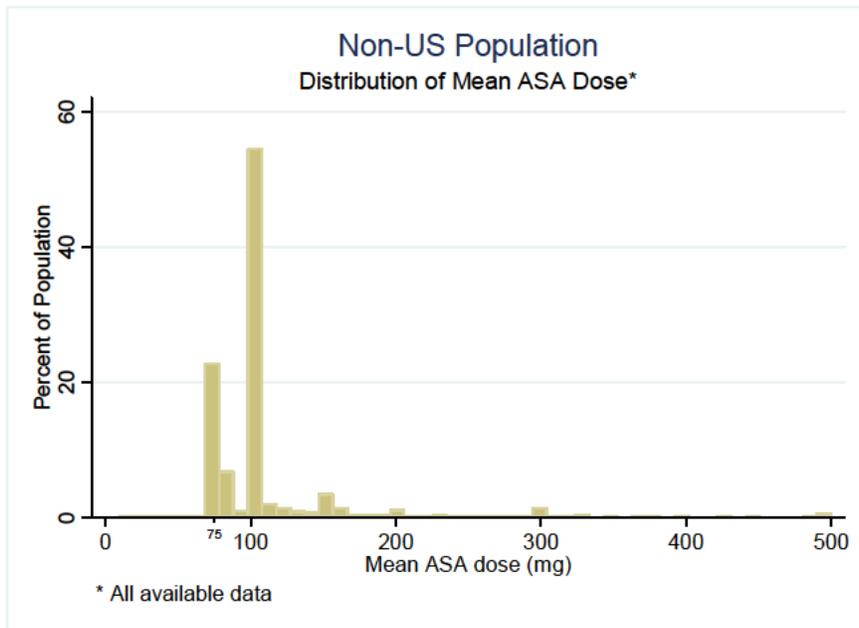
Source: R. Fiorentino, Clinical Reviewer

Figure 35. Non-US: Distribution of Median ASA Dose
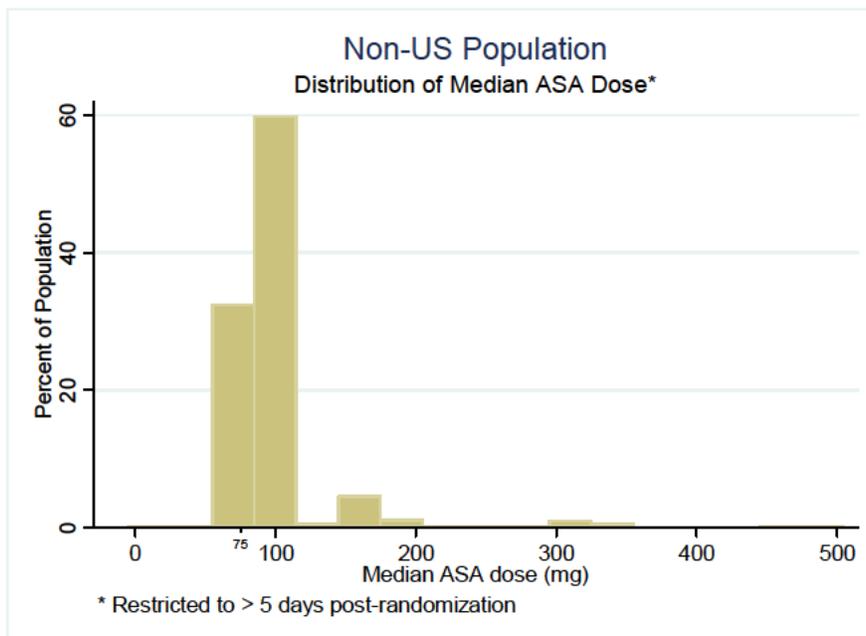
Source: R. Fiorentino, Clinical Reviewer

In general, the use of the revised definitions and data correction produced analyses that estimated a lower HR for the lower-dose (81mg subgroup) in the US than the original analysis. The clinical significance of this is unclear, but illustrates the moderate sensitivity of analyses using the ASA data to arbitrary derivations of mean and median doses.

However, as presented in Table 76 and Table 77, analyses on both the original dataset and the corrected and revised methodology are presented.

Table 76. US: Primary Endpoint by Mean ASA dose category*

Mean ASA Dose Group (mg)	ORIGINAL Analysis		REVISED* Analysis	
	n/N	HR (95%CI)	n/N	HR (95%CI)
<100	T:24/242 C:24/233	0.97 (0.55, 1.70)	T:17/233 C:21/228	0.80 (0.42, 1.52)
100 to 300	T:11/120 C:10/96	0.88 (0.38, 2.08)	T:6/107 C:6/86	0.80 (0.26, 2.45)
>300	T:49/345 C:33/377	1.67 (1.08, 2.60)	T:61/367 C:40/392	1.68 (1.13, 2.51)

* ASA Definition MEDIAN55; T=ticagrelor, C=clopidogrel
Source: R. Fiorentino, Clinical Reviewer

Table 77. US: Primary Endpoint by Median* ASA dose

Median ASA Dose (mg)	ORIGINAL Analysis		REVISED* Analysis	
	n/N	HR (95%CI)	n/N	HR (95%CI)
81	T: 28/295 C: 27/272	0.96 (0.57, 1.63)	T: 19/283 C: 23/262	0.76 (0.42, 1.40)
162	T: 2/21 C:1/14	1.51 (0.14, 16.7)	T: 2/18 C: 2/13	0.76 (0.11, 5.41)
325	T: 49/349 C: 34/368	1.56 (1.01, 2.41)	T: 40/320 C: 27/347	1.62 (0.99, 2.64)

* ASA Definition MEDIAN55; T=ticagrelor, C=clopidogrel
Source: R. Fiorentino, Clinical Reviewer

In contrast, corresponding Table 78 and Table 79 present the primary endpoint hazard ratios by mean and median aspirin dose strata (where data is available) in the *non*-US subgroup. All data is based on the corrected and revised methodology to analyzing the ASA datasets.

Table 78. Non-US: HR Primary Endpoint by Mean ASA Dose Category*

Mean ASA Dose (mg)	n/N	HR (95%CI)
<100	T: 181/2640 C: 246/2638	**0.73** (0.60, 0.88)
100 to 300	T: 447/5409 C: 535/5408	**0.83** (0.73, 0.94)
>300	T: 168/644 C: 180/598	**0.84** (0.67, 1.05)

*Mean55 definition; T=ticagrelor, C=clopidogrel
Source: R. Fiorentino, Clinical Reviewer

Table 79. Non-US: Outcomes by ASA Dose*

ASA Dose* (mg)	n/N	HR (95%CI)
<75	T:1/20 C:2/17	**0.42** (0.04, 4.64)
75	T:145/2134 C:204/2134	**0.70** (0.57, 0.87)
80/81mg	T:36/464 C:43/469	**0.85** (0.54, 1.31)
100	T:364/4830 C:450/4823	**0.80** (0.70, 0.92)
101-199	T:37/401 C:46/421	**0.84** (0.54, 1.29)
200/250	T:23/99 C:17/90	**1.29** (0.69, 2.42)
300	T:20/90 C:18/82	**1.01** (0.54, 1.92)
325	T:5/43 C:5/50	**1.17** (0.34, 4.03)
>325	T:3/7 C:0/8	n/a
unknown	T:144/534 C:162/491	**0.80** (0.64, 1.00)

Definition MEDIAN55 used. T=ticagrelor, C=clopidogrel
Source: R. Fiorentino, Clinical Reviewer

The above analyses illustrates that the majority of patients fall into only a few discrete ASA dose strata. In the US, this is represented by the 81mg and 325mg groups; outside the US, this is primarily the 75mg and 100mg groups. The small number of subjects in some ASA dose groups, particularly the non-US population with ASA >200mg, makes it difficult to establish clear outcome trends across multiple dose categories.

Further analyses were performed on ASA dose subgroups in the US to identify potential confounders in the relationship between higher-dose ASA and adverse outcomes.

Table 80 presents an analysis of baseline and treatment characteristics in the US population according to ASA dose category (81 or 325mg).

Table 80. US: Subject Characteristics by Median ASA Dose*Group

	Median ASA Dose	
	81mg (n=545)	325mg (n=667)
Age (yrs)	62	60
Body Mass Index (kg/m^2), median	29	29
Median Weight (kg)	89	88
Female sex	33%	25%
History of MI	27%	29%
History of PCI	28%	31%
Ex-smoker	36%	33%
Habitual smoker	34%	39%
Index event: UA	11%	9%
Index event: NSTEMI	70%	67%
Index event: STEMI	13%	19%
GPI use during index hosp	45%	57%
abciximab	4%	6%
tirofiban	2%	1%
eptifabatide	34%	44%
Heparin Use	60%	70%
Planned Invasive Treatment	90%	96%
PCI during study*	61%	77%
Early PCI during study*	56%	72%
BMS or DES implantation	58%	74%
DES	45%	54%
BMS	19%	29%
Total BMS (mean)	0.27	0.43
Total DES (mean)	0.82	0.99
≥ 80% compliant with IP	91%	90%
Time from Index event to IP (median)	17 hrs	16 hrs

* Without prior primary event; IP = investigational product; DES=drug eluting stent; BMS = bare metal stent
Median55 ASA definition used
Source: R. Fiorentino, Clinical Reviewer

In the US, subjects treated with 325mg ASA tended to be male, have more intended invasive management, and have more PCIs with stenting. This may not be unexpected given the clinical use of dual antiplatelet therapy with ASA 325mg following PCI.

Table 80 also illustrates the potential for confounding between baseline characteristics or treatment strategy with ASA dose, primarily because ASA dose was left up to the investigator to determine on a patient-by-patient basis.

However, at this time, it is not clear why any of these non-ASA related differences would have a treatment interaction with ticagrelor in the US, particularly since a robust treatment interaction was not identified for these variables in the non-US population.

Additional analyses were performed in US subjects to understand the relationship between receiving higher vs. lower dose aspirin and undergoing PCI or invasive strategies. This was considered relevant since there appeared to be differences between the US and non-US with respect to baseline characteristics and treatment strategies (as previously presented in Table 60 & Table 61).

A review of the median ASA dose category (81mg vs. 325mg) by PCI or planned invasive treatment is presented in Table 81. Notable is the more frequent use of 325mg ASA in the PCI or invasive subgroups.

Table 81. US: Median ASA Dose by PCI Treatment Group

	N	Median ASA Dose	
		81mg	325mg
PCI			
No	365	210 (58%)	155 (42%)
Yes	847	335 (40%)	512 (60%)
Planned Invasive Treatment			
No	81	53 (65%)	28 (35%)
Yes	1,131	492 (44%)	639 (56%)

ASA definition MEDIAN55 used
Source: R. Fiorentino, Clinical Reviewer

Table 82 presents primary study outcomes in the US according to PCI and median ASA dose subgroups. Notable is an apparent trend towards larger hazard ratios in the ASA 325mg group compared to ASA 81mg, irrespective of treatment strategy.

Table 82. US: Primary Outcome by Planned Invasive Treatment and PCI vs. ASA Subgroup

		ASA 81mg		ASA 325mg	
Planned Invasive Strategy					
	Yes	T: 16/256	**0.82**	T: 35/304	**1.56**
		C: 18/236	(0.42, 1.61)	C: 25/335	(0.93, 2.60)
	No	T: 3/27	**0.55**	T: 5/16	**1.72**
		C: 5/26	(0.13, 2.30)	C: 2/12	(0.33, 9.06)
Any PCI*					
	Yes	T: 11/175	**0.84**	T: 31/238	**1.88**
		C: 12/160	(0.39, 1.90)	C: 19/274	(1.06, 3.32)
	No	T: 8/108	**0.68**	T: 9/82	**1.00**
		C: 11/102	(0.27, 1.70)	C: 8/73	(0.39, 2.61)

* excludes primary events prior to PCI; ASA dose as per definition MEDIAN55
Source: R. Fiorentino, Clinical Reviewer

Table 83 presents primary outcomes by index ACS event and ASA dose subgroups. Outcomes are numerically higher in the ASA 325mg compared to the 81mg subgroup across all three index event subtypes.

Table 83. US: Primary Outcome by Index ACS Event

	ASA 81mg		ASA 325mg	
STEMI	T: 3/39	**1.19**	T: 7/53	**2.45**
	C: 2/32	(0.20, 7.15)	C: 4/71	(0.72, 8.38)
NSTEMI	T: 13/194	**0.79**	T: 28/219	**1.49**
	C: 16/189	(0.38, 1.64)	C: 20/226	(0.84, 2.65)
UA	T: 3/35	**0.45**	T: 5/35	**1.10**
	C: 5/27	(0.11, 1.90)	C: 3/27	(0.26, 4.62)

ASA dose as per definition MEDIAN55
Source: R. Fiorentino, Clinical Reviewer

Figure 36 shows the result of the sponsor's original analysis of the primary endpoint in the non-US dataset and attempts to model the relationship between outcome and ASA dose. The estimated regression curve (green) is shown together with the associated 95% confidence band. Also highlighted are the observed HR and 95% CI for the US subgroup (red bar). The lower half of Figure 36 contains a histogram presenting the number of subjects in the non-US population that had ASA data available to perform this analysis (original).

Figure 36. Non-US Subjects: Regression Analysis of the Primary Endpoint
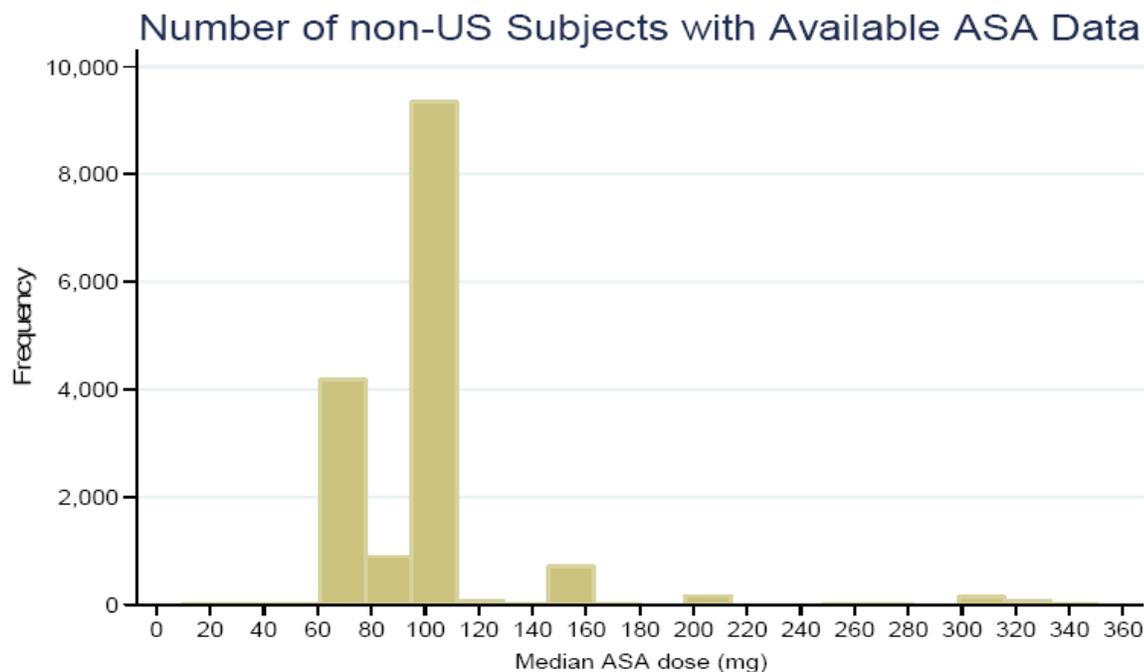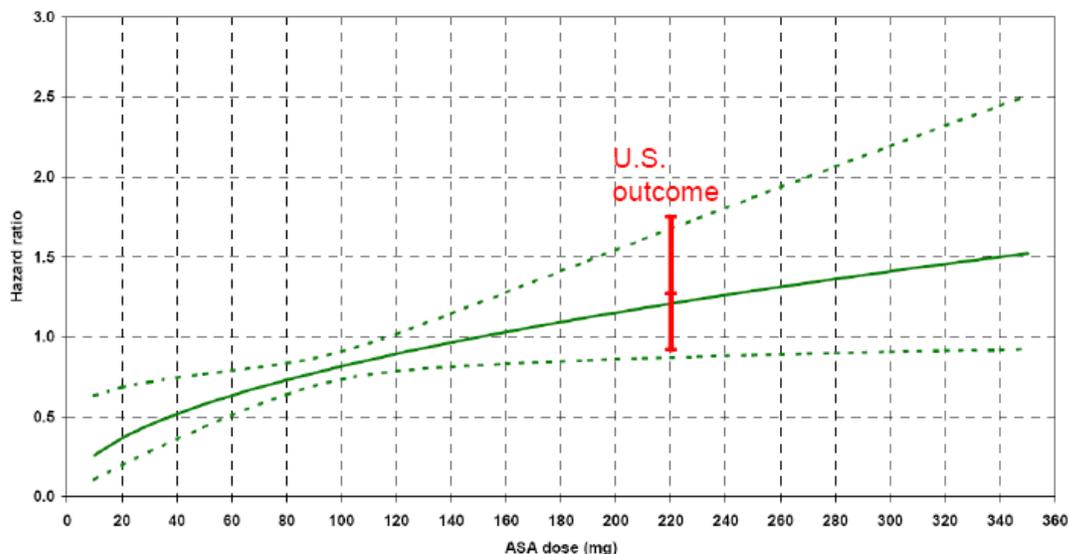
Source: R. Fiorentino with data reproduced from sponsor, p.64 Fig. 12, *Exploratory analyses of treatment interactions in PLATO* **(based on original ASA dataset submitted with NDA)**

Despite an apparent agreement between the "predicted" and actual US outcomes, Figure 36 demonstrates the relatively small numbers of subjects in the non-US population that provided the data used to model outcomes in the US. This raises concern about how robust the model is when estimating outcomes in the US subgroup.

Further, the lack of robustness of the treatment-by-region interaction in PLATO is illustrated by the sensitivity of the statistic to small event switching between the ticagrelor and clopidogrel arms (Table 84).

Table 84. Lack of robustness of the treatment-by-region interaction in PLATO

Events on Ticagrelor in NA region	Treatment-by-region interaction	HR & 95% CI in NA	Overall HR & 95% CI
Original data (102 for T vs. 82 for C)	0.046	1.25 (0.93, 1.67)	0.84 (0.77, 0.92)
1 event switching (101 for T vs. 83 for C)	0.065	1.22 (0.91, 1.63)	0.84 (0.77, 0.92)
2 events switching (100 for T vs. 84 for C)	0.091	1.19 (0.89, 1.59)	0.84 (0.76, 0.92)
3 events switching (99 for T vs. 85 for C)	0.123	1.16 (0.87, 1.55)	0.83 (0.77, 0.91)

C Clopidogrel; CI Confidence interval; HR Hazard ratio; NA North America; T Ticagrelor.
Source: Sponsor, Draft AC Briefing Document

Conclusion

In PLATO, a subject's aspirin dose appeared to be dependent on the country/region of enrolment and at a minimum, likely influenced by local practice patterns and market availability of various dosages and formulations (e.g., 81mg and 325mg in the US *vs.* 75mg and 100mg outside the US). Univariate subgroup analyses provide insight into what specific populations received what doses of ASA, including the observation that subgroup with possibly the highest prevalence of higher-dose daily aspirin was the on-study PCI group in the US. Correlations between aspirin dose and outcome are potentially confounded by these and unrelated factors, as well as arbitrary derivation of "usual" (median or mean) ASA doses across the time in trial for any given subject.

A number of *post hoc* analyses were performed to identify if other factors, independent of aspirin, could explain why a comparative treatment benefit was not seen in the U.S. subgroup. These multivariate analyses are addressed in the separate FDA Statistical review performed by Dr. Jialu Zhang.

7 Review of Safety

Please refer to the separate review of Safety by Dr. Melanie Blank.

8 Appendices

8.1 PLATO Study Definitions

Definition of Myocardial Infarction

a) **Recurrent MI within 18 hours of onset of a previous MI**

New ST elevation of ≥ l mm (0.1 mV) in at least 2 contiguous leads and recurrent cardiac ischemic symptoms[g] ≥ 20 minutes at rest[h].

b) **Recurrent MI after 18 hours of onset of a previous MI but before myocardial necrosis biomarkers have returned to normal**

Myocardial necrosis biomarker re-elevation (troponin or CK-MB) defined as an increase of at least 50% over a previous value that was decreasing and at least one of the following:

   i. Recurrent cardiac ischemic symptoms[g] ≥20 minutes at rest[h]

    OR

   ii. One of the following ECG changes:
      i. New ST elevation of ≥1 mm (0.1 mV) in at least 2 contiguous leads
      ii. Development of new pathological Q waves[i] on the ECG
      iii. New LBBB.

c) **MI in patients without an index MI, or patients with recurrent MI after myocardial necrosis biomarkers have returned to normal (excluding MI in patients undergoing PCI or CABG in the previous 24 hours).**

Elevation of myocardial necrosis biomarkers typical of acute MI[j] with at least 1 of the following:

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g Cardiac ischemic symptoms: chest pain or discomfort or equivalent (eg, neck or jaw symptoms, dyspnea believed to represent an angina pectoris equivalent) believed due to impaired coronary flow secondary to atherosclerotic disease.
h At rest: started with exercise or spontaneously and did not resolve with rest.
i Development of pathological Q waves: Development of any new or presumed new Q waves that are ≥0.03 sec in width and ≥1 mm (0.1 mV) in depth in at least 2 contiguous leads.
j Myocardial necrosis biomarker evidence of acute MI - any of the following: Maximal concentration of troponin T or I exceeding the 99th percentile of the values for a reference control group. Elevations should be seen on at least one occasion but preferably with a rising or falling pattern during the first 24 hours following the index clinical event. The coefficient of variation (CV; imprecision) at the 99th percentile should be lower or equal to 10%. Otherwise, the concentration at the 10% CV should be regarded as the diagnostic cut-off. For cardiac troponin T the diagnostic cut-off is equal to or greater than 0.03 ug/L. Cut-offs for cardiac troponin I assays vary among different manufacturers and should be read-off from approved tabulations. Maximal value of CK-MB (preferably CKMB mass) exceeding the

    i. Recurrent cardiac ischemic symptoms[g] ≥20 minutes at rest[h]
    ii. Development of new pathological Q waves[i] on the ECG
    iii. ECG changes indicative of ischemia[k]

OR

Pathological findings of an acute MI.

d) MI within 24 hours after PCI:

i. CK-MB ≥3x local or central laboratory upper normal limit[l] , and, if the pre-PCI CKMB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI (no symptoms are required)
OR
ii. Development of new pathological Q waves[i] on the ECG (no symptoms are required).

e) MI within 24 hours after CABG:

i. CK-MB ≥5x local or central laboratory upper normal limit[l] , and, if the pre-CABG CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI and development of new pathological Q waves[i] on the ECG (no symptoms are required)

OR

ii. CK-MB ≥ 10x local or central laboratory upper normal limit[l] and, if the pre-CABG CK-MB was >ULN, both an increase by at least 50% over the previous value and documentation that CK-MB was decreasing prior to the suspected recurrent MI (with or without Q-waves) (no symptoms are required).

f) For patients who die of suspected MI and for whom no myocardial necrosis biomarkers were obtained:
i. The presence of new ST-segment elevation[k] and new cardiac ischemic symptoms[g]

99th percentile of the values for a reference control group on 2 consecutive samples (mass), or maximal activity exceeding twice the upper limit of normal (CK-MB activity) for the specific institution on one occasion during the first hours after the index clinical event.
Values for CKMB should rise <u>and</u> fall.
k ECG changes indicative of ischemia - any of the following: ST-segment elevation: New or presumed new ST-segment elevation ≥1.0 mm (0.1 mV) in 2 or more contiguous leads. New or presumed new ST-segment depression of ≥0.5 mm (≥0.05 mV) in 2 or more contiguous leads. New or presumed new T-wave abnormalities - inversion of ≥1 mm (0.1 mV) in 2 or more contiguous leads.
l Laboratory upper normal limit: This is the value that is considered abnormal. For institutions that report an intermediate or indeterminate range for troponin I or T, these values are considered abnormal for this study.

OR

    ii. Pathological evidence of an acute MI.

g) Silent MI:

    i. Development of new or presumed new pathological Q waves[i] , in the absence of cardiac ischemic symptoms[g]

Definition of Recurrent Cardiac Ischemia

Recurrent cardiac ischemia
Cardiac ischemic symptoms[g] ≥10 minutes at rest[h], resulting in hospitalization if an outpatient or prolongation of hospitalization if an inpatient but not fulfilling criteria for MI.

Severe recurrent cardiac ischemia
Recurrent cardiac ischemia and at least one of the following, but not fulfilling the criteria for MI:

    i. New or presumed new ischemic ECG changes (ST elevation ≥1 mm (0.1 mV). or ST depression ≥0.5 mm (0.05 mV), or T wave inversion ≥1 mm (0.1 mV) in at least 2 adjacent leads)
    ii. Leading to urgent revascularization (PCI or CABG) unless not advised on reasoned grounds.

Urgent revascularization (PCI or CABG) must occur during the same hospitalization as an inpatient episode of recurrent ischemia or be performed during the re-hospitalization resulting from an out-patient episode of recurrent myocardial ischemia. In countries where waiting lists for revascularization procedures exist, revascularization within 30 days of an episode of recurrent ischemia will qualify as urgent. For patients with a previous PCI it will be recorded if revascularization is necessary for previously treated vessels (i.e., urgent target vessel revascularization) and any occurrences of stent thrombosis will be documented. PCI is defined as any attempt at revascularization even if not successful (e.g. angioplasty, atherectomy, or stenting).

Definition of Stroke/TIA

A stroke is defined as a neurological deficit caused by an ischemic or hemorrhagic central nervous system event with residual symptoms at least 24 hours after onset or leading to death.

Stroke will be further sub-classified as:
- Hemorrhagic: A stroke with documentation of intracranial hemorrhage on imaging (e.g., computed tomography (CT) scan or magnetic resonance imaging (MRI) scan) either in the cerebral parenchyma, or a subdural, epidural or subarachnoid hemorrhage. Evidence of hemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis.
- Ischemic: A stroke that results from a thrombus or embolus impairing central nervous system perfusion (and not due to hemorrhage). Hemorrhagic conversion of an ischemic stroke that becomes symptomatic should be recorded as a new hemorrhagic stroke event.

- Unknown/No imaging performed: if the type of stroke could not be determined by imaging or other means (from lumbar puncture, neurosurgery, or autopsy).

A TIA is defined as a focal neurological deficit that resolves spontaneously without any evidence of residual deficit by 24 hours. For inclusion in the third secondary composite efficacy endpoint the TIA must either require hospitalization if an outpatient or prolong hospitalization if an inpatient or have objective confirmation of cerebrovascular disease.

Definition of Arterial Thrombotic Events

A diagnosis of an Arterial Thrombotic Event (non-cardiac, non-cerebrovascular) will be made from a positive clinical presentation that is associated with a positive imaging or other diagnostic study. An Arterial Thrombotic Event is defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion due either to embolism or thrombosis in the absence of other likely mechanisms (e.g., instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires clear evidence of abrupt arterial occlusion from diagnostic imaging tests or pathology analyses. Diagnosis of embolism to the lower extremities should be made with extreme caution and requires arteriographic demonstration of abrupt arterial occlusion. Clinical presentation would include:
1. Peripheral artery occlusion will be considered for abrupt development of pain, absent pulses, pallor, and/or paresis in an extremity (at least an entire digit).
2. Renal infarction will be considered when sudden flank pain or a change in renal laboratory findings occurred.
3. Abdominal vascular/visceral infarction will be considered if acute abdominal symptoms or referred symptoms developed along with a change in abdominal examination or appropriate laboratory values.
4. Retinal infarction will be considered for the abrupt onset of visual loss based on the clinical report from an appropriate physician, such as an ophthalmologist, and any supporting diagnostic procedure reports.

Acceptable imaging studies include angiogram, CT scan, MRI, Ultrasound, or colonoscopy.

Classification of Death

All deaths reported post-enrollment would be recorded and adjudicated.

Deaths will be further sub-classified by vascular or non-vascular primary cause. Death from vascular causes includes cardiovascular deaths, cerebrovascular deaths; deaths from any other vascular abnormality or deaths for which there was no clearly documented nonvascular cause.

Some specific examples are given below:
- Vascular death: sudden death, MI, VA, other CAD, stroke, arterial embolism, pulmonary embolism, ruptured aortic aneurysm, aortic dissection, heart failure, cardiac arrhythmia or death from bleeding (not related to trauma).

- Non-vascular death: cause of death was respiratory failure, pneumonia, cancer, trauma, suicide, sepsis, multi-organ failure or any other clearly defined cause (e.g., liver failure or renal failure).

Deaths with unknown/uncertain cause will be categorized as vascular death and included in the primary composite endpoint. Any death with unknown/uncertain cause within 30 days of a stroke, MI or procedure/surgery will be considered a death due to the stroke, MI or procedure/surgery respectively

Definition of Bleeding Events

Major bleed – fatal/life-threatening

Anyone of the following:
- Fatal
- Intracranial
- Intrapericardial bleed with cardiac tamponade
- Hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery
- Clinically overt or apparent bleeding associated with a decrease in Hb of more than 50 g/L[m] (3.1 mmol/L[n]; 0.775 mmol/L[o])[p]
- Transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.

Major bleed - other

Anyone of the following:
- Significantly disabling (e.g., intraocular with permanent vision loss)
- Clinically overt or apparent bleeding associated with a decrease in Hb of 30 g/L[m] (1.9 mmol/L[n]; 0.465 mmol/L[o])[p] to 50 g/L (3.1 mmol/L[n]; 0.775 mmol/L[o])[p]
- Transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

Minor bleed

- Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).

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m Reference range 130 to 180 g/L (males); 120 to 160 g/L (females)

n Reference range Hb tetramer 8.1 to 11.2 mmol/L (males); 7.4 to 9.9 mmol/L (females)

o Reference range Hb monomer 2.02 to 2.80 mmol/L (males); 1.85 to 2.47 mmol/L (females)

p To account for transfusions, Hb measurements will be adjusted for any PRBCs or whole blood given between 2 blood measurements. A transfusion of one unit of blood will be assumed to result in an increase of 10 g/L[m]; 0.62 mmol/ L[n]; 0.155 mmol/L[o] in Hb. Therefore, to calculate the true change in Hb if there has been an intervening transfusion between 2 blood measurements, the following calculations should be performed: Δ Hb = [baseline Hb - post transfusion Hb] + [number of transfused units x conversion factor in Hb]. Conversion factor = Conversion factor = 10 g/L[m]; 0.62 mmol/L[n] ; 0.155 mmol/L[o]

Minimal bleed

All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

STENT THROMBOSIS

The definition of stent thrombosis is taken from the recommendations proposed by the Academic Research Consortium (ARC) [Circulation 2007; 115; 2344-235l].

Definite Stent Thrombosis - is considered to have occurred by either angiographic or pathological confirmation:

- The presence of thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour window (The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis {silent occlusion}):
  - o Acute onset of ischemic symptoms at rest
  - o New ischemic ECG changes that suggest acute ischemia
  - o Typical rise and fall in cardiac biomarkers that represent a spontaneous MI
  - o Nonocclusive Thrombus: Intracoronary thrombus defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.
  - o Occlusive Thrombus: TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)
- Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable Stent Thrombosis - Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:
- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible Stent Thrombosis - Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

Timing of Stent Thrombosis

- Acute stent thrombosis: 0 to 24 hours after stent implantation

- Subacute stent thrombosis: >24 hours to 30 days after stent implantation
- Late stent thrombosis: >30 days to 1 year after stent implantation
- Very late stent thrombosis: >1 year after stent implantation

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheter laboratory.

8.2 Phase II Studies

8.2.1 DISPERSE [Study D5130C00008]: Phase 2 Study

Study Dates: August 2003 to November 2003

Title
A 28-Day, Randomised, Double-blind, Double-dummy, Parallel Group, Dose Finding Study to Investigate the Pharmacodynamics and Pharmacokinetics of AZD6140 plus Acetyl Salicylic Acid (ASA) Compared with Clopidogrel plus ASA in Subjects with Atherosclerosis

Primary objective
To assess the pharmacodynamic (PD) effects of AZD6140 at doses of 50 mg twice daily (bd), 100 mg bd, 200 mg bd and 400 mg once daily (od) in the presence of acetyl salicylic acid (ASA) compared to clopidogrel 75 mg od plus ASA, in subjects with documented atherosclerotic disease, by evaluation of:
- Inhibition of adenosine diphosphate (ADP)-induced and collagen-induced platelet aggregation at Days 14 and 28 (expressed as a percentage of Day 1 pre-dose baseline).
- The bleeding time at Day 28 and the corresponding within-subject change from Day 1 pre-dose baseline.

Study design
This was a 28-day randomized, double-blind, double-dummy, parallel group, multicentre study comparing the PD, PK, safety and tolerability of AZD6140 (50 mg bd, 100 mg bd, 200 mg bd and 400 mg od) plus ASA with clopidogrel (75 mg od) plus ASA.

Duration of treatment
Twenty-eight days for all treatments.

Target subject population and sample size
Male and female subjects, aged 25 to 85 years, with documented atherosclerotic disease (either coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral arterial occlusive disease (PAOD)) were randomized to treatment. A sample size of 200 (40 per treatment arm) was chosen to ensure an acceptable degree of precision in the comparison of the mean values for platelet aggregation inhibition of the 5 treatment groups.

Results

AZD6140 (50 mg bd, 100 mg bd, 200 mg bd and 400 mg od) and clopidogrel (75 mg od), administered in the presence of ASA, inhibited ADP-induced platelet aggregation at Days 1, 14 and 28 of treatment. At Day 1 all AZD6140 regimens inhibited ADP-induced platelet aggregation to a greater extent than clopidogrel with rapid inhibition (2hrs) and the 400 mg od dose of AZD6140 produced the greatest mean IPA compared to lower doses. At Days 14 and 28, AZD6140 50 mg bd resulted in inhibition of ADP-induced platelet aggregation comparable to clopidogrel 75 mg od. The higher doses of AZD6140 resulted in greater ADP-induced IPA compared to clopidogrel; comparisons between the higher doses at Days 14 and 28 (Visits 4 and 6, respectively) gave only modest differences in IPA.

Figure 37. Plot of mean ADP-induced platelet aggregation (IPA) data
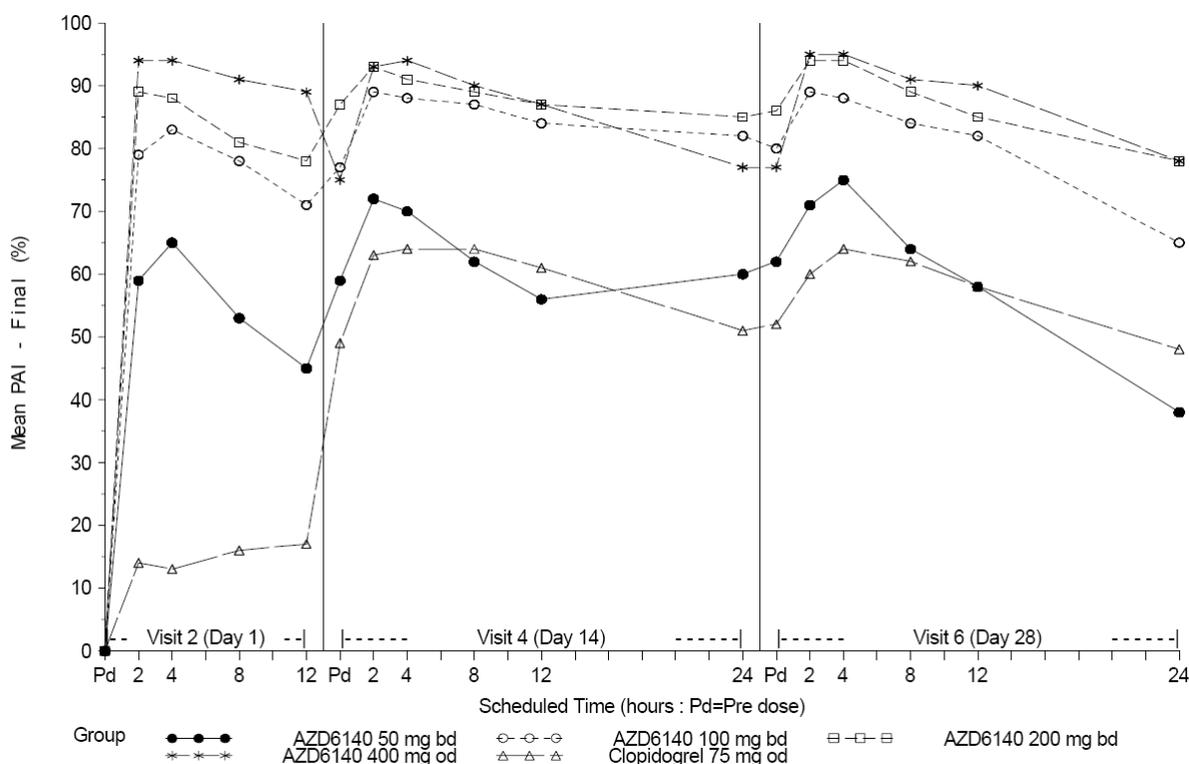
Source: Sponsor, Clinical Study Report Synopsis, Document No. D5130C00008, page 5, FigureS1

The most frequently reported AE in DISPERSE (excluding bleeding events) was dyspnea, followed by dizziness and headache (see Table 85). Dyspnea appeared dose-related, was not observed with clopidogrel and was previously unreported in studies with AZD6140. Dizziness and headache showed no clear relationship to AZD6140 dose and both AEs also occurred with clopidogrel administration.

Table 85. Number (%) of subjects with the most commonly reported adverse events (excluding bleeding events)

MedDRA PREFERRED TERM NAME	AZD6140 50 mg bd	AZD6140 100 mg bd	AZD6140 200 mg bd	AZD6140 400 mg od	Clopidogrel 75 mg od
DYSPNOEA	4 (10%)	4 (10%)	6 (16%)	9 (20%)	0 (0%)
DIZZINESS	4 (10%)	2 (5%)	1 (3%)	4 (9%)	1 (3%)
HEADACHE	0 (0%)	5 (13%)	1 (3%)	1 (2%)	3 (8%)
RED BLOOD CELLS URINE	3 (7%)	0 (0%)	4 (11%)	0 (0%)	1 (3%)
DIARRHOEA NOS	0 (0%)	1 (3%)	2 (5%)	2 (4%)	2 (5%)
NASOPHARYNGITIS	2 (5%)	1 (3%)	2 (5%)	0 (0%)	2 (5%)
FATIGUE	2 (5%)	1 (3%)	0 (0%)	0 (0%)	2 (5%)
ABDOMINAL PAIN UPPER	2 (5%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)
CHEST PAIN	1 (2%)	0 (0%)	2 (5%)	1 (2%)	0 (0%)
BACK PAIN	1 (2%)	2 (5%)	0 (0%)	0 (0%)	1 (3%)
PAIN IN EXTREMITY	1 (2%)	2 (5%)	0 (0%)	1 (2%)	0 (0%)
CYSTITIS NOS	1 (2%)	0 (0%)	0 (0%)	1 (2%)	2 (5%)
COUGH	0 (0%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)

a   Events with a total frequency of at least 5% within any treatment group

Source: Sponsor, Clinical Study Report Synopsis, Document No. D5130C00008, page 9, FigureS5

Conclusions

DISPERSE demonstrated in patients with stable coronary arterial disease that 100 mg bd or 200 mg bd of ticagrelor provided greater inhibition of platelet aggregation, compared to that in patients taking 75 mg daily clopidogrel. Also, an IPA with 50 mg bd ticagrelor appeared equivalent to that with 75 mg daily clopidogrel. Thus the lowest ticagrelor dose, 50 mg, seemed unlikely to provide an efficacy advantage to clopidogrel.

Finally, it was shown during development that a mannitol-based 100 mg tablet showed a 17% higher area under the concentration-time curve than the lactose-based 100 mg tablets; therefore, a new mannitol-based IR tablet strength of 90 mg (used in DISPERSE2) was produced.

8.2.2 DISPERSE-2 [Study D5130C00002]: Phase 2 Study

Title
A Double-blind, Double-dummy, Parallel Group Randomized Dose Confirmation and Feasibility Study of AZD6140 + Acetyl Salicylic Acid (ASA) Compared with Clopidogrel + ASA in Patients with Non-ST Segment Elevation Acute Coronary Syndromes (DISPERSE2-TIMI 33)

Study Design
A double-blind, double-dummy, parallel group, randomized, multicentre study comparing the safety and tolerability of 2 doses of AZD6140 with clopidogrel (all in combination with ASA) in patients with non-ST segment elevation ACS.

Blinding was ensured by the provision of 2 tablets bid plus one capsule od for all patients, using a double-dummy design.

Duration of treatment was 4, 8 or 12 weeks. All patients were randomized to at least 4 weeks' treatment with some patients continuing to either 8 or 12 weeks' treatment duration. It was planned that 50% patients would be randomized to 12 weeks' treatment, and 25% each to 8 weeks' and 4 weeks' treatment.

Objectives
Primary objective was to assess the safety and tolerability of different doses of AZD6140 (ticagrelor) in the presence of acetyl salicylic acid (ASA), compared with clopidogrel plus ASA, in patients with non-ST segment elevation ACS.

Secondary objectives included the following:

- To assess the PD effects of AZD6140 in the presence of ASA compared to clopidogrel plus ASA (in clopidogrel-naïve patients).
- To compare the platelet aggregation response to AZD6140 in clopidogrel-naïve patients and clopidogrel pre-treated patients
- To evaluate the PK of AZD6140 and metabolite AR-C124910XX
- To evaluate the relationship between AZD6140 PK and platelet aggregation inhibition.
- To evaluate the relationship between AZD6140 and AR-C124910XX exposures and the occurrence of major and minor bleeding.
- To compare the safety and tolerability of AZD6140 plus ASA with clopidogrel plus ASA

A number of other exploratory (tertiary) objectives were used.

Study Endpoints

Primary variable
ICAC-adjudicated total bleeding events (excluding minimal) observed within the first 4 weeks of treatment (Day 29).

Secondary variables
ICAC-adjudicated total bleeding events (excluding minimal) at Weeks 8 and 12, plus overall bleeding rate using total patient exposure.

Treatments
AZD6140 90 mg bd and 180 mg bd, administered as 90 mg tablets; and placebo to AZD6140 90 mg tablets. Half of all patients on each AZD6140 arm also received a loading dose of 270 mg AZD6140. Patients receiving no loading dose took their standard first dose plus additional placebo tablets to maintain blinding. All patients also received ASA 75-100 mg daily with their study drug.

Clopidogrel 75 mg od, was administered as encapsulated tablets (capsules). All patients allocated to clopidogrel received a 300 mg clopidogrel loading dose, unless the patient was already on a maintenance dose or had received an open-label loading dose of clopidogrel as part of their local clinical care prior to randomization. An additional 300 mg clopidogrel could be given with the first dose, or within 48 hours post-first dose, for patients proceeding to PCI within 48 h after randomization. All patients also received ASA 75-100 mg od with their study drug.

Results

In total, 1018 patients were enrolled into the study, 990 were randomized and 984 (99%) patients received at least one dose of study drug. Of the patients who received study drug, 190 (19%) withdrew prematurely and 794 (81%) patients completed all visits required by the study protocol. Of the 984 patients who received study drug, 719 (73%) were clopidogrel-naïve and 265 (27%) were clopidogrel pre-treated. A total of 250 (25%) patients were randomized to receive study drug for 4 weeks, 243 (25%) for 8 weeks and 491 (50%) for 12 weeks.

At Week 4 (steady state), AZD6140 180 mg bd produced greater inhibition of ADP-induced platelet aggregation than clopidogrel 75 mg od: higher mean IPA was observed for 180 mg bd compared to clopidogrel 75 mg od (IPA$_{max}$ 97% vs. 73%). AZD6140 90 mg bd produced an intermediate effect (IPA$_{max}$ 88%). Similar results were seen at Weeks 8 and 12, although the numbers of patients with available data at these 2 visits were smaller than Week 4.

On Day 1, for AZD6140 90 mg, 180 mg and 270 mg the final extent mean IPA was higher than for clopidogrel 300 mg od. For both clopidogrel-naïve and clopidogrel pre-treated patients on Day 1, all AZD6140 groups had lower ADP-induced platelet aggregation than clopidogrel 300 mg (e.g., clopidogrel pre-treated: AZD6140 90 mg group 10% to 12% over 12 h; the clopidogrel 300 mg group was higher 27% to 36%). In addition, lower levels of ADP-induced platelet aggregation for a given AZD6140 dose were seen in clopidogrel pre-treated patients than clopidogrel-naïve patients, (i.e., AZD6140 90 mg had the same aggregation in clopidogrel pre-treated patients [10% to 12% over 12 h] as 270 mg in clopidogrel-naïve patients [9% to 12%]), indicating that AZD6140 confers an additional antiplatelet effect onto clopidogrel pre-treatment.

ICAC-adjudicated clinical endpoints are summarized at Week 4 and overall in Table 86.

Table 86. DISPERSE-2: ICAC-adjudicated clinical endpoint events at Week 4 and overall

Endpoint event	AZD6140 90 mg bd (n=334)		AZD6140 180 mg bd (n=329)		Clopidogrel 75 mg od (n=327)	
	Week 4[a]	Overall[b]	Week 4[a]	Overall[b]	Week 4[a]	Overall[b]
All cause death	6 (1.8%)	7 (2.1%)	3 (0.9%)	6 (1.8%)	2 (0.6%)	4 (1.2%)
- CV death	6 (1.8%)	6 (1.8%)	3 (0.9%)	6 (1.8%)	2 (0.6%)	4 (1.2%)
- Non CV death	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Unknown cause death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total MI (including silent MI)[c]	4 (1.2%)	9 (2.7%)	2 (0.6%)	7 (2.1%)	10 (3.1%)	14 (4.3%)
- MI (excluding silent MI)[c]	4 (1.2%)	9 (2.7%)	2 (0.6%)	7 (2.1%)	10 (3.1%)	14 (4.3%)
- Silent MI	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stroke	2 (0.6%)	2 (0.6%)	0 (0%)	0 (0%)	1 (0.3%)	1 (0.3%)
Severe recurrent ischaemia	2 (0.6%)	5 (1.5%)	4 (1.2%)	9 (2.7%)	2 (0.6%)	3 (0.9%)
Recurrent ischaemia	10 (3.0%)	13 (3.9%)	4 (1.2%)	9 (2.7%)	5 (1.5%)	9 (2.8%)

a Number of patients with at least one endpoint event during the first 4 weeks of treatment.
b Number of patients with at least one endpoint event during the whole study.
c Post database lock, 5 new MI endpoint events were identified – 3 patients (AZD6140 90 mg bd), 1 patient (AZD6140 180 mg bd) and 1 patient (clopidogrel 75 mg od). These new events are not included in the above table.
Source: Sponsor, DISPERSE2 CSR, p.152, Table 42

Table 87. Composite clinical endpoints Overall

Composite	AZD6140 90 mg bd (n=334)[a]	AZD6140 180 mg bd (n=329)[a]	Clopidogrel 75 mg od (n=327)[a]
Overall study			
CV death / MI (excl silent)	15 (4.5%)	10 (3.0%)	16 (4.9%)
CV death / MI (excl silent) / stroke	16 (4.8%)	10 (3.0%)	16 (4.9%)
CV death / MI (excl silent) / stroke / SRI	21 (6.3%)	17 (5.2%)	18 (5.5%)
CV death / total MI (inc silent) / stroke / SRI / RI	29 (8.7%)	25 (7.6%)	26 (8.0%)
All cause death / total MI (inc silent) / stroke / SRI /RI	30 (9.0%)	25 (7.6%)	26 (8.0%)

a Post database lock, 5 new MI endpoint events were identified – 3 patients (AZD6140 90 mg bd), 1 patient (AZD6140 180 mg bd) and 1 patient (clopidogrel 75 mg od). These new events are not included in the above table.
CV=cardiovascular; SRI=severe recurrent ischemia; RI = Recurrent ischemia
Source: Sponsor, DISPERSE2 CSR, p.155, Table 44

Holter Study
Holter monitoring was performed in 312 (93%) AZD6140 90 mg bd patients, 295 (90%) AZD6140 180 mg bd patients, and 307 (94%) clopidogrel 75 mg od patients. Of these, the following provided data for summary purposes: AZD6140 90 mg bd 312 (93%) patients, AZD6140 180 mg bd 290 (88%) patients, and clopidogrel 75 mg od 305 (93%) patients

In total, 24% patients experienced episodes of ischemia ≥1.0 mm ST depression or elevation on Holter monitoring; there were no apparent differences between the treatment groups. Of those patients who had episodes of ischemia, the mean total durations were similar across the treatment groups (114 to 122 min).

Retrospective evaluation of adverse event (AE) reports of arrhythmias for the entire study population showed small absolute increases in the numbers of patients and events of ventricular and supraventricular arrhythmias reported in the AZD6140 groups compared with the clopidogrel group

As presented in Table 88 and Table 89, apparent increases in dropped beats, bradycardia and pauses >2.5 seconds and >5 seconds were observed in the AZD6140 groups compared with clopidogrel , with the pauses >2.5 seconds showing the clearest evidence for a dose relationship with AZD6140. For dropped beats, bradycardia and pauses , the greater overall occurrences in the AZD6140 180 mg bd group appear to be primarily accounted for by the number of patients with >4 episodes.

Table 88. Number (%) patients with at least 1 episode of dropped beats bradycardia or pauses

	AZD6140 90 mg bd (n=334)	AZD6140 180 mg bd (n=329)	Clopidogrel 75 mg od (n=327)
N	305	284 [a]	297
At least one of the below	155 (51%)	155 (55%)	142 (48%)
Dropped beats	88 (29%)	89 (31%)	73 (25%)
Bradycardia	103 (34%)	107 (38%)	96 (32%)
Pauses >2.5 seconds	17 (6%)	28 (10%)	13 (4%)
Pauses >5 seconds	5 (2%)	6 (2%) [b]	1 (0%)

a 283 patients for dropped beats and bradycardia.
b For 1 patient with adjacent 5 and 34 second pauses without symptoms these are thought to be due to technical failure of equipment, so the actual number of cases is 5.
Source: Sponsor, Addendum to Clinical Study Report, Study code: D5130C00002, p. 14, Table 4-9

Table 89. Number (%) patients with episodes of dropped beats

Number of episodes	AZD6140 90 mg bd (n=334)	AZD6140 180 mg bd (n=329)	Clopidogrel 75 mg od (n=327)
N	305	283 [a]	297
At least one	88 (29%)	89 (31%)	73 (25%)
0	217 (71%)	194 (69%)	224 (75%)
1	18 (6%)	29 (10%)	27 (9%)
2	17 (6%)	14 (5%)	10 (3%)
3	7 (2%)	8 (3%)	9 (3%)
4	5 (2%)	1 (0%)	3 (1%)
>4	41 (13%)	37 (13%)	24 (8%)

Source: Sponsor, Addendum to Clinical Study Report, Study code: D5130C00002, p. 14, Table 4-10

Dyspnea
The number of patients experiencing the AE of *dyspnea* in the AZD6140 90 mg bd and 180 mg bd groups, was 26 (8%) and 38 (12%), respectively and greater than clopidogrel 75 mg od with 15 (5%) patients.

At enrolment, the proportion of patients with a history of dyspnea or current dyspnea was 233 (24%) and 145 (15%), respectively. Of those patients reporting dyspnea during the treatment period, 66 patients were reporting dyspnea for the first time; 25 (7%), 30 (9%) and 11 (3%) in the AZD6140 90 mg bd, AZD6140 180 mg bd and clopidogrel 75 mg od groups, respectively. During the treatment period, the total number of patients who experienced the sensation of

shortness of breath in terms associated with dyspnea in the AZD6140 90 mg bd and 180 mg bd groups, was 35 (10%) and 51 (16%), respectively and greater than clopidogrel 75 mg od with 21 (6%) patients. Of note, the number of patients with a history of dyspnea in each of the AZD6140 90 mg bd and clopidogrel 75 mg od groups was identical; with a slightly higher number of patients in the AZD6140 180 mg bd group.

Discussion

DISPERSE2 studied the target dose for PLATO (phase 3), 90 mg bd, and double that dose, 180 mg bd in patients with NSTEMI-ACS. It showed similar total bleeding amongst 90 mg bd ticagrelor, 180 mg bd ticagrelor, and 75 mg daily clopidogrel groups. These results suggested 180 mg bd ticagrelor dose for PLATO. According to the sponsor, clinical pharmacology studies, modified this choice because of greater drug exposure in patients receiving moderate inhibitors of cytochrome P450 isoenzyme 3A (CYP3A4), such as diltiazem: the initial protocol started patients at 180 mg bd ticagrelor and provided for dose reduction to 90 mg bd for those taking moderate CYP3A4 inhibitors or for those intolerant of the 180 mg bd dose.

Subsequent information, according to the sponsor, resulted in further modification to the development program. First, a post-hoc analysis of Holter monitoring data in patients from DISPERSE2 (originally collected to detect ischemia) revealed ventricular pauses in all 3 arms of the study, and numerically more patients with pauses in the 180 mg bd ticagrelor group. A post-hoc analysis, including incidence of arrhythmias, suggested an apparent dose-related effect of ticagrelor on ventricular pauses. However, those observations were from only 1 study and there were a number of possible confounding factors; thus those data could not confirm a dose relationship.

Second, prior to enrolment of patients in PLATO, in Phases I and II studies, ventricular pauses and adverse events related to bradycardia were observed with ticagrelor, including in a few individual healthy volunteers during Phase I single ascending dose and Thorough QT studies. One healthy volunteer in a single ascending dose study (Study D5130C00049) experienced severe nausea, vomiting, and syncope following ingestion of 1260 mg ticagrelor (14-fold the 90 mg dose). Two ventricular pauses were observed, maximum duration 11 seconds. Despite uncertainty regarding the mechanism, relationship to dosing, and clinical impact of ventricular pauses, chronic dosing with 180 mg bd dose appeared to carry safety concerns for high exposure sub-populations, driving an amendment in PLATO for a single 90 mg bd ticagrelor dose. This change in dosing regimen alleviated the need for dose adjustment for concomitant use of CYP3A inhibitors. Based on these considerations, the sponsor concluded that the 90 mg bd maintenance dose appeared to provide the best balance of efficacy and safety. The change in dose for PLATO was made before study start; no patients received 180 mg bd.

8.3 Effect of Censoring Methodology on Primary Endpoint

Because of the study close-out procedure (discussed in Section 6.1.4) additional data was requested from the sponsor that contained detailed accounting of the censoring times, events and relation to study visits.

Table 90 presents the results of an FDA analysis of the adequacy of study follow-up. The US appeared to have worse follow-up rates compared to the non-US population.

Table 90. Adequacy of Follow-Up

	Lost to follow up or withdrew consent	Died or reached last visit with no premature discontinuation
Non-US (n=17,211)	2101 (12.2%)	15110 (87.8%)
US (n=1,413)	261 (18.5%)	1152 (81.5%)

Source: Jialu Zhang, FDA Statistical Reviewer

In a sensitivity analysis, only the date (not the time) were counted for each variable since some variables have both date and time information and some only have the date information. If a subject had a primary endpoint, the time to event is calculated as the time from the randomization date to the event date. If a subject did not have a primary event, the subject will be censored at the latest visit recorded (with vital signs). If a subject died of non-CV cause, the subject was censored at death.

Based on the sensitivity analysis, overall HR estimate is 0.86 with 95% CI (0.78, 0.94). The US population has HR=1.21 with 95% CI (0.88, 1.67)

Figure 38 presents the cumulative percentage of subjects who did not make it to the expected last visit (loss to follow up).

Figure 38. Cumulative Percentage of Subject that had no Last Visit (Lost to Follow-Up)
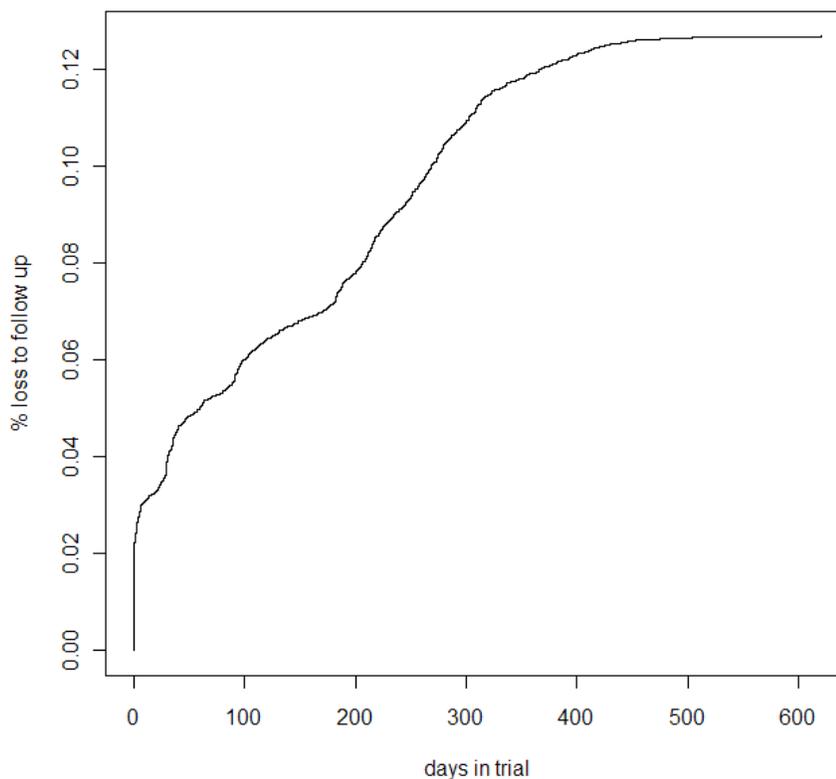
Source: Jialu Zhang, FDA Statistical Reviewer

These analyses do not provide evidence that the censoring and study close-out procedures significantly affected the study outcome, but it may suggest that the validity of the study results has been somewhat diminished.

8.4 Adjudication of Primary Efficacy Events

8.4.1 General Considerations

The initial evaluation of the adjudication process focused on the rates of events submitted for adjudication. The number of subjects who had events submitted for adjudication by investigators, regardless of whether an agreeing adjudication was made, was compared to the total number of subjects in each arm.

Overall in PLATO, 40% of ticagrelor subjects and 42% of clopidogrel subjects had events submitted for adjudication. A breakdown by select countries that constitute the largest enrollers is presented in Table 91. The purpose of this analysis was to identify any discrepancies in events reported for adjudication that may indicate biased outcomes in countries with low HRs.

Table 91. Adjudicated events by select countries

Country	Treatment	Subjects / arm	Reports Submitted for Adjudication	% subjects / arm with events submitted for adjudication
Czech Republic	TICAGRELOR	510	194	38%
	CLOPIDOGREL	511	211	41%
Germany	TICAGRELOR	580	221	38%
	CLOPIDOGREL	576	236	41%
Hungary	TICAGRELOR	632	199	31%
	CLOPIDOGREL	635	207	33%
Poland	TICAGRELOR	1337	466	35%
	CLOPIDOGREL	1329	501	38%
USA	TICAGRELOR	707	332	47%
	CLOPIDOGREL	706	319	45%

Source: Robert Fiorentino, Clinical Reviewer

Although there was some variability by country, generally the number of subjects with events submitted for adjudication was balanced across countries. Of note is that in contrast to the other countries shown in Table 91, the USA had more events submitted in the ticagrelor arm, in parallel to the unfavorable outcomes observed in that country.

To further evaluate the adjudication process in countries with outcomes more favorable to ticagrelor, the rates of adjudicated "NO EVENTs" or documented downgrades from the investigator's determination were analyzed.

The outcomes of this analysis for Hungary and Poland, two countries with the most favorable outcomes, are tabulated in Table 92.

Table 92. Downgraded Events (Hungary & Poland)

Country	# Subjects	Country HR	Arm	Subjects	# events submitted for adjudication*	Reports adjudicated as "NO EVENT" as a % of all reports submitted
Hungary	1,267	0.588	Ticagrelor	632	117	18.8%
			Clopidogrel	635	152	12.5%
Poland	2,666	0.693	Ticagrelor	1337	234	9.4%
			Clopidogrel	1329	284	8.5%

*excludes bleeding events & triggered MIs
Source: Robert Fiorentino, Clinical Reviewer

Of note is the greater difference between arms regarding apparent *downgrades* in Hungary (6.3% difference). Another country with downgrades more favorable to ticagrelor was the Czech Republic (9.2% difference, N=1021). In contrast, the USA tended to have downgrades in favor of clopidogrel (-1.7%, N=1413).

Despite this analysis, there was no relationship between differences in rates of downgraded adjudications by treatment arm and better or worse outcomes across countries. This is illustrated in Figure 39.

Figure 39. Difference in Adjudicated "downgrade" Rates Between Study Arms, by Country Haz. Ratio
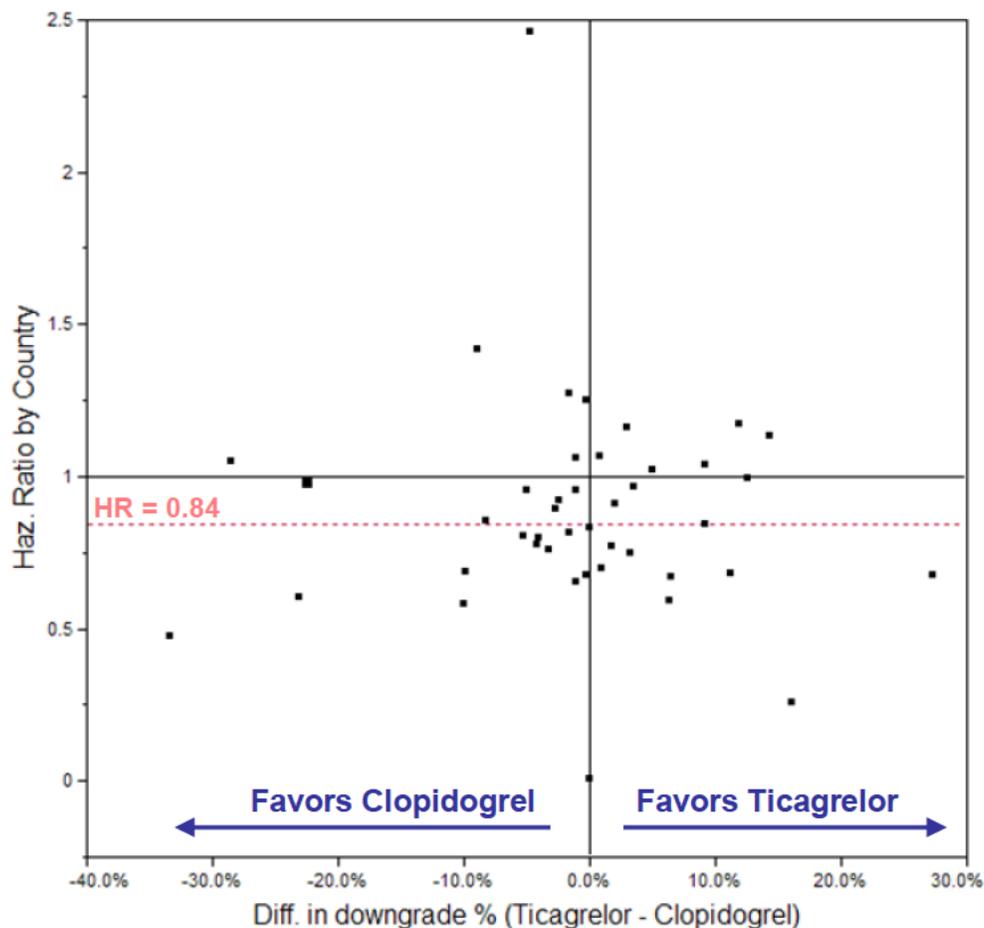
Source: Robert Fiorentino, Clinical Reviewer

As such, it does not appear that *downgrades* of investigator reported events during adjudication were done in a manner that biased the outcome of the trial.

Reporting of events for adjudication

As for any trial, it is conceivable that events could have been selectively submitted for adjudication in a biased manner if treatment assignment became unblinded.

To investigate this possibility, both serious adverse event datasets (ASAE.xpt) and hospital admission datasets (AHOSPLOG.xpt) were screened in detail for potential cardiac events that possibly should have been forwarded for adjudication. From the hospital dataset, subjects were identified who had either a cardiac ischemic event or SAE noted as the reason for admission. Of these, discharge diagnoses of MIs were noted in 553 subjects, 262 in ticagrelor and 291 in the clopidogrel arm. Of this group, 98.9% of ticagrelor and 98.6% of clopidogrel subjects had cardiac ischemic events submitted for adjudication, whether from the SAE or hospitalization or not. This analysis failed to provide evidence that SAEs and hospitalizations due to cardiac events were not being submitted for adjudication.

Of those with cardiac events submitted (as above) 84% of ticagrelor subjects and 91% of clopidogrel subjects went on to have positively adjudicated MIs. From another perspective, of those with cardiac events also submitted as above, 76% in ticagrelor arm and 89% in clopidogrel arm went on to have MIs counted in the primary analysis.

This suggests that most subjects with suspected cardiovascular events were being adjudicated and were having primary events adequately assessed.

Further analyses were performed on those subjects who were subsequently hospitalized following their index event/hospitalization. This analysis was carried out in order to further identify any biases or imbalances between the occurrence of potential adverse events and primary outcomes.

The proportions of subjects who were subsequently hospitalized (any cause) and had no primary event presented in the final analysis are shown in Table 93.

Table 93. Hospitalizations and Primary Events

Treatment	N	Hospitalization after index event	Hospitalized AND NO primary event
Ticagrelor	9333	35.6% (3314)	29.8% (2777)
Clopidogrel	9291	35.5% (3294)	28.7% (2666)

Source: R. Fiorentino, Clinical Reviewer

Table 93 demonstrates that on-study hospitalization rates were similar in both arms. Also, the proportion of subjects who were hospitalized, yet did not have any primary event, is comparable between the two arms (29.8% vs. 28.7%). However, this analysis does not constitute convincing evidence to suggest that subjects were being hospitalized for primary events that were not reported and in a manner that favored of the ticagrelor group.

8.4.2 CV Deaths

Sponsor provided narratives, CRFs and event summaries for all deaths. The CRFs for subjects in the ticagrelor arm that were adjudicated as non-cardiovascular were individually reviewed. The purpose of this review was to gain an understanding of how CV deaths were adjudicated and also to determine the possibility of CV deaths being mis-classified as non-CV deaths in the treatment arm.

In general the vast majority of CV deaths appear to have been appropriately adjudicated as best as can be determined. In particular, deaths that were adjudicated as having an "unknown" cause appear to have been appropriately classified as "CV deaths," being that no other cause could be attributed to them. A portion of these deaths represented deaths outside of the health care system, including deaths home or at outside health care centers.

There were a very few cases in which death appeared to be CV in nature, but which were adjudicated as non-CV. This includes the one curious finding of an acute infarct noted on autopsy despite the death being adjudicated as non-CV (subject E1809091).

Occasionally, cases were identified that had very little objective data available for review.

There were a large proportion of non-CV deaths due to infectious causes, especially pneumonia and also cancer.

There were a number of subjects who had prolonged, complicated clinical courses, in which a specific cardiovascular cause could not be attributed, despite multi-organ failure. These were generally not classified as CV deaths.

Site Reported Event Analysis: CV Death

An analysis of site-reported CV deaths was performed on datasets that contained adjudication tracking data. Site-reported deaths were classified as vascular, non-vascular or unknown. These data were used to specifically identify subjects who had site-reported CV deaths.

Two approaches were undertaken to characterize outcomes using site-event data. The first was to present the number of subjects (and proportion) in each treatment arm. The second analysis was performing an imputed time-to-event analysis in order to derive Kaplan-Meier estimates, HR and significance testing. This analysis required revising the analysis data for CV deaths such that site-reported events were substituted for adjudicated events in a manner that accounted for both changes in the time-to-event and censoring. Adjudicated events that were removed caused the time to event to default to the total time the subject was in study.

The results of this analysis are tabulated in Table 94.

Table 94. Site Reported CV Deaths

Treatment	N	Subj. with site-reported events	Two sample test of proportions	KM%/ 365 days	HR (95% CI)	Cox p-value
Clopidogrel	9291	369 (3.97%)	p=0.02	4.04%	0.81 (0.69, 0.94)	0.007
Ticagrelor	9333	311 (3.33%)		3.17%		

Source: Robert Fiorentino, Clinical Reviewer

The results of the site-reported analysis can be compared to the prespecified adjudicated analysis performed on the secondary endpoint of CV death, as shown below in Table 95.

Table 95. Adjudicated CV Deaths (Prespecified)

	N	Subj. with Events	KM%/yr	HR (95% CI)	P value
Clopidogrel	9291	442 (4.8%)	5.1%	0.79 (0.69, 0.91)	0.0013
Ticagrelor	9333	353 (3.8%)	4.0%		

Source: Sponsor. CSR page 146, table 28.

One can see that there is a significant difference in both analyses between the ticagrelor and clopidogrel treatment arms. Generally it appears that adjudication resulted in more CV deaths in both arms, regardless of site-identification. Hazard ratios were also similar in both analyses.

8.4.3 Myocardial Infarctions

An analysis was performed to evaluate the adjudication of MIs and the validity of site-reported events on trial outcome. This was relevant in that some adjudicated MI events originated from cardiac enzyme data entered into the electronic data capture systems, resulted in a "triggered" event that was sent for adjudication.

As shown in Table 96, for first MI events, 1.2% of ticagrelor patients and 1.3% of clopidogrel patients had MIs that were detected by cardiac enzyme biomarkers alone, accounting for about 20% of all the first MIs adjudicated by the ICAC. The remainder of the first MIs in each group was detected as MIs by the investigators.

Table 96. MI: Method of Detection

First Event	Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od N = 9291
All MI (excl. silent MI)	504 (5.4%)	593 (6.4%)
MI detected by Investigator	395 (4.2%)	482 (5.2%)
MI detected from cardiac enzyme biomarkers	114 (1.2%)	121 (1.3%)

Source: Reproduced from sponsor, CSR page 3380, Table 11.2.7.5

In order to ascertain the validity of adjudicated MIs based on site-reported events, an analysis similar to the one described for CV deaths was performed. However, MIs that were detected from cardiac enzyme biomarkers, such as from the "trigger" program, were excluded from this analysis.

Within the adjudication tracking dataset, site-reported MI events could be clearly described as STEMI or NSTEMI or also identified via "other" categories, such as "Other (MI)" and also unstable angina events that were also included a report that stated an associated MI on the same data string. There were also clear misspellings, such as "miocardial" or "infaction" (sic) that were included in the analysis. Subjects determined to have site-reported MIs were then compared against adjudicated outcome, including "Myocardial infarction," "No Event," "Recurrent Ischemia," or "Severe Recurrent Ischemia." This analysis is notable more inclusive than the sponsor's analysis presented in Section 8.4.5, since it includes actual site terms that may not have been included as formal site-reported terms (e.g., misspellings and miscategorizations).

Table 97 describes the cumulative number of subjects who had site-reported MI events. Although the numbers of events in the ticagrelor arm were numerically lower, a simple two-sample test of proportions in this analysis was non-significant. (Although this type of statistical testing is inappropriate for a time-to-event trial.)

Table 97. Site-Reported MI Analysis

Treatment	N	Subj. with site-reported MI events	Two sample test of proportions
Clopidogrel	9291	548 (5.9%)	p=0.13
Ticagrelor	9333	504 (5.4%)	

Source: R. Fiorentino, Clinical Reviewer

All site reported MI events were broken down according to final adjudication and compared to the total number of (MI and non-MI) site reported events submitted for adjudication, as shown in Table 98. Because subjects could have multiple events submitted, the numbers in Table 97 and Table 98 are not in agreement.

Table 98. Site Reported vs. Adjudicate Events: MIs

Site MI Event?	Adjudicated MI Event?	Ticagrelor Total: 5280 events submitted for adjudication	Clopidogrel Total: 5425 events submitted for adjudication
No	Yes	209 (4.0%)	217 (4.0%)
Yes	No	184 (3.5%)	158 (2.9%)
Yes	Yes	402 (7.6%)	472 (8.7%)
No	No	4485 (84.9%)	4578 (84.4%)

Source: R. Fiorentino, Clinical Reviewer

Both ticagrelor and clopidogrel arms had events equally likely to have been adjudicated as MIs not reported as such by site (4.0%). This would occur when unstable angina or recurrent ischemia cases meet the criteria for an MI but are not deemed to be MIs at the site.

174 ticagrelor subjects had 184 site MI events downgraded to no adjudicated MI. The individual efficacy response data, adjudication packets and CRFs of 8 subjects in the ticagrelor arm who had more than one downgraded event were examined. In addition, numerous "random" reviews of adjudication reports of MIs were performed. In general, it appeared that the adjudication of MIs adhered appropriately (and rigorously) to the definitions provided in the protocol and ICAC charters. Some patients were noted to have had other cardiac ischemic events (CIE) adjudicated as MIs despite other events not satisfying the adjudication criteria. Of note, there were a number of site-reported MIs that could be determined *not* to be MIs relatively easily, based on clinical, laboratory or ECG criteria presented. In general, the quality of the data submitted in the adjudication packet appeared to be appropriately detailed.

In a similar analysis, there were 90 events (in 85 subjects) identified in the clopidogrel arm who had adjudicated MIs but no clear diagnosis of MI by the site. The majority of these sites reported cardiac events were reported as unstable angina. A select review of the site reported events (e.g., stable angina or atypical chest pain, recurrent ischemia) did not reveal systematic biases in reports submitted or in the adjudication process. Overall there was adequate submission of ECGs and cardiac enzyme data to support the adjudications.

In contrast, ticagrelor was numerically more likely to have site reported events later adjudicated not to be an MI. On review of the adjudication materials there was no systematic evidence discernible of biased assessments or adjudications. A combination of multiple events per subjects somewhat complicates this analysis.

As shown in Table 99, almost half of all subjects with events submitted for adjudication had multiple events submitted.

Table 99. Frequency of MIs Reported per Subject

Category: Number of MI Events (all) submitted for adjudication	Number of Subjects
1	4807
2	1627
3	469
4	161
5	75
6	20
7	4
8	6
10	1
12	1

Source: R. Fiorentino, Clinical Reviewer

Further analysis was performed to assess the frequency of any potential MIs that may not have been captured because no data was sent for adjudication. A hospital admission dataset (AHOSPLOG.xpt) was screened for potential MIs in the admitting diagnosis and combined with similar assessments in the Serious Adverse Event datasets. Terms typical for suspected MIs were included into searches. Data from these datasets was compared to both adjudication and primary analysis datasets. From this analysis the numbers of subjects with any event or cardiac ischemic event could be compared to the final adjudication result and whether that event counted towards the primary analysis.

The results of this analysis are shown in Table 100.

Table 100. Hospitalization and Adverse Events: MIs

Treatment	Any Event Submitted for adjudication	Any cardiac ischemic event submitted	Adjudicated Result: MI	MI event in primary analysis
Ticagrelor	98.9%	97.3%	82.8%	75.6%
Clopidogrel	98.6%	96.9%	89.7%	87.3%

Source: R. Fiorentino, Clinical Reviewer

In general it appeared that the large majority of suspect events noted in hospital admission and SAE datasets were submitted for adjudication and that many of these subsequently resulted in adjudicated events that counted toward the primary analysis.

8.4.4 Strokes

Sponsor submitted an analysis dataset (ADJUD.xpt) containing adjudication tracking data. From this dataset, event details and outcome from the sites were compared to the final adjudication results for each event.

- 73 subjects were identified from this dataset who had a "Stroke/TIA" event type noted at the site and either had "No Event," "Stroke" or "TIA" listed as the final adjudicated results.

Of these, the event documentation, including CRFs were scrutinized for subjects that had site reported strokes "downgraded" to either "TIA" or "No Event." Specifically, the clinical course and adjudication comments (where available) were subjectively evaluated to determine the appropriateness of the final adjudicated result.

The purpose of this review was to investigate the validity of the adjudication process and to ensure that strokes were appropriately assessed.

In this analysis, 17 ticagrelor and 15 clopidogrel subjects with site-reported "strokes" were down-classified to "No Event" to "TIA" after adjudication.

The following conclusions were made by this reviewer following this analysis:

1) In general, the cases where suspected strokes were downgraded appear to have been appropriately and reasonable adjudicated.
2) No systematic adjudication problem or misclassification was identified.
3) Comments regarding the reason for adjudication and down-classification were not universally available
4) It appeared that down-classification from "stroke" to "no event" was due to insufficient information on the clinical presentation and outcome, which ranged from inadequate to entirely non-existent
5) The presence of concomitant illness/diagnoses were occasionally suggest alternative explanations (e.g., cerebral ischemia due to not due to CVA)
6) The lack of adequate follow-up of suspect events and objective assessment, especially those based on 3rd party accounts (such as family), made some adjudication events impossible.

8.4.5 Sponsor's Analysis of Site-Reported vs. Adjudicated Events

Table 101 and Table 102 present the sponsor's analysis of adjudicated vs. site reported events.

Table 101. Ticagrelor: Investigator vs. Adjudicated Deaths

Investigator Reported	ICAC Adjudicated			TOTAL
	Vascular Death	Non-Vascular Death	Other Death	
Vascular Death	296	6	9	311
Non-vascular Death	16	44	7	67
Other Death	19	0	20	39
TOTAL	331	50	36	**417**

Source: Reproduced from Sponsor, data dated May 11, 2010, Table 6.9.6

Table 102. Ticagrelor: Investigator vs. Adjudicated Events

Investigator Reported	ICAC Adjudicated							TOTAL
	Stroke	TIA	Myocardial Infarction	Severe Recurrent Cardiac Ischemia	Recurrent Cardiac Ischemia	Other Arterial Thrombotic Event	No Event	
Stroke	134	2					16	152
TIA	7	17					8	32
Myocardial Infarction			389	76	25		57	547
Unstable Angina			64	227	167		54	512
Stable Angina			2	13	28		27	70
Other CIE			34	38	35		57	164
Other Arterial Thrombotic Event						25	34	59
TOTAL	141	19	489	354	255	25	253	**1536**

Source: Reproduced from Sponsor, data dated May 11, 2010, Table 6.9.6

Table 103 and Table 104 present the sponsor's analysis of adjudicated vs. site reported events in the clopidogrel arm.

Table 103. Clopidogrel: Investigator vs. Adjudicated Deaths

Investigator Reported	ICAC Adjudicated			
	Vascular Death	Non-Vascular Death	Other Death	TOTAL
Vascular Death	351	5	13	369
Non-vascular Death	28	58	7	93
Other Death	30	3	25	58
TOTAL	409	66	45	**520**

Source: Reproduced from Sponsor, data dated May 11, 2010, Table 6.9.7

Table 104. Clopidogrel: Investigator vs. Adjudicated Events

Investigator Reported	ICAC Adjudicated							TOTAL
	Stroke	TIA	Myocardial Infarction	Severe Recurrent Cardiac Ischemia	Recurrent Cardiac Ischemia	Other Arterial Thrombotic Event	No Event	
Stroke	107	1					14	122
TIA	8	28					19	55
Myocardial Infarction			450	68	16		48	582
Unstable Angina			59	257	159		55	530
Stable Angina			5	15	43		16	79
Other CIE			46	43	52		69	210
Other Arterial Thrombotic Event						35	37	72
TOTAL	115	29	560	383	270	35	258	**1650**

Source: Reproduced from Sponsor, data dated May 11, 2010, Table 6.9.7

In general the numbers track with my own analysis based on actual site-reported terms submitted by the investigators. Where there is some disagreement, it is not clearly favorable toward ticagrelor. One reason why the actual numbers contrast somewhat from my own analysis is that the sponsor's analysis is limited to those events that were submitted for adjudication, whereas events eventually adjudicated as MI without a site-reported event available may not have been included. For instance, in the adjudication tracking dataset, (ACADJ.xpt) there are 1,300 adjudicated MI events (in 1,147 subjects). However the above data contains only 1,049 adjudicated MIs. Where the numbers are not readily comparable, they provide insight into the appropriateness of the adjudication process.

8.5 Labeling Recommendations

Pending at the time of completion of this review.

8.6 Advisory Committee Meeting

Pending at the time of completion of this review.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT FIORENTINO
06/25/2010
Initial clinical efficacy review (pre-AC meeting)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: N022433 **Applicant:** AstraZeneca **Stamp Date:** 11/16/09

Drug Name: Ticagrelor **NDA/BLA Type:** Priority

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: DISPERSE & DISPERSE2 Sample Size: DISPERSE: 363 treated (200 T* and 163 C**, DISPERSE2: 1641 treated (984 T and 657 C) Arms: DISPSERSE (5 arms), DISPERSE2 (3 arms) Location in submission: Module 2 *Ticagrelor **Clopidogrel	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: PLATO	X			FDA agreed to a single pivotal study

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

1

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: ACS				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	US + OUS data
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MEDRA 11.1 located in AE data set
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are			X	

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[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?				
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver submitted
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

n/a

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

n/a

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Robert Fiorentino   December 10, 2009
_____
Reviewing Medical Officer #1   Date

Melanie Blank   December 30, 2009
_____
Reviewing Medical Officer #2   Date

Tom Marciniak   December 30, 2009
_____
Clinical Team Leader   Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MELANIE J BLANK
12/30/2009

ROBERT FIORENTINO
12/30/2009
efficacy reviewer

THOMAS A MARCINIAK
12/30/2009

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22433
Priority or Standard	Standard
Submit Date(s)	November 18, 2009
Received Date(s)	November 18, 2009
PDUFA Goal Date	September 16, 2010
Division / Office	Division of Cardiovascular and Renal Products/ ODE 1
Reviewer Name(s)	Melanie Blank, MD
Review Completion Date	June 28, 2009
Established Name	Ticagrelor
(Proposed) Trade Name	Brilinta
Therapeutic Class	cyclopentyltriazolopyrimidine
Applicant	AstraZeneca
Formulation(s)	Tablet
Dosing Regimen	90 mg bd
Indication(s)	Acute Coronary Syndrome
Intended Population(s)	Acute Coronary Syndrome Population

Clinical Review
Melanie J. Blank, MD
NDA 22433
Ticagrelor (Brilinta)

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Clinical Review
Melanie J. Blank, MD
NDA 22433
Ticagrelor (Brilinta)

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1 Recommendations/Risk Benefit Assessment

1.3   Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A medication guide for practitioners has been proposed by the sponsor. This should be sufficient for informing providers on the main ticagrelor safety issues, contraindications, and administration instructions.

1.4   Recommendations for Postmarket Requirements and Commitments

I have no recommendations for Postmarket requirements and commitments at this time. If the sponsor chooses to do another long term study, I would suggest that they concentrate their efforts on the U.S. population and control the aspirin dose

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1   Chemistry Manufacturing and Controls

Ticagrelor is a round, biconvex, yellow, film-coated tablets containing 90 mg of Ticagrelor. Ticagrelor is an immediate release (IR) formulation intended for twice-daily (bd) administration. The 90 mg ticagrelor IR tablet formulations were used in the Sponsor's worldwide clinical development program, and the Phase 3 tablet is the proposed commercial formulation of ticagrelor.

4.3   Preclinical Pharmacology/Toxicology

Paraphrased from Dr. Elizabeth Hausner's review:

Ticagrelor toxicology was assessed in mice, rats, rabbits and marmosets. The non-clinical toxicology studies indicated that the target organs of toxicity were the gastrointestinal tract (dogs, rats, marmosets), liver (rats), bone marrow (rats, marmosets), immune system (marmosets, rats), adrenal (rodents) and endocrine system (mice and female rats).

Findings pertinent to the clinical review:

Respiratory System findings: In rats, safety pharmacology studies showed that there were pulmonary function changes after administration of ticagrelor. There was increased respiratory rate (up to 20% of pre-dose baseline, p<0.01), increased peak inspiratory flow (up to 35% of pre-dose baseline, p>0.05) and increased expiration time (decreased by up to 20% from pre-dose baseline, p<0.01). Other studies showed that foamy alveolar macrophages were present in the lungs of rats at doses ≥180 mg/kg/day. These were described as minimal changes. Similar changes were not reported for marmosets.

Hematology findings: Across species, the hematology findings were relatively consistent with minor blood loss associated with regeneration.

Hepatic findings: Liver effects in rats occurred at doses ≥80 mg/kg and included indications of altered function or damage evidenced by decreased triglycerides (67%, p<0.001), increased AST (20%, p<0.001) or ALP (31%, p<0.001) when compared to the control groups. Centrilobular hypertrophy was inconsistently reported (mice ≥250 mg/kg/day; rats ≥180 mg/kg). Liver effects in marmosets were inconsistent.

Evaluation of Fertility: The main study animals did not show histologic effects on the testes or epididymides.

Embryo-fetal development: Studies showed effects on the liver and the skeletal systems in both rats and rabbits. Delayed development of the gallbladder and incomplete ossification of the hyoid, pubis and sternebrae were seen in rabbits. Supernumerary liver lobes and incomplete ossification of the parietal bone, sternebrae, misshapen/misaligned sternebrae, displaced articulation of the pelvis, and supernumerary ribs were seen in the rats. The pre- and post-natal development study in rats indicated that exposure to ticagrelor in late gestation or during lactation also affected development. Pinna unfolding delays and eye opening delays were common.

Reproductive System findings: There were reported drug-related effects on the reproductive organs of both sexes. In male mice, very high doses caused seminiferous epithelial degeneration of the testes. Female mice had an absence of corpora lutea at very high doses. In rats, endocrine effects were manifested as dose-related decreases in regular estrus cycles at relatively low doses ≥10 mg/kg. The relatively non-specific finding of irregular estrus cycles became more important in light of the carcinogenicity study where female rats showed statistically significant incidences of uterine adenocarcinoma and uterine squamous cell carcinoma. The rat carcinogenicity study also demonstrated a significant decrease in female survival (Cox: p=0.018, Kruskal-Wallis: p=0.0424), possibly due to metastatic uterine neoplasia. Fourteen of the 31 HD females who died ahead of scheduled termination had (metastatic) uterine adenocarcinoma listed as the cause of death.

The salient nonclinical findings formed the basis for much of my in-depth system oriented review. I focused my evaluation on not only the clinical safety issues that were known prior to the phase 3 experience (bleeding, cardiac and respiratory), but also on hepatic safety issues, the potential neoplastic effects and potential hormonally mediated effects of ticagrelor in the human.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ticagrelor, (also referred to as AZD6140 in my review), substantially reduces platelet aggregation, blocking the pathophysiologic process leading to intracoronary thrombosis in ACS. The first of a new chemical class of antiplatelet agents called **cyclopentyltriazolopyrimidines**, it has properties that importantly distinguish it from the thienopyridines. Ticagrelor is rapidly absorbed following oral administration, and binds reversibly to the P2Y12 platelet ADP receptor. In the acute setting, a rapid onset of effect theoretically may provide better protection during a period of particularly high risk for the ACS patient.

4.4.2 Pharmacodynamics

The pharmacodynamic (PD) effect of antiplatelet agents is traditionally assessed in blood samples from patients by measuring IPA. Because ticagrelor is not a prodrug requiring metabolic activation, it promptly achieves both a higher and more consistent inhibition of platelet aggregation (IPA) than clopidogrel. For example, following oral administration of a 600 mg loading dose of clopidogrel, measured IPA increases gradually, reaching a level after 8 hours that is achieved after only 30 minutes following a 180 mg loading dose of ticagrelor, which then continues to increase to 87% to 89% by 2 hours.

Ticagrelor's reversible binding to the P2Y12 receptor permits the return of platelet aggregation upon cessation of therapy. This process does not require the generation of new platelets. In experiments designed to document this, ticagrelor demonstrated a statistically significant, faster rate of IPA offset compared with clopidogrel from 4 to 72 hours following cessation of administration; IPA measurements are similar for ticagrelor at 3 days and for clopidogrel at 5 days following the last dose.

4.4.3 Pharmacokinetics

Ticagrelor undergoes rapid absorption with peak plasma concentrations attained 2 to 3 hours after oral administration to patients with ACS. An active metabolite forms rapidly, attaining peak plasma concentrations 2 to 3 hours after oral ticagrelor ingestion. Ticagrelor's steady-state volume of distribution, 87.5 L, indicates it does not extensively distribute into or bind to tissues. Both ticagrelor and its primary active metabolite bind extensively (>99.7%) to plasma proteins; age, gender, severe renal impairment, and mild hepatic impairment do not affect protein binding. Both the AUC and Cmax of both ticagrelor and its active metabolite show approximately proportional increases with increasing oral doses, indicating linear PK. Mean terminal elimination half-life (t1/2) for ticagrelor was 6.9 hours (range 4.5 to 12.8 hours). Ingestion of a high-fat meal had no effect on ticagrelor Cmax, but resulted in a 21% increase in the area under the concentration-time curve (AUC). These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food. The primary route of ticagrelor metabolism is via hepatic metabolism. The active metabolite is at least as potent as ticagrelor at blocking the P2Y12 receptor *in vitro*. As CYP3A4 enzymes are mainly responsible for ticagrelor metabolism and the formation of its active metabolite, the potential for important drug-drug interactions involving other substrates, inhibitors or inducers of this common metabolic pathway was assessed in the development program and will be discussed in my review.

The active metabolite most likely undergoes excretion in bile. Neither ticagrelor nor the active metabolite depend on renal excretion, with <1% recovery in urine for parent and active metabolite. Ticagrelor has a mean t½ of 6.9 hours and the t½ of the active metabolite is 8.6 hours.

7 Review of Safety

7.1.1 Safety Summary and Summary of Studies/Clinical Trials Used to Evaluate Safety

There are several safety issues that need to be considered before making an executive decision on whether or not approve ticagrelor, particularly in the light of the evidence that ticagrelor may not benefit the U.S. population.

There were 9235 patients that received at least one dose of ticagrelor and 9186 patients that received at least one dose of clopidogrel-in PLATO. These patients comprised the "safety set", according to the sponsor, and their data were used for most of my safety review. When I analyzed adverse events I included only those patients who had at least one dose of drug before having an adverse event.

One of the most significant findings from PLATO was the all-cause mortality benefit seen for ticagrelor. There were statistically significant fewer overall deaths in the ticagrelor group compared to the clopidogrel. In total there were 399 (4.28%) adjudicated deaths within the efficacy period in the ticagrelor treatment arm compared

to 506 (5.45%) in the clopidogrel treatment arm (RR=0.78). Vascular deaths accounted for most deaths (~ 95% of deaths in both treatment groups). The term "vascular death" includes cardiovascular deaths, cerebrovascular deaths, bleeding deaths and any other death for which there was no clearly documented nonvascular cause. Bleeding deaths were not as common as other causes of death (0.2% of patients died of bleeds). Causes of death were similar between treatment groups. The most common cause of death was myocardial infarction occurring in about 1% of randomized patients. Sudden death, heart failure, other vascular events and stroke were among the more common causes of death. The U.S. population when it came to death prevalence was an outlier. In the U.S., there were more deaths in the ticagrelor treatment group compared to the clopidogrel treatment group [35 (3.8%) vs. 29 (3.2%), respectively.

The most important safety issue for ticagrelor was bleeding. PLATO defined its own definitions of bleeding severity. The PLATO defined bleeding severity scale is included in the full body of the review. All bleeds were adjudicated according to these definitions which are, in my opinion, superior to the TIMI bleeding definitions in that the severity of bleeds is based on clinical relevance as well as on hemoglobin loss. Ticagrelor –treated patients had only a few more major bleeds than clopidogrel-treated patients ([1031 (11.2%) vs. 997 (10.9%), respectively and this difference was not statistically significant. However the frequency of major + minor bleeding (any bleed requiring intervention or treatment) was greater in the ticagrelor treatment group compared to the clopidogrel treatment group [1339 (14.5%) vs. 1215 (13.2%), respectively (log-rank = 0.0083)] .The reason for this increase was primarily the increased frequency of spontaneous (non-procedural/ non-CABG) bleeds in ticagrelor-treated patients. There was no increase in overall major/life-threatening or fatal bleeds in the ticagrelor treatment group compared to the clopidogrel treatment group as a whole. However, the pattern of increased non-procedural bleeds in ticagrelor-treated patients was also operative for major/life-threatening/fatal bleeds. When it comes to spontaneous bleeds, there were more in the ticagrelor group at all degrees of severity.

Most bleeds in PLATO were CABG-related [737(8%) vs. 783 (8.5%) for ticagrelor and clopidogrel, respectively]. There was a slightly lower CABG-related frequency of bleeding in most PLATO-defined categories of bleeding for ticagrelor-treated patients. However, if one looks at risk of CABG-related bleeding by time after stopping drug, one can see that there is increased bleeding in the ticagrelor group compared to the clopidogrel treatment group until day 5 after stopping drug when the pattern reverses. More importantly, however, is the fact that despite the increased frequency of major/life-threatening CABG-related bleeds in the ticagrelor group related to early CABG, the all-cause mortality following CABG was less for ticagrelor than for clopidogrel when considering any time interval between the last dose of study treatment and beginning CABG.

Dyspnea was also an important safety issue for ticagrelor. Dyspnea occurred frequently in patients treated with ticagrelor in all clinical phase 2 studies and in PLATO (14.6% of

ticagrelor-treated patients vs. 8.7% of clopidogrel-treated patients). Dyspnea SAEs occurred in less than 0.9% of ticagrelor-treated patients and in less than 0.6% of clopidogrel-treated patients. Dyspnea in ticagrelor-treated patients resulted in more discontinuations than dyspnea in clopidogrel-treated patients (0.9% vs. 0.1%, respectively). More impressively, nearly 10% of ticagrelor-treated patients that had dyspnea discontinued treatment for other AEs compared to <6% of clopidogrel-treated patients. Additional concerning observation is that the onset of dyspnea was considerably earlier in the ticagrelor-treated patients compared to the clopidogrel-treated patients, lasted usually >20 days (up to approximately 400 days) and at any length of episode, the ticagrelor treatment group had numerically A Pulmonary Function Substudy was conducted to see if there were any effects of ticagrelor on pulmonary function tests. The substudy did not reveal any differences between treatment groups but it was designed, conducted and analyzed in such a way that might have obscured differences if they existed.

On the reassuring side, dyspnea is a symptom that resolved in 2/3 of the patients during the study. This suggests to me that it is unlikely that ticagrelor is causing chronic pulmonary changes in most patients. While two ticagrelor-treated patients with dyspnea AEs died, it is hard to assign the cause of these deaths to ticagrelor because of other comorbidities and confounding circumstances. Most reassuringly, patients with dyspnea know they have it and can discontinue ticagrelor if they are troubled by it. And importantly, despite its exploratory nature, a retrospective analysis of PLATO outcomes data showed that patients with dyspnea at any time during the trial had favorable clinical outcomes.

Arrhythmias were a concern for ticagrelor because of an increased frequency of arrhythmia related deaths in phase 2 data. In PLATO, the data for ticagrelor is unfavorable for atrial arrhythmias and ventricular pauses but it is favorable for sudden death and ventricular arrhythmias. There was a Holter Monitor Substudy that confirmed the increased frequency of ventricular pauses. These data in addition to the higher frequency of syncope, presyncope, dizziness, wooziness, and giddiness events in the ticagrelor arm of PLATO, is compelling enough evidence to conclude that the product label should include a warning about the potential for syncope and presyncope and cardiac arrhythmias, particularly ventricular pauses. While it might be attractive to limit ticagrelor's use to patients without histories of sick sinus syndrome, second or third degree AV block, recurrent dizziness, history of loss of consciousness, syncope, advanced COPD or sleep apnea, the reduced frequency of cardiac arrest should outweigh these other concerns.

Renal effects were a concern because of observations of increased serum creatinine levels during treatment with ticagrelor in the phase 1 and 2 studies. In PLATO, there was an increased frequency of patients that had extreme decreases in eGFR (>30% - 100%) in the ticagrelor group as compared to the clopidogrel group. There was no difference between the treatment groups in frequency of deaths or discontinuations for renal AEs. However, there were more renal AEs and renal SAES in the ticagrelor-treated patients compared to the clopidogrel-treated patients that was greatly magnified in patients with preexisting stage 4 renal insufficiency. Additionally, ticagrelor-treated patients with eGFR less than 30 are at higher risk for endpoint events, renal failure, all-cause death and major bleeds. It may be wise to limit the use of ticagrelor in this patient population.

A troubling observation in PLATO was the increased frequency and earlier time to overall stroke and intracranial hemorrhagic bleeding events (mostly from strokes) in the ticagrelor-treated patients. Hemorrrhagic bleeds carry a very high mortality. There were 11 patients in the ticagrelor treatment group that died of intracranial hemorrhagic events (almost 1/2 of the patients with intracranial bleeds) while 1/14 patients in the clopidogrel-treatment group died of intracranial bleeding.

Only ~ 400 patients with baseline mild hepatic impairment were enrolled. Nevertheless, such patients were more likely to have major bleeds if on ticagrelor (11.2%) vs. 8.7% if on clopidogrel. There were also more deaths (3.2% vs. 0.9%) in ticagrelor vs. clopidogrel-treated hepatically impaired patients, respectively. There were also more SAEs and AEs in the mildly hepatically impaired patient who was treated with ticagrelor. Consideration should be given to contraindicating ticagrelor in hepatically impaired patients.

Other important safety explorations were uric acid level increases, hepatic events, hormonally mediated events and neoplastic events. An interesting observation was the increased frequency of gynecomastia in the ticagrelor-treated patients. None of these explorations were major safety concerns
In addition to the pivotal 3 study, PLATO I reviewed 4 phase 2 studies that will be considered in the safety review when applicable. In all, there were 960 patients exposed to ticagrelor in the phase 2 studies with doses ranging from 50 mg twice a day to 400 mg once a day. The study names (numbers) are: DISPERSE (Study D5130C00008), DISPERSE2 (Study D5130C00002), OFFSET (Study 5130C00048), and RESPOND (Study D5130C00030).

There were also 41 phase I studies performed that focused on pharmacokinetic (PK) and PD parameters for ticagrelor and its primary metabolite in different populations, and characterization of drug-drug interactions with ticagrelor. The studies were designed to examine specific characteristics of the drug. The Sponsor did not pool the data to address additional safety issues. FDA agreed that pooling of data was not necessary. I reviewed these studies if I felt they were important for my review.

Additionally, I reviewed current literature on ticagrelor and the PLATO study, other literature pertaining to potential safety issues.and I familiarized myself with the Prasugrel safety reviews.

The phase 3 and 2 trials are briefly summarized below:

PLATO was a randomized, double-blind, double-dummy, parallel group, international, multicenter study comparing the efficacy and safety of ticagrelor 90 mg administered twice daily twice daily with clopidogrel 75 mg once daily for the prevention of vascular events in patients with non-ST or ST elevation ACS. PLATO included 18624 randomized patients, 13336 males and 5288 females, aged 18 years and over, with a non-ST or ST segment elevation ACS (index event) and with high risk of secondary thrombotic events. Patients were randomized to treatment as soon as possible after presentation but at the latest within 24 hours of the onset of their index event. In PLATO, the overall mean exposure was 248 days, with a median exposure of 277 days (see D5130C05262 CSR, Table 11.3.1.2). Two substudies were conducted as part of the PLATO study to assess specific safety issues, including a Holter monitoring substudy and a pulmonary function substudy.

DISPERSE was a randomized, double-blind, double-dummy, parallel group, multicenter, multinational study to assess the PD and PK effects of ticagrelor at doses of 50 mg twice a day, 100 mg twice a day, 200 mg twice a day and 400 mg once a day in the presence of ASA compared to clopidogrel 75 mg once a day plus ASA, in subjects with documented atherosclerotic disease, DISPERSE enrolled 146 male and 54 female patients, age 34 to 84 years. In DISPERSE, the overall mean exposure was 27.9 days.

DISPERSE2 was a randomized, double-blind, double-dummy, parallel group, multicenter, multinational trial of 4, 8 or 12 weeks to assess the safety and tolerability of ticagrelor at doses of 90 mg twice a day and 180 mg twice a day, in the presence of ASA, compared with clopidogrel 75 mg once a day plus ASA, in patients with non-ST segment elevation ACS by evaluation of Independent Central Adjudication Committee (ICAC)-adjudicated bleeding events observed within the first 4 weeks of treatment (Day 29). DISPERSE2 treated 632 male and 352 female patients. In DISPERSE2, the overall mean exposure was 54.4 days.

OFFSET was a multi-center, randomized, double-blind, double-dummy, parallel group study of the onset and offset of the antiplatelet effects of 90 mg twice a day ticagrelor (with 180 mg loading dose) compared with 75 mg once a day clopidogrel (with 600 mg loading dose) and placebo with acetylsalicylic acid (ASA) as background therapy with additional detailed assessment of cardiopulmonary function in patients with stable CAD.

OFFSET randomized 93 male and 30 female patients, 18 years of age and over with documented stable CAD. In OFFSET, the overall mean exposure was 40.9 days.

RESPOND was a multi centre, randomized, double-blind, double-dummy crossover study comparing the anti-platelet effects of 90 mg twice a day ticagrelor with 75 mg once a day clopidogrel in patients with stable CAD previously identified as clopidogrel non-responders or responders. In RESPOND a total of 98 patients were randomized, 48 male and 9 female patients to the responder cohort and 28 male and 13 female patients to the non-responder cohort. All patients who participated in RESPOND were18 years of age and over with documented stable CAD. In RESPOND, the overall mean exposure was 26.9 days, with a median exposure of 29.0 days.

The Phase 1 clinical pharmacology program comprises a diverse range of studies with a focus on formulation development, evaluation of PK and PD parameters for ticagrelor and its primary metabolite in different populations, and characterization of drug-drug interactions with ticagrelor. Individual studies were designed to understand the properties of ticagrelor and provide adequate information for safe use of the drug. One of the caveats from the phase 1 studies is that several formulations were used during that stage of clinical development. The FDA clinical pharmacology review has reviewed this issue and thoroughly and thinks that the data from the phase 1 program is fully applicable to the current formulation.

7.1.2   Categorization of Adverse Events

The sponsor used MedDRA 11.1 to categorize adverse events. As a sensitivity test, I combined certain AE terms together that had similar pathophysiological or anatomical characteristics and recoded the adverse event data set to ensure that I would not be missing signals that could be obscured by the MedDRA coding system. In my adverse events sections I specify if the table or graph is from my analysis or the sponsor's analysis.

7.1.3   Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The sponsor provided data from the phase 2 studies. However, they were not pooled with the PLATO data. As necessary, I looked at data values from the phase 2 studies while conducting my review.

7.2   Adequacy of Safety Assessments

7.2.1   Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In PLATO, 9235 patients received ticagrelor, with over 6300 patient-years of exposure. The phase 2 studies, when pooled, included only 960 ticagrelor-treated patients in the safety population. However, the duration of exposure was much shorter, ranging from 4 to 12 weeks. The PLATO exposure is clearly much greater than the phase 2 exposure and therefore, most of my review concentrates on this trial. The sponsor chose to not pool the safety data and in the minutes from the April 17, 2009 pre-NDA meeting, FDA agreed to this strategy.

Table 1 provides a tabular summary of the exposure to ticagrelor in the safety analysis of PLATO. The safety analysis set for ticagrelor contained 9235 patients and for clopidogrel, the safety analysis set contained 9186 patients. > 70% of patients were exposed to treatment for over 270 days, and >40% were exposed for over 1 year. The numbers of patient-year exposures were 6301 for ticagrelor and 6388 for clopidogrel.

Table 1: Exposure for PLATO (safety analysis set)

Characteristic	Category	Actual Treatment	
		Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Days in Study	N	9235	9186
	Mean	298.6	298.4
	SD	96.31	96.06
	Median	357	356
	Min	1	1
	Max	575	548
	1-30	308 (3.3%)	306 (3.3%)
	31-90	145 (1.6%)	157 (1.7%)
	91-180	299 (3.2%)	290 (3.2%)
	181-270	1840 (19.9%)	1835 (20.0%)
	271-360	2506 (27.1%)	2542 (27.7%)
	>360	4137 (44.8%)	4056 (44.2%)
	>0	9235 (100%)	9186 (100%)
	>30	8927 (96.7%)	8880 (96.7%)
	>90	8782 (95.1%)	8723 (95.0%)
	>180	8483 (91.9%)	8433 (91.8%)
	>270	6643 (71.9%)	6598 (71.8%)
	>360	4137 (44.8%)	4056 (44.2%)
Patient Years		6301	6388

Source: PLATO study report, p.799

Table 2 is a tabular listing of the exposure in the phase 2 studies. As you can see, the exposure in the phase 2 studies equals 211 patient-years compared to the 6301 patient-year exposure in PLATO..

Table 2: Exposure for phase 2 studies

Actual Treatment	Number of Patients	Mean Days of Treatment	Patient-years
Ticagrelor 180 mg bd	360	51.9	51.2
Ticagrelor 90 mg bd	513	44.4	62.4
Ticagrelor 50 mg bd	41	27.9	31.3
Ticagrelor 400 mg od	46	27.5	3.5
Clopidogrel 75 mg od	498	45.2	61.7
Placebo	12	40.7	1.3

Source: Adapted from Integrated Summary of Safety, p.65

7.2.2 Explorations for Dose Response

DISPERSE2 studied the target dose for Phase 3, 90 mg bd, and double that dose, 180 mg bd in patients with NSTEMI-ACS. There was similar total bleeding amongst the 90 mg bd ticagrelor, 180 mg bd ticagrelor, and 75 mg daily clopidogrel groups. These results suggested that the 180 mg bd ticagrelor dose would be best for PLATO. Clinical pharmacology studies, however, played a role in the decision to modify this choice because of greater drug exposure in patients receiving moderate inhibitors of cytochrome P450 isoenzyme 3A (CYP3A4), such as diltiazem. Also, the Holter data from DISPERSE 2 revealed that there were numerically more patients with pauses in the 180 mg bd ticagrelor group. An analysis of the data suggested that there was an apparent dose-related effect of ticagrelor on ventricular pauses. Also, ventricular pauses and adverse events related to bradycardia were observed with ticagrelor, including in a few individual healthy volunteers during the Phase I Single Ascending Dose and Thorough QT studies. Based on these considerations, the 90 mg bd maintenance dose appeared to provide the best balance of efficacy and safety.

Please refer to the clinical pharmacology review for a more detailed discussion.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the pharmacology toxicology review. Important animal data is presented when appropriate in this review.

7.2.4 Routine Clinical Testing

The testing was done in a central laboratory and appeared to be adequate.

I suspect that capture of AEs may have been spotty after drug discontinuation or even prior to drug discontinuation. The reason for my suspicion is that many patients missed their last visits because of the early wrap-up of the trial. While attempts were made to assess the survival of these patients, not much attempt was made to capture the other efficacy endpoint measures or to collect AEs.

7.2.5 Metabolic, Clearance, and Interaction Workup

There was a thorough workup of these safety issues

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Currently Available Related Drugs for Indication:

Clopidogrel bisulfate (PLAVIX and generic) and ticlopidine hydrochloride (TICLID and generic) are ADP receptor antagonists of the thienopyridine class that inhibit platelet activation and aggregation and carry cardiovascular claims.

Prasugrel HCl (Effient) Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets

Ticagrelor differs from the others in the class of platelet inhibitors in that it reversibly binds to the P2Y12 class of ADP receptor on platelets. The clinical importance of this reversibility will be explored in this review.

1. **Clopidogrel** is indicated for the reduction of atherothrombotic events as follows:
Recent MI, Recent Stroke or Established Peripheral Arterial Disease
For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease…to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.
Acute Coronary Syndrome For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Qwave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG…to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia For patients with ST-segment elevation acute myocardial infarction, PLAVIX has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, reinfarction
or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

2. **Ticlopidine** is indicated for the following conditions:
• To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke.
• As adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation.

Ticlopidine carries black box warnings for thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis, and aplastic anemia, and the indication states that the drug "…should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy."

3. **Prasugrel** is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI).

- Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

Effient™ has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death *[see Clinical Studies (14)]*.

It is generally recommended that antiplatelet therapy be administered promptly in the management of ACS because many cardiovascular events occur within hours of initial presentation. In the clinical trial that established the efficacy of Effient, Effient and the control drug were not administered to UA/NSTEMI patients until coronary anatomy was established. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial *[see Warnings and Precautions (5.2)]*. Because the large majority of patients are managed without CABG, however, treatment can be considered before determining coronary anatomy if need for CABG is considered unlikely. The advantages of earlier treatment with Effient must then be balanced against the increased rate of bleeding in patients who do need to undergo urgent CABG.

Since ticlopidine is associated with increased risk for thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis, and aplastic anemia, I examined the ticagrelor data for evidence of these types of adverse events.

Prasugrel provides substantially better (>80%) IPA and clinical efficacy than clopidogrel, but at the cost of a marked increase in major bleeding events, especially in patients over 75 years old, those with body weight <60 kg, those with a history of transient ischemic attack or stroke, and in those undergoing CABG surgery (Wiviott et al 2007). Like clopidogrel, prasugrel inhibits aggregation permanently in circulating platelets. Its greater antiplatelet effect, coupled with the same property of irreversible binding leading to permanent platelet inhibition, seems to translate into a higher bleeding risk. For this reason, bleeding was the main focus of my review. Since prasugrel also was associated with an excess of new malignant tumors, I also focused on cancer incidence.

7.3   Major Safety Results

7.3.1   Deaths

Deaths in Phase 1 and 2

There were 13 (4 in the follow-up period) deaths in the ticagrelor treatment groups in the Phase 1 and 2 programs. These all occurred in the DISPERSE2 (phase 2) study in ACS patients. There were 3 treatment groups in this trial randomized 1:1:1 (ticagrelor 90 mg bd, ticagrelor 180 mg bd and clopidogrel 75 mg od). 11 of the deaths in the ticagrelor treatment arm were categorized as cardiac death (many secondary to arrhythmias). There were 4 deaths (3 in the follow-up period) in the clopidogrel treatment group (no arrhythmias). In DISPERSE2, a study of approximately 1000 patients, there was no suggestion of a death benefit for ticagrelor.

Deaths in PLATO

Conversely, in PLATO, ticagrelor-treated patients had a significantly lower risk of all-cause mortality compared to clopidogrel- treated patients. There are a number of criteria one can use to count deaths as can be seen in. No matter which criterion one uses to define the numbers of deaths, i.e., total deaths, actual treatment deaths, on treatment deaths, as randomized events, adjudicated deaths, etc., the death benefit of ticagrelor is statistically significant. Please note that one of the adjudicated deaths was found to be alive at the end of the study.

Table 3: Sponsor's Analysis of PLATO: Summary of Deaths adjudicated by the Independent Central Adjudication Committee (ICAC)

Deaths	Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291	Total N=18624	RR
Total known deaths	443 (4.75)	540 (5.81)	983	**0.82**
Discovered after withdrawal of consent, not adjudicated	25 (0.27)	20 (0.22)	45	**1.24**
All adjudicated deaths	418 (4.48)	520 (5.6)	938	**0.8**
Adjudicated deaths within efficacy period (randomisation to last scheduled visit date)	399 (4.28)	506 (5.45)	905	**0.78**
Adjudicated deaths 1 to 30 days after efficacy period (PSOP)	15 (0.16)	12 (0.13)	27	**1.24**
Adjudicated deaths after PSOP	4 (0.04)	2 (0.02)	6	**1.99**
Adjudicated deaths counted in safety analyses	408 (4.37)	505 (5.44)	913	**0.8**
Deaths in safety on-treatment analysis (randomization to 7 days after the last dose of study drug)	283 (3.03)	339 (3.65)	622	**0.83**
Within efficacy period	281 (3.01)	339 (3.65)	620	**0.83**
After efficacy period	2 (0.02)	0 (0.0)	2	
Deaths in safety off-treatment analysis (>7 days after the last dose of study drug)	125 (1.34)	166 (1.79)	291	**0.75**
Adjudicated deaths not counted in safety analyses – patient never took study drug	10 (0.11)	15 (0.16)	25	**0.66**

Source: Source: Adapted from PLATO study report, p. 250

PSOP = Post-study observational period (30-day after the last scheduled visit of the efficacy follow-up study period (60-days off drug).

I have chosen to take the example of the unadjudicated all-cause deaths by actual treatment group after one dose of treatment to highlight the ticagrelor death benefit.

The Kaplan-Meier curve in Figure 1 demonstrates that 389 (4.21% of ticagrelor-treated patients died compared to 491 (5.65%) of clopidogrel-treated patients. The log-rank score for these patients is 0.0001 and highly statistically significant.

Figure 1: All-cause mortality, Unadjudicated and by Actual Group in Patients After at Least One Dose
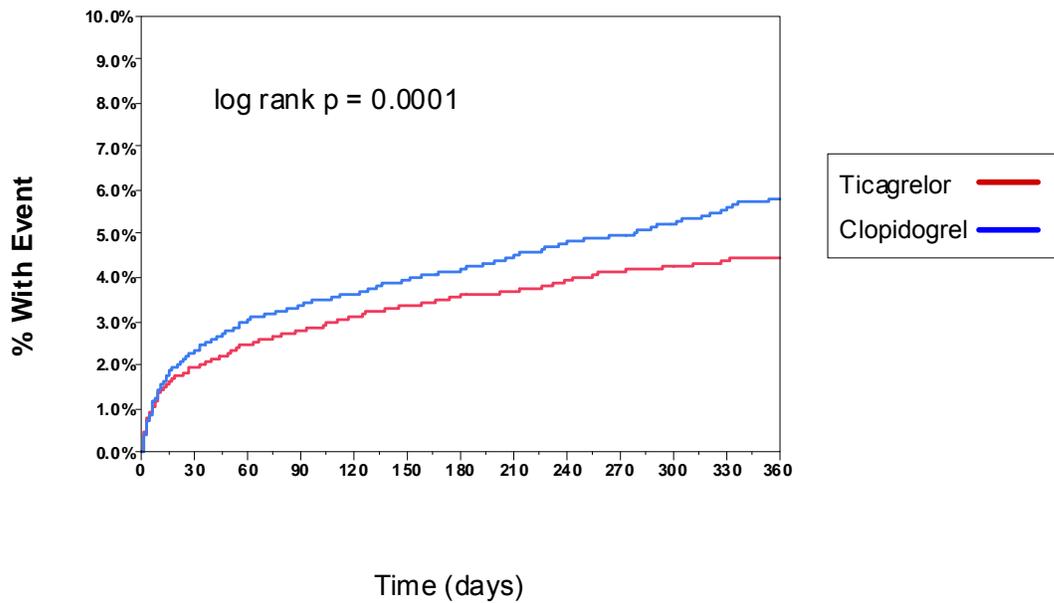
Group	Number failed	Number censored	Percent failed
Ticagrelor 90 mg bd	389	8846	4.21%
Clopidogrel 75 mg od	491	8695	5.65%
Combined	880	17541	5.02%

In the all-deaths per patient year analysis using the same criterion for defining death (all-cause, unadjudicated deaths by actual treatment where the patients took at least one dose of treatment medication), there were 389 total deaths/ 6301 ticagrelor patient years = 62 deaths/ 1000 patient-years vs. 491 deaths/ 6388 clopidogrel patient years = 77 deaths/ 1000 patient-years.

In North America (mostly U.S.), I used the data from the efficacy data set by randomized treatment in patients that received drug. In this important subpopulation, there was a higher frequency of all-cause adjudicated deaths in ticagrelor-treated patients than in clopidogrel –treated patients [35 (3.8%) vs. 29 (3.2%)], respectively. A Kaplan-Meier curve for deaths in North America by randomized treatment is shown in Figure 2. While the overall frequency of death in North America was somewhat lower than in the rest of the world, ticagrelor did not confer a death benefit. Also, in North America there were twice as many deaths attributed to myocardial infarction in the ticagrelor group compared to the clopidogrel group (equal frequency of death from myocardial infarction seen in the rest of the world). In light of the numerical difference in deaths that does not favor ticagrelor, the increased frequency of death from myocardial infarction in the ticagrelor-treated U.S. group and the negative efficacy findings in North America, it appears that there is an unacceptably high risk-benefit ratio in the U.S. Nevertheless, the U.S. population was relatively small (~2000 patients) and other random or treatment-related factors may have played a role in creating these discouraging results.

In Appendix A I reviewed the deaths of patients in North America that occurred when the K-M curves began to split until they began to plateau again. There was one case of noncompliance. On further investigation, the U.S. population had more noncompliance than the rest of the world but this difference did not seem to explain the difference in mortality between treatment arms.

Figure 2: KM: All-cause Mortality, by randomized treatment (North America only), adjudicated deaths
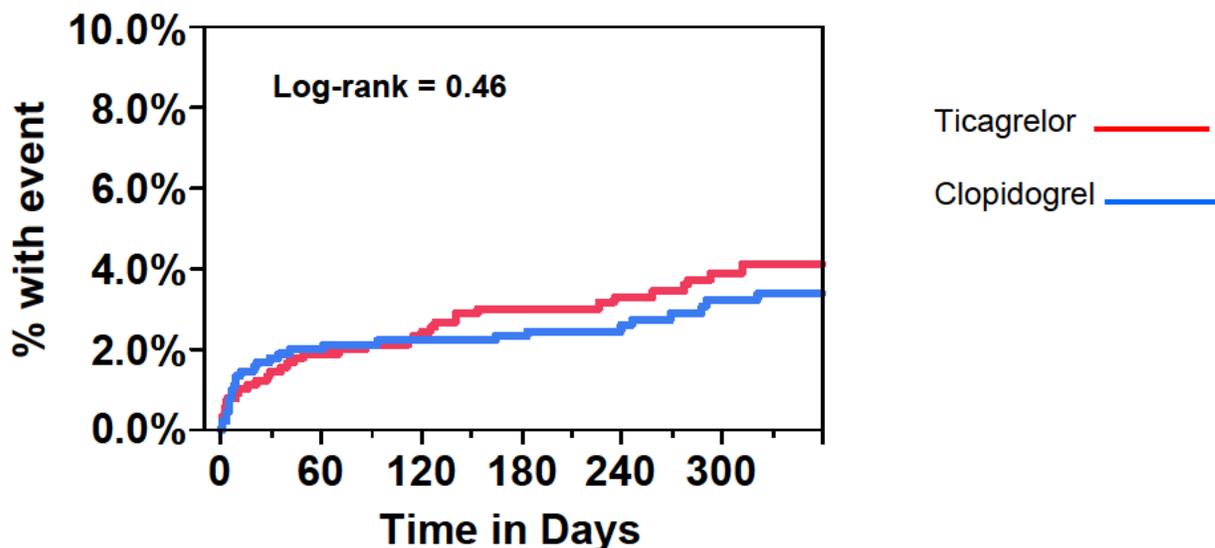
Group	Number failed	Number censored	Percent failed
Ticagrelor 90 mg bd	35	877	3.84%
Clopidogrel 75 mg od	29	873	3.22%
Combined	64	1750	3.53%

Causes of Death

Table 4 provides a categorical breakdown of causes of death. Vascular deaths accounted for most deaths (~ 95% of deaths in both treatment groups) in PLATO. The term "vascular death" includes cardiovascular deaths, cerebrovascular deaths, bleeding deaths and any other death for which there was no clearly documented nonvascular cause. Bleeding deaths were not as common as other causes of death (0.2% of patients) and occurred equally in both groups.

Table 5 is a listing of investigator assignments for cause of death. Causes of death were similar between treatment groups. The most common cause of death was myocardial infarction occurring in about 1% of randomized patients. Sudden death, heart failure, other vascular events and stroke were among the more common causes of death.

Table 4: Sponsor's analysis: Summary of deaths on treatment – safety analysis set

Category	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N=9186
All deaths[a]	283 (3.1%)	339 (3.7%)
Vascular deaths	271 (2.9%)	317 (3.5%)
Bleeding deaths	17 (0.2%)	20 (0.2%)
Trauma	2 (0.0%)	1 (0.0%)
Non-trauma	15 (0.2%)	19 (0.2%)
Non-vascular death	12 (0.1%)	22 (0.2%)

[a] Patients in the full analysis set who did not take any study drug were excluded from the safety analysis set.
Therefore, some deaths that occurred among patients in the full analysis set are excluded from this table.
bd Twice daily dosing; od Once daily dosing.

Source: PLATO study report, p. 251

Table 5: Listed Causes of Death from Efficacy Data Set (by randomized treatment)

```
                                            Randomised Treatment
                                        Ticagrelor      Clopidogrel
                                        90 mg bd        75 mg od
    Characteristic                      N - 9333        N - 9291
    _____   _____    _____

    Aortic dissection                    1 ( 0.0%)        2 ( 0.0%)
    Arterial embolism                    0 ( 0.0%)        2 ( 0.0%)
    Cancer                              14 ( 0.2%)       17 ( 0.2%)
    Cardiac arrhythmia                  20 ( 0.2%)       28 ( 0.3%)
    Death from bleeding (not related to trauma)  13 ( 0.1%)   15 ( 0.2%)
    Endocarditis                         0 ( 0.0%)        0 ( 0.0%)
    Heart failure                       51 ( 0.5%)       62 ( 0.7%)
    Liver failure                        0 ( 0.0%)        1 ( 0.0%)
    Multiorgan failure                   9 ( 0.1%)       14 ( 0.2%)
    Myocardial infarction               89 ( 1.0%)       88 ( 0.9%)
    Other coronary artery disease        4 ( 0.0%)        4 ( 0.0%)
    Other non-vascular cause             8 ( 0.1%)       11 ( 0.1%)
    Other vascular cause                44 ( 0.5%)       55 ( 0.6%)
    Pneumonia                           10 ( 0.1%)        8 ( 0.1%)
    Pulmonary embolism                   2 ( 0.0%)        8 ( 0.1%)
    Renal failure                        2 ( 0.0%)        5 ( 0.1%)
    Respiratory failure                 13 ( 0.1%)       12 ( 0.1%)
    Ruptured aortic aneurysm             1 ( 0.0%)        0 ( 0.0%)
    Sepsis                               7 ( 0.1%)       23 ( 0.2%)
    Stroke                              20 ( 0.2%)       18 ( 0.2%)
    Sudden death                        60 ( 0.6%)       77 ( 0.8%)
    Suicide                              1 ( 0.0%)        1 ( 0.0%)
    Trauma                               3 ( 0.0%)        1 ( 0.0%)
    Unstable angina                      7 ( 0.1%)        8 ( 0.1%)
    Valvular disease                     0 ( 0.0%)        1 ( 0.0%)
    Vascular death, sub-classification missing   0 ( 0.0%)   1 ( 0.0%)
    Unknown                             39 ( 0.4%)       58 ( 0.6%)
```

Summary
In PLATO, ticagrelor-treated patients had a lower risk of all-cause mortality compared to clopidogrel- treated patients (4.28% vs. 5.45% when examining deaths by randomized treatment and examining efficacy period). These differences were statistically significant. In North America (mostly U.S.), however, the results were different. There was a higher frequency of all-cause adjudicated deaths in ticagrelor-treated patients than in clopidogrel –treated patients.

Vascular deaths were the most common cause of death. Within the category of vascular death, the most common cause of death for both treatments was myocardial infarction (9.3% of all deaths for both treatment groups). Other common causes of death were sudden death and heart failure. The frequency of dying from stroke was higher in the ticagrelor group (2.2% of all deaths for ticagrelor, 1.9% of all deaths for clopidogrel). Bleeding deaths were not as common as other causes of death (0.2% of patients) and occurred equally in both groups. In the U.S. there were twice as many deaths attributed to myocardial infarction in the ticagrelor group compared to the clopidogrel group.

7.3.2 Nonfatal Serious Adverse Events

According to the sponsor's analysis, as shown in Table 6, there are 6 SAEs that occurred ≥ 0.2% in the ticagrelor treatment group where there was ≥0.2% absolute or 50% relative difference between frequency in the clopidogrel treatment group. Dyspnea, cerebrovascular accident post procedural hemorrhage, anemia, abdominal pain and epistaxis are included in the list. By my analysis, in which I combined different PT terms to reveal AEs and SAES that could be obscured by "splitting", I discovered that there were other SAE terms that fell into that category including hematuria, intracranial hemorrhage or hematoma, gastroenteritis, pulmonary embolism, and vertigo/dizziness/giddiness. These are listed in Table 7. These events are further explored in the body of the review.

Table 6: Sponsor's analysis: SAEs (≥0.2% where the difference between groups was ≥0.2% absolute or 50% relative)

Characteristic	Ticagrelor 90 mg bd (N = 9235)	Clopidogrel 75 mg od (N = 9186)
Dyspnea	65 (0.7%)	36 (0.4%)
Cerebrovascular accident	62 (0.7%)	42 (0.5%)
Post procedural hemorrhage	51 (0.6%)	37 (0.4%)
Anemia	29 (0.3%)	22 (0.2%)
Abdominal pain	19 (0.2%)	8 (0.1%)
Epistaxis	15 (0.2%)	9 (0.1%)

Source: Adapted from table from the Summary of Safety, p. 99

Some of the most common and important SAEs were bleeding related: hematuria, intracranial hemorrhage or subdural or other intracranial hematoma, epistaxis, retroperitoneal hemorrhage or hematoma. In the following sections of my review it will become clear that spontaneous bleeding in general occurred with a higher frequency in the ticagrelor group. Since ticagrelor at the doses used in PLATO has a higher percentage of inhibition of platelet aggregation (IPA) than clopidogrel, as well as quicker action because it is not a prodrug, one would rightly expect there to be a higher frequency of spontaneous bleeding events and spontaneous serious bleeding events in the ticagrelor treatment group.

There was a higher frequency of dyspnea SAEs in the ticagrelor treatment group. Dyspnea was a common and important AE in the ticagrelor treatment group in PLATO as will be discussed later in the review.

Interestingly, while there fewer deaths with a preferred term of pulmonary embolism (2 for ticagrelor patients vs. 8 for clopidogrel patients), there was an increased frequency of serious AEs of pulmonary embolism in the ticagrelor treatment group [31 (0.34%) ticagrelor group, 20 (0.22%) clopidogrel]. Pulmonary embolism led to discontinuation more often in the ticagrelor group than in the clopidogrel group in PLATO [15 (0.2%) in

the ticagrelor group vs. 7 (0.2%) in the clopidogrel group]. Also in the prasugrel summary of safety, there were 3 cases of pulmonary embolism that led to death, all in the prasugrel treatment group. There were 3 SAE pulmonary embolism cases in the prasugrel group and 2 pulmonary embolism SAEs in the clopidogrel group. 4 prasugrel patients discontinued for pulmonary embolism compared to 2 clopidogrel patients. In both PLATO and TRITON-TIMI 38 (pivotal trial for prasugrel) there were only few cases of peripheral embolism.

In PLATO, there was an increased risk for stroke (usually an embolic event) in the ticagrelor treatment group and a slightly higher death rate from stroke (13 vs. 10 when counting stroke deaths on or off treatment), one adjudicated as being related to an embolic event. Of interest, in the TRITON-TIMI 38 trial, despite a large benefit being demonstrated for the composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, there was also no improvement in risk for stroke in the prasugrel group compared to the clopidogrel group with a relative risk of 1.055 (0.763, 1.460). There were 75/6813 strokes in the prasugrel group (1.10%) and 71/6795 strokes in the clopidogrel group (1.04%).

It might be reasonable to hypothesize that ticagrelor increases the risk for embolic events from the pulmonary and carotid arteries and deep venous thromboses. Perhaps ticagrelor is more likely to cause forming plaque to break off and embolize.

There were more SAEs of sick sinus syndrome, atrial flutter, syncope/presyncope, vertigo/dizziness/giddiness. This is important and will be addressed later in the section on ventricular pauses.

The sponsor's analysis did not differ greatly from mine. The sponsor reported that SAEs of dyspnea, cerebrovascular accident, post procedural hemorrhage, pulmonary embolism, abdominal pain, anemia and epistaxis occurred with a higher frequency (difference ≥0.2% absolute or 50% relative) with ticagrelor compared to clopidogrel. Additionally, by the sponsor's analysis, SAEs of gastrointestinal ulcerations and perforations occurred with twice the frequency in the ticagrelor group [38 (0.4%)] as compared to the clopidogrel group [18 (0.2%)]. There was no difference between treatment groups in "Major Bleeds" (which will be defined later) related to procedures. See **Error! Reference source not found.** for a tablular presentation of my SAE analysis using renamed AE terms. This analysis is similar to the sponsor'

Table 7: Serious AE Table (analysis done using renamed terms)

Serious Adverse Event	ticagrelor 90 mg bd N=9235	clopidogrel 75 mg od N=9186	RR	95% CI
Hematuria	23 (0.25%)	12 (0.13%)	1.91	(0.95, 3.83)
Intracranial hemorrhage or subdural or other hematoma	30 (0.32%)	16 (0.17%)	1.87	(1.02, 3.42)
Subcutaneous hemorrhage, Ecchymosis, Hematoma	23 (0.25%)	14 (0.15%)	1.63	(0.84, 3.17)
Sick sinus syndrome	8 (0.09%)	5 (0.05%)	1.59	(0.52, 4.86)
Atrial Flutter	11 (0.12%)	7 (0.08%)	1.56	(0.61, 4.03)
Pulmonary Embolus	31 (0.34%)	20 (0.22%)	1.54	(0.88, 2.7)
Epistaxis	15 (0.16%)	10 (0.11%)	1.49	(0.67, 3.32)
Retroperiotoneal hematoma or hemorrhage	9 (0.1%)	6 (0.07%)	1.49	(0.53, 4.19)
Diarrhea	15 (0.16%)	10 (0.11%)	1.49	(0.67, 3.32)
Dyspnea	79 (0.86%)	53 (0.58%)	1.48	(1.05, 2.1)
Syncope, Presyncope	51 (0.55%)	35 (0.38%)	1.45	(0.94, 2.23)
Vertigo, Dizziness, Giddiness	23 (0.25%)	16 (0.17%)	1.43	(0.76, 2.7)
PCI -related Bleed or Hematoma	38 (0.41%)	27 (0.29%)	1.4	(0.86, 2.29)
Thromoembolic event	45 (0.49%)	34 (0.37%)	1.32	(0.84, 2.05)
Cyanosis, Apnea, Respiratory Failure, Hypoxia	21 (0.23%)	16 (0.17%)	1.31	(0.68, 2.5)
Gastrointestinal/ Anal bleed	108 (1.17%)	87 (0.95%)	1.23	(0.93, 1.64)
Bleed, Hematoma	295 (3.19%)	243 (2.65%)	1.21	(1.02, 1.43)

7.3.3 Dropouts and/or Discontinuations

Figure 3 provides the reasons for premature permanent discontinuation of study drug. The dropout and discontinuation rate for ticagrelor was somewhat higher for ticagrelor-treated patients than for clopidogrel-treated patients (23.7% vs. 21.8%, respectively). Most discontinuations were attributed to patients "not willing to continue treatment" (10.2% vs. 9.4%, respectively) and adverse events (7.5% vs. 6.1%, respectively). The greatest difference in discontinuations between the two treatment groups was in the category of 'discontinuation because of adverse events (DAEs)', (7.5% vs. 6.1%, respectively) which was mostly attributed to dyspnea followed by epistaxis. Table 8 provides a tabular listing of the most common DAEs. The reasons that patients were not willing to continue treatment were not elaborated upon in the submission.

Figure 3: Reasons for Premature Permanent discontinuation of Study Drug
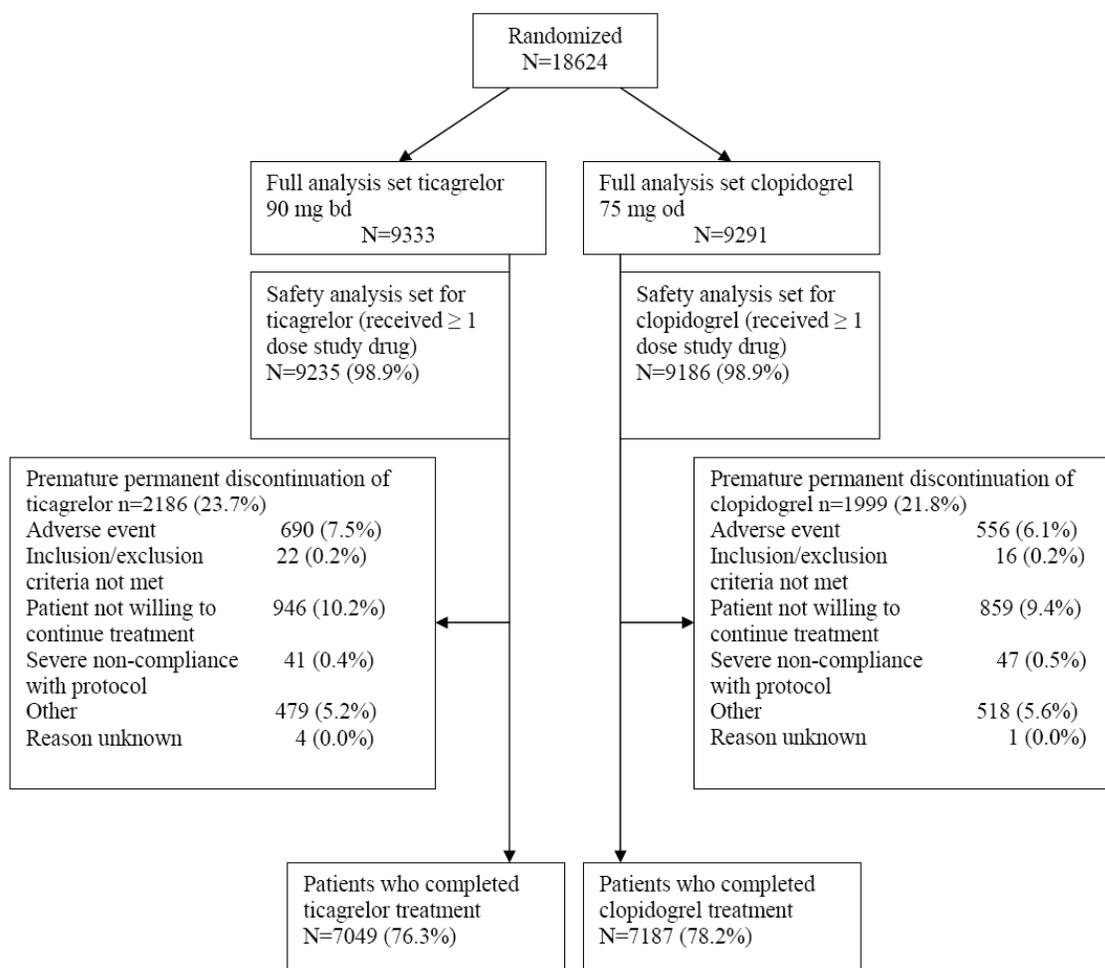
Data derived from sponsor's tables 11.1.1.2.2 and 11.1.1.4.1 in PLATO study report

Table 8: PLATO: Summary by PATIENT of the most common AEs (>0.1% in either group) leading to discontinuation

Characteristic	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N=9186
Patients with at least one event	687 (7.4%)	500 (5.4%)
Dyspnea	77 (0.8%)	10 (0.1%)
Epistaxis	38 (0.4%)	12 (0.1%)
Atrial fibrillation	27 (0.3%)	37 (0.4%)
Intracardiac thrombus	22 (0.3%)	17 (0.2%)
Gastrointestinal hemorrhage	19 (0.2%)	12 (0.1%)
Contusion	17 (0.2%)	7 (0.1%)
Nausea	15 (0.2%)	7 (0.1%)
Pulmonary Embolism	15 (0.2%)	7 (0.1%)
Diarrhea	14 (0.2%)	19 (0.1%)

Source: PLATO study report p. 262

7.3.5 Submission Specific Primary Safety Concerns

Bleeding

Bleeding was the major safety concern when the sponsor was designing PLATO. The primary safety endpoint designated in PLATO was time to first major bleeding event.

Most Phase II studies did not have adjudication committees for bleeding events, and bleeding was presented by investigator reported categorization. PLATO used an independent committee (ICAC) to adjudicate bleeding events. The ICAC judged each bleeding event against a set of definitions to maintain consistency and quality (Table 9).

The comparison of PLATO and TIMI definitions for different categories of bleeding are listed in Table 9. The PLATO categories consider certain bleeds that are likely to be severe, such as intrapericardial bleed with tamponade and intracranial hemorrhage, to be unconditionally major/ life-threatening while according to the TIMI definition these two types of bleeds are counted as minor, minimal or not at all unless they are symptomatic or are accompanied by a hemoglobin decrease of > 5 gm/dL. Also, when it comes to "major other" and minor and minimal bleeds, the PLATO definitions are concerned more with level of disability or intervention required. The TIMI definitions are more focused on drops in hemoglobin. In general, I think that the PLATO definitions are superior to the TIMI bleeding definitions because they are defined by more clinically meaningful criteria in addition to the standard TIMI criteria of hemoglobin loss and are more inclusive. All bleeds were adjudicated according to the PLATO definitions. As it turned out, in PLATO, the PLATO defined "Total Major" (which includes "Major/Life-threatening" and "Major") assigned bleeding events exceeded the TIMI defined Major + Minor bleeding events.

Table 9: Comparisons of PLATO and TIMI Bleeding Severity Scales

PLATO scale	TIMI scale

PLATO-defined Major Fatal/Life threatening
 	
Any one of the following:
  *Fatal
  *Intracranial
  *Intrapericardial bleed with tamponade
  *Hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery
  *Clinically overt or apparent bleeding associated with a decrease in hemoglobin of more than 5 gm/dL
  *Transfusion of 4 or more units whole blood or PRBCs for bleeding
	TIMI-defined Major
	Intracranial, or Clinically significant overt signs of hemorrhage associated with a drop in hemoglobin of > 5 g/dL (or, when hemoglobin is not available, an absolute drop in hematocrit of > 15%)

PLATO-defined Major Other Any one of the following: * Significantly disabling (eg, intraocular with permanent vision loss) * Clinically overt or apparent bleeding associated with a decrease in hemoglobin of 3 to 5 g/dL * Transfusion of 2-3 units (whole blood or PRBCs) for bleeding.	**TIMI-Life threatening** A subset of TIMI-Major that meets any of the following: is fatal; leads to hypotension requiring treatment with intravenous inotropic agents; requires surgical intervention for ongoing bleeding; necessitates the transfusion of 4 or more units of blood (whole blood or packed red blood cells) over a 48-hour period; is a symptomatic ICH
PLATO-defined Minor Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).	**TIMI-defined Minor** Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin of 3 to <=5 g/dL (or, when hemoglobin is not available, a fall in haematocrit of 9 to<=15%) NOTE: TRITON used 3 to <5 g/dL
PLATO-defined Minimal All others not requiring intervention or treatment	**TIMI-defined Minimal** Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin <3 g/dL (or, when hemoglobin is not available, a fall in hematocrit of <9%)

Source: ISS, p. 50.

The sponsor was successful in meeting their primary safety endpoint (time to first major bleeding event) and this is demonstrated in Table 10.. Note that the time to first event is not calculated for 'Life-threatening' and 'Major Other' bleeding because it may have been preceded by a more severe bleed. Also, patients may be counted in >1 bleeding event category.

Table 10: Sponsor's analysis: K-M% of major bleeds and hazard ratios

Characteristic	Ticagrelor 90 mg bd N = 9235		Clopidogrel 75 mg od N = 9186		
	Number of bleeding events	total bleeding events (%), KM % in one year	Number of bleeding events	total bleeding events(%), KM % in one year	Hazard ratio (95%CI)
Primary safety					
Total Major	1031	961 (10.4%),11.6%	997	929 (10.1%), 11.2%	1.04 (0.95, 1.13)
Secondary safety endpoints - Total Major bleeding by severity -					
Major Fatal/ Life-threatening	516	491 (5.3%), 5.8%	505	480 (5.2%), 5.8%	1.03(0.90, 1.16)
Fatal	21	20 (0.2%), 0.3%	24	23 (0.3%), 0.3%	0.87(0.48, 1.59)
Life-threatening	495	471 (5.1%), -	481	459 (5.0%), -	-
Major Other	515	494 (5.3%), -	492	474 (5.2%), -	-

Source: p. 182, PLATO study report

Despite this success, it is important to not downplay a few pieces of important information regarding bleeding:

Most major bleeds were CABG-related (~ 60%) (See Table 11) and most CABG bleeds were major (~85%).(see Table 15). As I will discuss later, the risk of CABG-bleeding is increased in ticagrelor patients who do not wait until day 5 after stopping treatment to have CABG. In other words, it is only because most of the CABG procedures occurred on day 5 or later of treatment cessation that the major bleeding risk was favorable for ticagrelor.

There was a statistically significant increased frequency of major + minor bleeds (overall bleeds that required any intervention) in the ticagrelor-treated group.

There was also an increase in spontaneous (non-procedure related) bleeds in the ticagrelor-treated group as compared to the clopidogrel group, (4.9% for ticagrelor vs. 3.6% for clopidogrel). Intracranial bleeds (to be discussed in the Spontaneous-Bleed section) fell within this category

There was a somewhat higher frequency of all major bleeds that were not procedure-related [(3.1% for ticagrelor vs. 2.3% for clopidogrel).

Ticagrelor-treated patients who had low baseline eGFRs (< 30 cc/min) and liver disease were more likely to have adjudicated "Major" bleeding events than clopidogrel-treated patients. 19.0% of ticagrelor treated patients with baseline eGFRs < 30 cc/min had major bleeding events whereas 11.3% of clopidogrel-treated patients with ≥ 30cc/min had major bleeds. 11.2% of ticagrelor-treated patients with hepatic impairment had major bleeding events whereas 8.7% of clopidogrel-treated patients with hepatic impairment had major bleeding events. See Table 12.


Table 11: Type of Major Bleed (CABG, other procedure, spontaneous) by treatment

Major Bleeds	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N= 9186
CABG-related	623 (6.7%)	659 (7.2%)
non-CABG procedure related	30 (0.3%)	46 (0.5%)
Spontaneous	251 (4.5%)	190 (0.21%)
Total	1031 (11.2%)	997 (10.9%)

Table 12: Frequency of Major Bleeds by Degree of Renal Disease and Presence of Liver Disease at Randomization

Characteristic	Category	ticagrelor		%	clopidogrel		%	RR
		total patients in category	total patients with major bleed		total patients in category	total patients with major bleed		
	N	9235	961	10.4	9186	929	10.1	1.03
Renal Disease								
	eGFR < 15 cc/min	8	2	25	9	0	0	
	eGFR 15-< 30 cc/min	113	21	18.6	133	16	12	1.54
	eGFR 30-<60 cc/min	1767	220	12.5	1812	233	12.9	0.97
	eGFR 60-<90 cc/min	3862	424	11	3808	396	10.4	1.06
	eGFR >=90 cc/min	3307	272	8.2	3252	262	8.1	1.02
Liver Disease	yes	196	22	11.2	217	19	8.8	1.28
	no	9039	939	10.4	8969	910	10.1	1.02

Figure 4: K-M time to event analysis for major + minor bleeds (requiring any intervention)
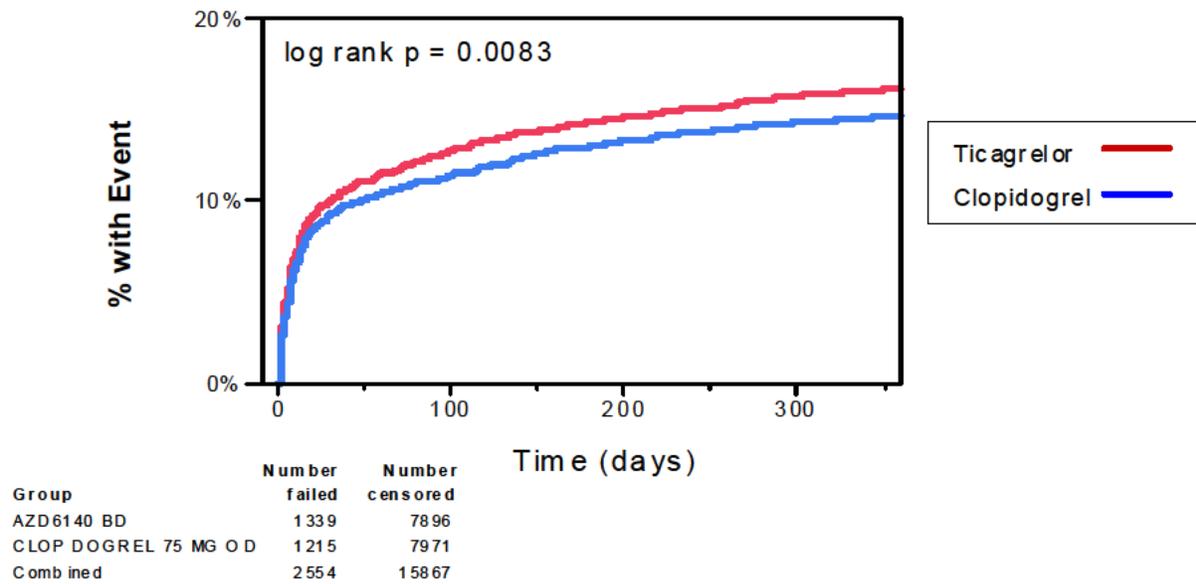
Group	Number failed	Number censored
AZD6140 BD	1339	7896
CLOPIDOGREL 75 MG OD	1215	7971
Combined	2554	15867

There was no increase in fatal bleeding events in the ticagrelor arm compared to the clopidogrel arm. See Table 13. Fatal bleeds are listed more than once because of the decision to subcategorize events. Additionally, some patients were deemed to have died from more than one bleeding event. Most fatal bleeds were not related to CABG or other procedures.

Table 13: Fatal Bleeding Events and Corresponding Characteristics

Characteristic	Total bleeding events		Patients with > =1 bleeding event	
	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Total Fatal	21	24	20 (0.2%)	23 (0.3%)
Not related to CABG surgery	15	17	15 (0.2%)	16 (0.2%)
Not procedure-related	13	13	13 (0.1%)	12 (0.1%)
Non-CABG procedural	2	4	2 (0.0%)	4 (0.0%)
Procedure-related	8	10	8 (0.1%)	10 (0.1%)
Non-coronary	1	2	1 (0.0%)	2 (0.0%)
Coronary	7	8	7 (0.1%)	8 (0.1%)
CABG-related	6	6	6 (0.1%)	6 (0.1%)
PCI-related	1	2	1 (0.0%)	2 (0.0%)
Coronary angiography related	0	0	0	0

Source: PLATO study report p. 3515

Since effectiveness of ticagrelor was not demonstrated in North America in PLATO, it is important to explore the K-M curve for major + minor bleeding in North America. One might expect that the difference in major + minor bleeds would be absent if the drug was not effective possibly because IPA levels were too low. The K-M curves are displayed in the Figure 5. While the log rank score is 0.3 for major + minor bleeds between K-Ms curves for both treatment groups in North America, the trend of increased overall bleeding in the ticagrelor treatment group is still present.

Figure 5: K-M Time to Event Analysis for Major + Minor Bleeds in North America
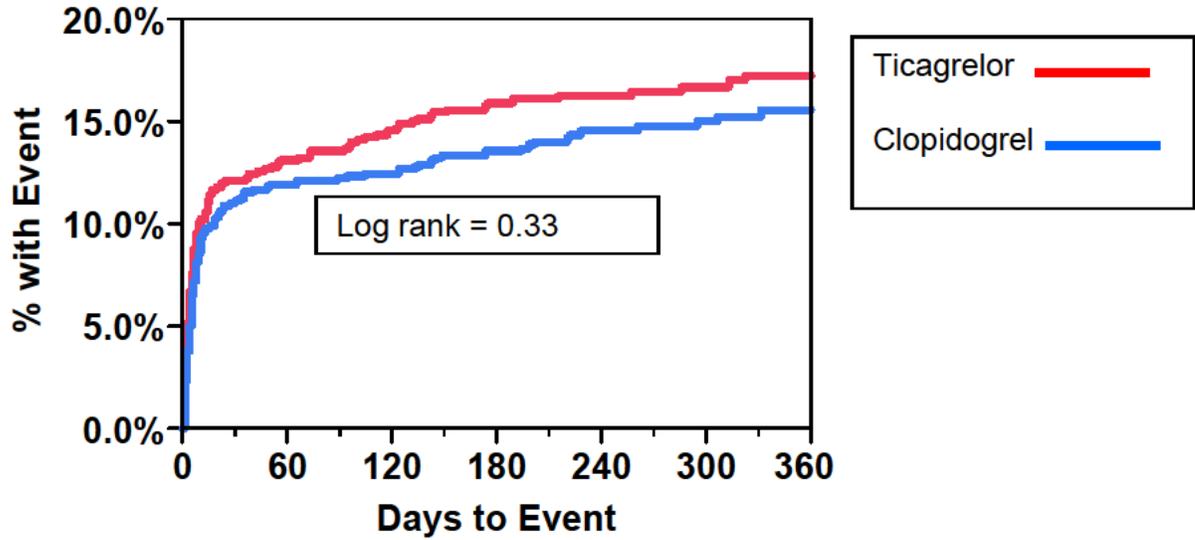
Group	Number failed	Number censored
AZD6140 BD	137	748
CLOPIDOGREL 75 MG OD	122	745
Combined	259	1493

Spontaneous bleeds accounted for ~ ¼ of all major bleeds. There was a significantly higher frequency of spontaneous bleeding in the ticagrelor group in PLATO as compared to the clopidogrel group. This is demonstrated graphically with K-M type to analysis curves in Figure 6. This difference in spontaneous bleeding frequency accounts for the difference in overall bleeding between the treatment groups. This pattern of increased spontaneous bleeding in the ticagrelor group was also evident in the North American population. One could make a conjecture that this increased frequency of spontaneous bleeding in the ticagrelor treatment group was because of the increased platelet aggregation inhibition of ticagrelor. One could also theorize that the reason that procedure-related bleeding was not different between treatment groups is because most interventions were probably done after 5 or more days of stopping study drug. The "quick reversibility" of ticagrelor isn't as quick as one would prefer as will be seen in the CABG bleeding data that I will present next. Figure 6 is a K-M time to event analysis of the difference between groups in time to event for first spontaneous bleed. Figure 7 is a whisker plot that shows that the pattern is present at all severities of spontaneous bleeding.

Figure 6: KM: Non-procedural (spontaneous) Major and Minor Bleeds
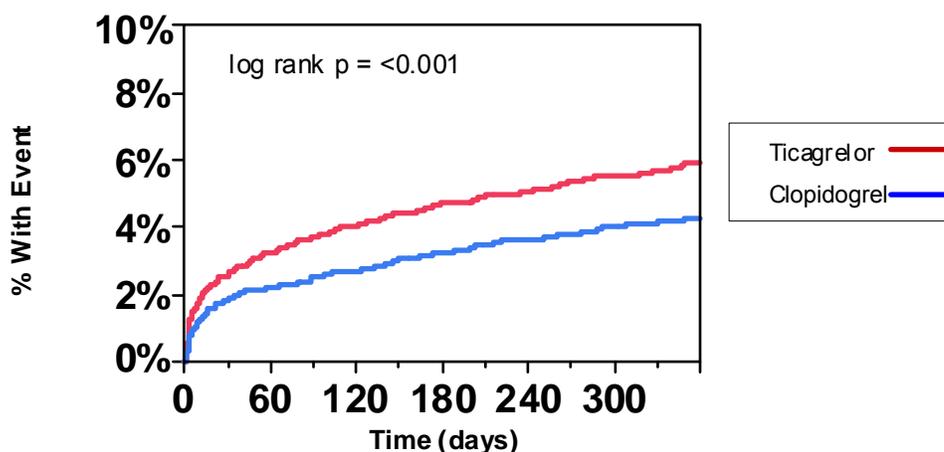
Group	Number failed	Number censored
AZD6140 BD	457	8778
CLOPIDOGREL 75 MG OD	332	8854
Combined	789	17632

Figure 7: Hazard Ratio (95%CI) for non-procedural bleeds by severity
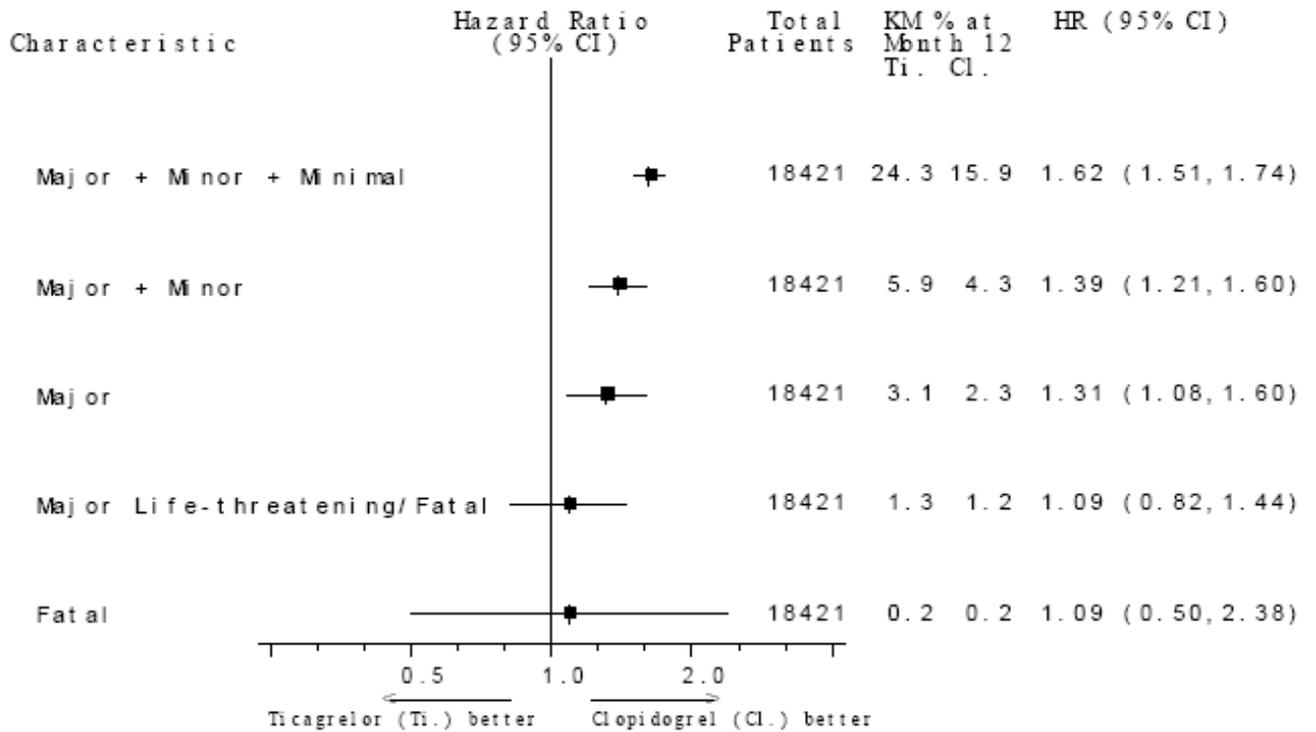
Characteristic	Hazard Ratio (95% CI)	Total Patients	KM % at Month 12 Ti. Cl.	HR (95% CI)
Major + Minor + Minimal		18421	24.3 15.9	1.62 (1.51, 1.74)
Major + Minor		18421	5.9 4.3	1.39 (1.21, 1.60)
Major		18421	3.1 2.3	1.31 (1.08, 1.60)
Major Life-threatening/Fatal		18421	1.3 1.2	1.09 (0.82, 1.44)
Fatal		18421	0.2 0.2	1.09 (0.50, 2.38)

0.5   1.0   2.0

←Ticagrelor (Ti.) better   Clopidogrel (Cl.) better→

Source: PLATO study report, p. 207

The 2 most common spontaneous major bleeds were as follows:

1. Gastrointestinal: [1.3% of ticagrelor-treated and 1.0% of clopidogrel-treated patients had major gastrointestinal bleeds .
2. Intracranial [0.3% of ticagrelor-treated and 0.15% of clopidogrel-treated patients had major intracranial bleeds.

While there was not much of a difference in the frequency of spontaneous bleeds that resulted in death (13 for ticagrelor and 12 for clopidogrel), in the ticagrelor arm, 11 of the 13 (84.6%) deaths were from intracranial hemorrhages and in the ticagrelor arm 1/12 (8.3%) deaths was from an intracranial hemorrhage. All but one of the patients who had an intracranial hemorrhage also had a stroke. One ticagrelor-treated patient died from an intracranial hemorrhage thought to be secondary to head trauma. Of the other ticagrelor patients that died of bleeding, one was from pericardial bleeding and the other was from hemoptysis. Of the spontaneous bleeds that resulted in fatal events in the clopidogrel group, 5/13 were gastrointestinal and only 1 was intracranial. The reason that the total number of fatal bleeds is 12 in the clopidogrel group and the number of reasons for death is 13 in the clopidogrel group is that one clopidogrel-treated patient had 2 bleeds that were considered to be fatal.

Table 14 provides a tablular listing of all major/fatal-lifethreatening/ and fatal nonprocedure bleeding events by primary anatomic location.

Table 14: Sponsor's Analysis: Summary of 'Major Fatal/Life-threatening' and Fatal non-procedure bleeding events by primary anatomic location

Primary location	Total Major		Fatal/Life-threatening		Fatal	
	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Total bleeds	251	190	109	99	13	13
Gastrointestinal	124	94	47	47	0	5
Intracranial	27	14	27	14	11	1
Urinary	13	14	4	4	0	0
Pericardial	11	11	10	10	1	2
Subcutaneous/dermal	11	4	3	1	0	1
Epistaxis	6	8	0	3	0	0
Haemoptysis	2	3	2	0	1	0
Retroperitoneal	0	3	1	3	0	1
Intraocular	0	2	0	0	0	0
Intraarticular	0	0	0	0	0	0
Other	46	37	15	17	0	3

Source: Intracranial hemorrhage report, p. 8

Spontaneous bleeding is an important safety issue, particularly when it comes to intracranial bleeding. If approved, the ticagrelor label should include a warning about increased risk for intracranial bleeding and specifically, hemorrhagic strokes.

Bleeding Related to CABG Surgery

Of the 18,421 patients in the safety data set, 1584 patients received CABG surgery (~ 12% over the first year). Table 15 shows the bleeding events related to CABG surgery by treatment in the safety analysis set (patient received one or more doses of study treatment). Most patients had CABG related bleeds. There was a slightly lower CABG-related frequency of bleeding in most PLATO-defined categories of bleeding for ticagrelor-treated patients. Since there was a slightly higher risk of minimal bleeding in ticagrelor-treated patients it is attractive to think that ticagrelor may have converted some minor bleeds or even major bleeds into minimal bleeds.

Table 15: Summary of Bleeding Events Related to CABG surgery – safety analysis set

Characteristic/Bleed Severity	Ticagrelor 90 mg bd	Clopidogrel 75 mg od
Patients with CABG procedures	770 (100%)	814 (100%)
No bleeding event	33 (4.3%)	31 (3.8%)
Any bleeding event	737 (95.7%)	783 (96.2%)
Major	619 (80.4%)	654 (80.3%)
Major Fatal/Life-threatening	329 (42.7%)	341 (41.9%)
Fatal	6 (0.8%)	6 (0.7%)
Major Other	290 (37.7%)	313 (38.5%)
Minor	47 (6.1%)	58 (7.1%)
Minimal	71 (9.2%)	71 (8.7%)

Source: PLATO study report, p. 199

Table 16 provides data on major, life-threatening/fatal, and fatal CABG-related bleeding. First, it should be noticed that there were more early CABG procedures in the ticagrelor treatment group. This difference between groups is not explained in the submission and it is not clear if there is anything other than chance that could explain this finding. Second, there was a low frequency of CABG-related deaths in both treatment groups. Third, CABG done within the first 24 hours of stopping study drug resulted in a higher frequency of "fatal/life-threatening bleeds" than when CABG was done after longer periods of stopping study drug. Fourth, there were differences between treatment groups in CABG-related bleeding complications depending on when the drug was stopped prior to CABG. CABG done between 24 and 96 hours after stopping study drug resulted in a higher frequency of both major and fatal/ life-threatening bleeds in the ticagrelor group than in the clopidogrel group and was accompanied by a larger volume of chest tube drainage and transfusions. When CABG was done after 96 hours of stopping study drug, the ticagrelor arm had a more favorable bleeding profile. There was a

general trend of higher frequencies of major to fatal bleeds in the ticagrelor group when CABG was done within 96 hours after stopping study drug. When CABG was done after 96 hours, the trend was reversed so that there was a higher frequency of bleeds in the clopidogrel arm. I agree with the sponsor's suggestion to wait if possible until 5 days after stopping ticagrelor to perform CABG to decrease the frequency and severity of CABG-related bleeding

Table 16: Sponsor Analysis: ICAC-adjudicated PLATO-defined 'Major, Life-threatening/Fatal, Fatal' CABG-related bleeding by time from last dose of study drug to procedure – safety analysis set

Hours from last dose to CABG	Patients with CABG		Major		Life-threatening/Fatal		Fatal	
	Tica-grelor 90 mg bd	Clopi-dogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od
0-24	84	88	70 (83.3%)	78 (88.6%)	55 (65.5%)	52 (59.1%)	2 (2.4%)	1 (1.1%)
>24-48	106	86	95 (89.6%)	70 (81.4%)	50 (47.2%)	42 (48.8%)	1 (0.9%)	1 (1.2%)
>48-72	114	73	94 (82.5%)	56 (76.7%)	56 (49.1%))	33 (45.2%)	0	0
>72-96	84	69	72 (85.7%)	54 (78.3%)	39 (46.4%)	29 (42.0%)	1 (1.2%)	3 (4.3%)
>96-120	79	96	59 (74.7%)	76 (79.2%)	22 (27.8%)	27 (28.1%)	1 (1.3%)	0
>120-144	91	110	67 (73.6%)	83 (75.5%)	29 (31.9%)	45 (40.9%)	0	1 (0.9%)
>144-168	74	107	56 (75.7%)	87 (81.3%)	25 (33.8%)	40 (37.4%)	0	0
8-14 days	109	147	86 (78.9%)	123 (83.7%)	43 (39.4%)	65 (44.2%)	1 (0.9%)	0
Total	**741**	**776**	**599 (80.8%)**	**627 (80.8%)**	**319 (43.0%)**	**333 (42.9%)**	**6 (0.8%)**	**6 (0.8%)**

Source: PLATO study report, p. 201

On a reassuring note, as shown in Figure 8, despite the increased frequency of Major/Life-threatening CABG-related bleeds in the ticagrelor group related to early CABG, the all-cause mortality following CABG was less for ticagrelor than for clopidogrel when considering any time interval between the last dose of study treatment and beginning CABG.

Figure 8: Sponsor's Analysis: Deaths (all-cause) during or after CABG by Time from Last Dose of Study Drug to Procedure
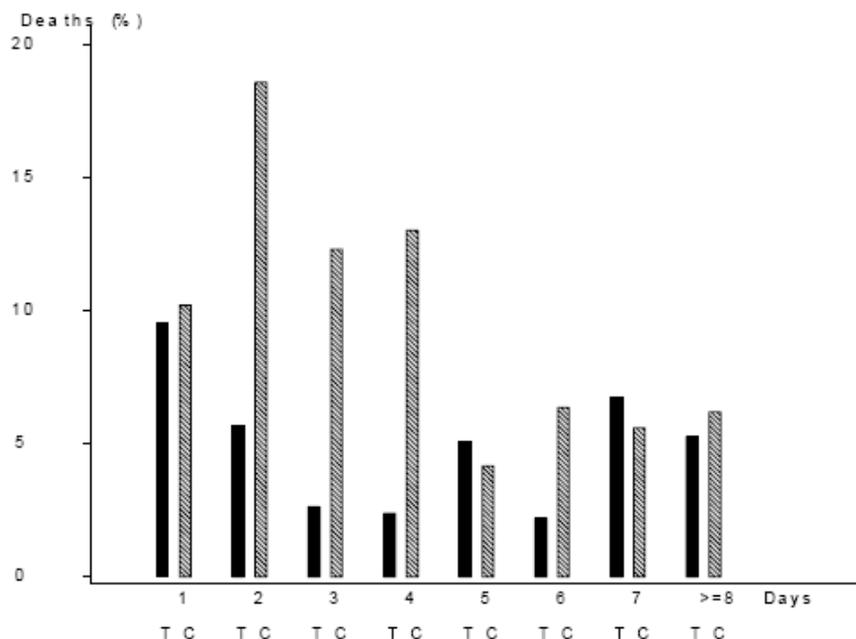
Source: ISS

In summary, the most important safety issue for ticagrelor was bleeding. All bleeds were adjudicated according to definitions designed specifically for the ticagrelor development program, a definition system which is probably better than TIMI bleeding definitions in that the severity of bleeds was based more on clinical relevance as opposed to grams of hemoglobin loss. Ticagrelor increased the frequency of major + minor bleeding. The reason for this increase was primarily due to the increased frequency of spontaneous (non-procedural/ non-CABG) bleeds. There was no increase in overall major/life-threatening or fatal bleeds in the ticagrelor treatment group compared to the clopidogrel treatment group as a whole. However, the pattern of increased non-procedural bleeds in ticagrelor-treated patients was also operative for major/life-threatening/fatal bleeds. When it comes to spontaneous bleeds, there were more in the ticagrelor group at all degrees of severity.

Overall, CABG did not cause increased bleeding in the patients that were in the ticagrelor treatment group. However, if one looks at risk of CABG-related bleeding by time after stopping drug, one can see that there is increased bleeding in the ticagrelor group compared to the clopidogrel treatment group until day 5 after stopping drug when the pattern reverses. More importantly, however, is the fact that despite the increased frequency of major/life-threatening

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CABG-related bleeds in the ticagrelor group related to early CABG, the all-cause mortality following CABG was less for ticagrelor than for clopidogrel when considering any time interval between the last dose of study treatment and beginning CABG.

Dyspnea

Dyspnea has been reported with currently available antiplatelet drugs, clopidogrel, prasugrel and aspirin in approximately 4.5% of patients. However, discontinuation for dyspnea occurred in only approximately 0.1% of patients.

Dyspnea associated with ticagrelor administration was first observed in Phase 2 studies (DISPERSE and DISPERSE2) and was confirmed in the large Phase 3 PLATO study. PLATO did not exclude patients with COPD, CHF, or asthma.

i) Deaths after dyspnea AEs

There were 2 dyspnea AEs with an outcome of death (1 in each treatment group) reported during study treatment. Both were reported to have died from pneumonia.

One additional dyspnea AE with an outcome of death occurred after permanent discontinuation of ticagrelor treatment. This patient permanently discontinued study medication on day 4 and died on Day 124 of pneumonia and cardiac decompensation.

It is difficult to ascertain from these narratives what role ticagrelor played in the deaths of these patients.

ii) Dyspnea SAEs

In PLATO, according to my analysis of AEs, 79 (0.86%) of ticagrelor –treated patients had dyspnea SAEs and 53 (0.58%) of clopidogrel-treated patients had dyspnea SAES while on treatment [RR=1.48,(1.05,2.1)].

iii) Discontinuations because of dyspnea

Overall, dyspnea accounted for 79 (0.9%) of discontinuations in ticagrelor-treated patients and 13 (0.1%) of discontinuations in the clopidogrel-treated patients. SAEs of dyspnea accounted for 10 (0.1%) of discontinuations in the ticagrelor-treated patients and only 1 of discontinuations in the clopidogrel-treated patients. Importantly, patients who had any dyspnea AE during treatment were more likely to discontinue study medication due to any AE in both treatment groups, with 9.4% of ticagrelor-treated patients with dyspnea and 5.7% of clopidogrel-treated patients with dyspnea discontinuing as a result of any AE, whereas 4.6%

vs. 4.4% of patients without dyspnea in the ticagrelor vs. clopidogrel groups, respectively, discontinued for any AE. This high frequency of discontinuations for AEs in ticagrelor-treated patients who developed dyspnea suggests that dyspnea is troublesome to patients.

iv) All Dyspnea AEs

In PLATO, most cases of dyspnea were in the mild to moderate range of severity. According to my analysis, (1345/9235) 14.6% of the ticagrelor-treated patients had at least one episode of dyspnea (including dyspnea at rest and on exertion, nocturnal and paroxysmal nocturnal dyspnea), while (803/9186) 8.7% of the clopidogrel-treated patients had at least one episode of dyspnea while on treatment. It is important to note that 22.3% of patients in the USA had dyspnea on ticagrelor (10.7% on clopidogrel).

According to the sponsor's analysis, the largest difference in dyspnea prevalence between the two treatment groups was in the subgroup of patients whose etiology for dyspnea was reported as "unexplained/unknown etiology". 4.1% and 1.8% of the ticagrelor-treated and clopidogrel-treated patients fell into that category, respectively. There was also a difference in prevalence between the two treatment groups was in the subgroup of patients whose etiology for dyspnea was reported as cardiac-related reasons for dyspnea. 7.7% and 5.8% of the ticagrelor-treated and clopidogrel-treated patients fell into that category, respectively.

Of interest, there were no differences between groups in reports of abnormal breath sounds, tachypnea, bronchospasm or COPD/ COPD exacerbations.

25% of patients on strong CYP3 inhibitors at time of randomization developed dyspnea suggesting that there is a direct dose relationship. Additional support for a direct dose relationship comes from the DISPERSE2 study where ACS patients treated with ticagrelor 90 mg bd and 180 mg bd for 4-12 weeks had a reported incidence of dyspnea of 10% and 16%, respectively.

Also supporting a dose relationship for dypsnea, an exploratory exposure-response analysis evaluating pre-specified safety endpoints was performed with ticagrelor using predictive modeling. The analysis identified a time-dependent exposure-response relationship, with increasing ticagrelor exposure increasing the likelihood of dyspnea, which was most pronounced at the start of the treatment period (first 90 days) which is when most dyspnea AEs began.

v) Risk Factors for Developing Dyspnea

Age appeared to be a risk factor for developing dyspnea. 18.3% of patients ≥ 75 years old had dyspnea on ticagrelor (12% on clopidogrel). Patients on an ACE inhibitor, aspirin, and/or a beta blocker at time of randomization did not have a higher likelihood of developing dyspnea on ticagrelor. Being on an ARB, however, was an added risk for developing dyspnea on ticagrelor (176/823, 21.4%), not so for clopidogrel (80/807, 9.9%). The highest weight quintile

had a higher incidence of dyspnea events. One would imagine that heavier patients with recent ACS would have a greater tendency to be dyspneic compared to thinner patients. Perhaps ticagrelor may just push heavier people over the threshold and make them more likely to report dyspnea to the investigator. This weight relationship was not seen with clopidogrel.

According to the sponsor's analysis, dyspnea AEs occurred more frequently in patients with UA/NSTEMI (14.6%) compared with STEMI (12.6%) in the ticagrelor treatment group. The number of patients with dyspnea AEs in the clopidogrel group was similar regardless of the final diagnosis of ACS (7.8% for patients with UA/NSTEMI vs 7.9% for patients with STEMI). The significance if any of this difference is unclear. As one would expect, patients with baseline COPD, asthma and CHF had a higher prevalence of dyspnea AEs than patients without a history of these underlying cardiopulmonary conditions.

vi) Onset of Dyspnea

Dyspnea occurred earlier in the ticagrelor group than in the clopidogrel treatment group as shown in Figure 9. The analysis of the time to first event showed a statistically significant difference between ticagrelor and clopidogrel [HR 1.84 (95% CI 1.68, 2.02)]. The median time to onset of dyspnea was a median of 20 days for ticagrelor-treated patients and a median of 33 days for clopidogrel-treated patients.

Figure 9: Kaplan-Meier plot of time to first dyspnea AE
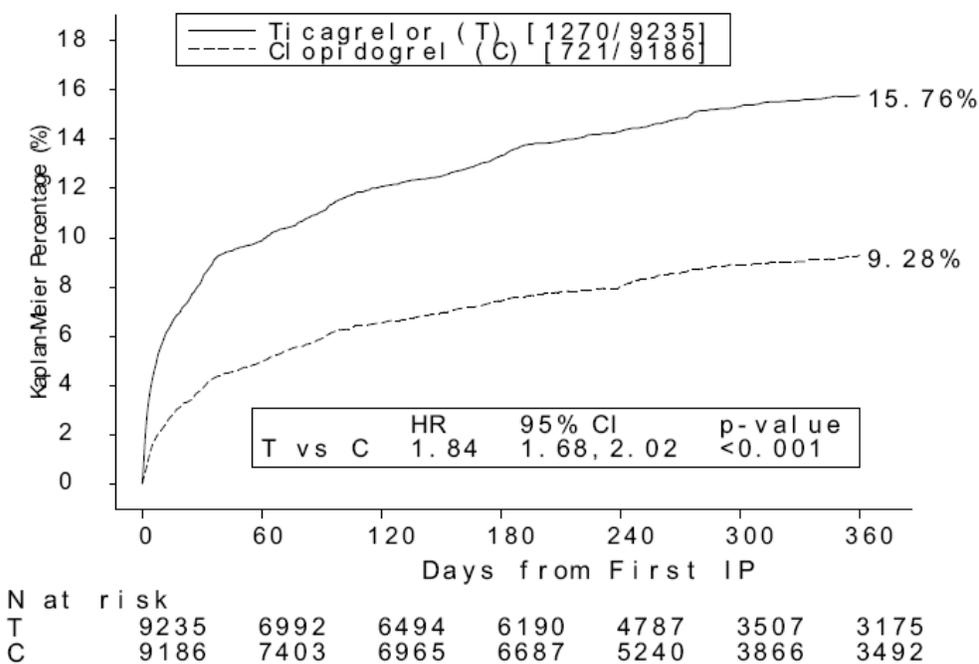
Source: PLATO study report, p. 22959

vii) Length of Dyspnea Episodes

Figure 10 and Figure 11 present my analysis of lengths of dyspnea events during PLATO in a graphic format. The difference between the figures is the scale of the X axis. In Figure 10, I divided the scale so that lengths of 20 days or less were grouped together. In Figure 11 events lasting ≥ 20 days were lumped together. While it might appear from Figure 10 that most of the dyspneic episodes are short lived, it is clear from Figure 11 that more episodes lasted ≥ 20 days.   One can conclude from this analysis that most dyspnea episodes lasted more than 20 days. Additionally, for any length of dyspnea episode (from 0-2 days to 440 days), the ticagrelor treatment group had numerically more patients with dyspnea than did the clopidogrel treatment group. On a reassuring note, 2/3 of dyspnea AEs resolved during treatment.

Figure 10: Frequency of Different Lengths of Dyspnea Episodes I

Figure 11: Frequency of Different Lengths of Dyspnea Episodes II

vii) Mechanism of Dyspnea

Dyspnea could be related to adenosine re-uptake inhibition. Adenosine (when given by IV infusion) causes dyspnea and is believed to have a direct effect on receptors in the bronchial tree but the exact effect is not known. Although ticagrelor does not act as an adenosine analogue, it does inhibit reuptake of endogenous adenosine into red blood cells and therefore could lead to dyspnea by increasing the presence of endogenous adenosine in the circulation and interstitium of the bronchial tree.

ix) Effect of Dyspnea on Outcomes

An exploratory analysis conducted by the sponsor of the primary efficacy endpoint (CV death, MI and stroke) in patients with dyspnea strongly supports that patients who reported dyspnea during PLATO benefited as much from ticagrelor treatment as the entire PLATO population. While done as a retrospective analysis, it is reassuring that the outcome data support the effectiveness of ticagrelor in patients who reported dyspnea.

x) Pulmonary Function Substudy

In Section 7.4.5, there is a summary of the Pulmonary Function Substudy that enrolled a subgroup of randomly chosen patients at the same time that they were enrolled in PLATO. The goal of the study was to determine if patients on ticagrelor had an increased likelihood of having abnormal pulmonary function tests (PFT)s during ticagrelor treatment compared to the

clopidogrel-treated patients. The study had several deficiencies that relate to the study design, execution and analysis and make interpretation of the results difficult. These deficiencies were as follows:

1. No baseline values (would be hard to do).
2. Outlier data was eliminated and substituted with averages of other data during the study which could obscure differences.
3. High percentage of patients in both treatment groups with h/o current or past smoking (ticagrelor 62%, clopidogrel 55%) which could obscure differences because of preexisting PFT abnormalities
4. Fewer patients than expected enrolled in this substudy.
5. The exposure was 6 months only in most of these patients.
6. Few of the patients had dyspnea, especially unexplained dyspnea at enrollment.
7. PFTs were not done at time of dyspneic episodes
8. The smaller than expected sample size reduced the power for detecting differences between groups.
9. Using mean values reduced the power for detecting differences.

While the conclusion of the sponsor was that there were no differences in pulmonary function tests between treatment groups, the Pulmonary Function Substudy was not well enough designed to convince this reviewer that ticagrelor has no effect on PFTs.

xi) Dyspnea Summary

In summary, dyspnea occurred frequently in patients treated with ticagrelor in all clinical phase 2 studies and in PLATO (14.6% of ticagrelor-treated patients vs. 8.7% of clopidogrel-treated patients). Dyspnea SAEs occurred in less than 0.9% of ticagrelor-treated patients and in less than 0.6% of clopidogrel-treated patients. Dyspnea in ticagrelor-treated patients resulted in more discontinuations than dyspnea in clopidogrel-treated patients (0.9% vs. 0.1%, respectively). More impressively, nearly 10% of ticagrelor-treated patients that had dyspnea discontinued treatment for other AEs compared to <6% of clopidogrel-treated patients. Additional concerning observation is that the onset of dyspnea was considerably earlier in the ticagrelor-treated patients compared to the clopidogrel-treated patients, lasted usually >20 days (up to approximately 400 days) and at any length of episode, the ticagrelor treatment group had numerically more patients with dyspnea than did the clopidogrel treatment group. In my opinion, the Pulmonary Function Substudy was not conducted or analyzed in a way that made it interpretable.

On the reassuring side, dyspnea is a symptom that resolved in 2/3 of the affected patients during the study. This suggests to me that it is unlikely that ticagrelor is causing chronic pulmonary changes in most patients. While two ticagrelor-treated patients with dyspnea AEs died, it is hard to assign the cause of the deaths in these patients to ticagrelor because of other comorbidities and confounding circumstances. Most reassuringly, patients with dyspnea know it and can discontinue ticagrelor if they are troubled by it. And importantly, despite its

exploratory nature, a retrospective analysis of PLATO outcomes data showed that patients with dyspnea at any time during the trial had favorable clinical outcomes.

Being on an ARB was an added risk for developing dyspnea on ticagrelor (176/823, 21.4%). If patients develop dyspnea, consideration should be given to discontinuation of ARBs if possible.

Bradycardia and Arrhythmias

In a hERG study, ticagrelor blocked the hERG encoded potassium channel with a half maximal inhibitory concentration (IC50) value of 1.72 μM. However, the nonclinical data from Purkinje fiber and anesthetized dog showed no cardiac effects.

In phases 1 and 2, sinus pauses, ventricular pauses and adverse events related to bradycardia were observed in ticagrelor-treated patients and healthy volunteers. Additionally, as discussed earlier, in DISPERSE2 (the only phase 2 study where there were deaths) there were 3 deaths that were listed as sudden death, ventricular fibrillation or tachycardia out of 23 deaths in the entire study. None of the clopidogrel treated patients had arrhythmia related deaths. In the phase 2 pooled studies there were 6 arrhythmia AEs in the ticagrelor treatment groups that resulted in discontinuation: 1 cardiac arrest, 1 ventricular tachycardia, 1 ventricular fibrillation, 1 ventricular tachyarrhythmia, 1 bradycardia and 1 atrial tachycardia. None of these events occurred in the clopidogrel arms.

Theoretically, the inhibition of erythrocyte adenosine uptake which is the most potent activity of ticagrelor independent of $P2Y_{12}$ receptor function could result in increased interstitial adenosine in the myocardium. Adenosine depresses sinoatrial node activity, AV nodal conduction, and ventricular automaticity, attenuates cardiac stimulatory action of catecholamines and the release of norepinephrine from nerve terminals (Belardinelli and Lerman 1991). An obvious concern is that if you have an ACS patient who is already predisposed to arrhythmias and then you expose this patient to a proarrhythmic drug, you might be putting that patient at considerable risk for life-threatening and fatal arrhythmias.

In PLATO there was close tracking of cardiac related AEs. The AE data are shown in my analysis (Table 17).

Contrary to expectations, in PLATO there were few differences in most arrhythmia AEs between treatment groups. Scrutinizing the data more carefully, it appears that there was a higher frequency of patients who had "supraventricular arrhythmias" (a renamed category in which I included atrial fibrillation, atrial flutter, premature atrial contractions and non- specified supraventricular arrhythmias) in ticagrelor-treated patients but a lower frequency of patients who had "ventricular arrhythmias" (in which I included premature ventricular contractions, nonsustained ventricular tachycardia, sustained ventricular tachycardia, and ventricular fibrillation) and a lower frequency of ventricular fibrillation. There were also a lower frequency

of patients that fell into the "Sudden Death, Arrest, Electromechanical Dissociation, Cardiogenic Shock" in the ticagrelor-treated patients.

However, other adverse events that are potentially symptomatic of arrhythmias did not favor ticagrelor and provokes one to question the reliability of reports of adverse events of ECG diagnosed arrhythmias.

For instance, there was a higher frequency of patients on ticagrelor compared to clopidogrel of the following symptomatic AEs: syncope/ presyncope [ticagrelor: 152(1.7%), clopidogrel 146(1.59%), RR 1.24(1,1.54)] and "vertigo, dizziness, and giddiness" [ticagrelor 603 (6.53%), clopidogrel 536(5.87%), RR 1.12(1,1.25]. While not reported in Table 17, there was a similar frequency of hypotension in both groups (0.3% range) .

Table 17: Arrhythmia-Related and Conduction Disturbance AEs

AE Category (renamed)	ticagrelor 90 mg bd N=9235	clopidogrel 75mg od N=9186	RR	95% CI
Arrhythmia	1349 (14.61%)	1330 (14.48%)	1.01	(0.94, 1.08)
Atrial fibrillation	447 (4.84%)	455 (4.95%)	0.98	(0.86, 1.11)
Atrial Flutter	48 (0.52%)	46 (0.5%)	1.04	(0.69, 1.55)
Atrio-ventricular block	104 (1.13%)	104 (1.13%)	0.99	(0.76, 1.3)
Bradycardia	398 (4.31%)	369 (4.02%)	1.07	(0.93, 1.23)
Bundle Branch Blocks and QRS prolongation	20 (0.22%)	25 (0.27%)	0.8	(0.44, 1.43)
Conduction disturbance	145 (1.57%)	142 (1.55%)	1.02	(0.81, 1.28)
Nodal, Junctional or Idioventricular rhythm	13 (0.14%)	13 (0.14%)	0.99	(0.46, 2.14)
Nonsustained ventricular tachycardia, SVT, unspecified Ventricular tachycardia	193 (2.09%)	191 (2.08%)	1.01	(0.82, 1.23)
Premature atrial contraction	41 (0.44%)	35 (0.38%)	1.17	(0.74, 1.83)
Premature ventricular contraction	107 (1.16%)	130 (1.42%)	0.82	(0.63, 1.06)
Serious Atrioventricular Block (type 2b, 3)	64 (0.69%)	61 (0.66%)	1.04	(0.74, 1.48)
Sick sinus syndrome	28 (0.3%)	23 (0.25%)	1.21	(0.7, 2.1)
Sinus Arrest, Pause, Block, Dysfunction	20 (0.22%)	17 (0.19%)	1.17	(0.61, 2.23)
Sudden Death/ arrest, Electromechanical dissociation, cardiogenic shock	160 (1.73%)	199 (2.17%)	0.8	(0.65, 0.98)
Supraventricular arrhythmia	688 (7.45%)	659 (7.17%)	1.04	(0.94, 1.15)
Sustained Ventricular Tachycardia	5 (0.05%)	6 (0.07%)	0.83	(0.25, 2.72)
Syncope, Presyncope	182 (1.97%)	146 (1.59%)	1.24	(1, 1.54)
Tachycardia	357 (3.87%)	358 (3.9%)	0.99	(0.86, 1.15)
Ventricular Arrhythmia	375 (4.06%)	415 (4.52%)	0.9	(0.78, 1.03)
Ventricular Fibrillation	73 (0.79%)	95 (1.03%)	0.76	(0.56, 1.04)
Vertigo, Dizziness, Giddiness	603 (6.53%)	536 (5.83%)	1.12	(1, 1.25)

In the sponsor's AE table, syncope occurred in 100 (1.1%) and in 76 (0.8%) of the ticagrelor and clopidogrel-treated patients, respectively. As for dizziness, there were 418(4.5%) patients in the ticagrelor arm and 355 (3.9%) in the clopidogrel arm. The sponsor's SAE table included 26 syncopes SAEs (0.3%) for ticagrelor and 23(0.3%) syncope SAEs for clopidogrel. The lower numbers in the sponsor's analysis for both treatment groups are likely due to the splitting of arrhythmia-related symptoms.

As for SAEs, there was a higher frequency of ticagrelor- treated patients with SAEs in the "syncope/presyncope" category [51 (0.55%) for ticagrelor and 35 (0.38%) for clopidogrel]. There were no substantial differences in frequency of arrhythmia-related SAEs between treatment groups for the other terms that were listed in Table 17.

Additionally, during the full course of the Holter substudy, patients with pauses ≥ 3 seconds during the Holter period were more likely to experience the following symptoms if they were on ticagrelor: Dizziness, 6 patients on ticagrelor, and syncope (4 patients on ticagrelor:1 patient on clopidogrel).

On the reassuring side, Fatal AEs such as sudden cardiac death (10 patients [0.1%] with ticagrelor vs 21 patients [0.2%] with clopidogrel) and deaths due to ventricular fibrillation (4 patients [<0.1%] with ticagrelor vs 8 patients [0.1%] with clopidogrel) occurred in numerically fewer patients in the ticagrelor group compared to clopidogrel. There was no difference in DAEs in the arrhythmia or arrhythmia-related categories.

A Holter monitor substudy was done. A summary of the study is included in section 7.4.5.

In brief, the Holter substudy was well designed and demonstrated that ticagrelor causes more arrhythmias and pauses than clopidogrel. However, in the substudy, the frequency of symptomatic events was no greater in the ticagrelor-treated patients. There was a numerically higher occurrence of nocturnal pauses with ticagrelor compared to clopidogrel in patients that had 5 or more ventricular pauses of ≥ 3 seconds during Holter monitoring periods. This observation raised the possibility that ticagrelor could worsen sleep apnea.

One limitation of the PLATO study is that patients with an increased risk of bradycardic events (eg, no pacemaker and known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker) were excluded from the study so there is limited information of the effect of ticagrelor on patients with these conditions.

In summary, the data from DISPERSE2 is not favorable for ticagrelor vis-à-vis cardiac arrhythmias. In PLATO, the data for ticagrelor is not favorable for atrial arrhythmias and ventricular pauses but it is favorable for sudden death and ventricular arrhythmias. This data in addition to the higher frequency of syncope, presyncope, dizziness, wooziness, and giddiness events in the ticagrelor arm of PLATO, is compelling enough evidence to conclude that the product label should include a warning about the potential for syncope and presyncope and

cardiac arrhythmias, particularly ventricular pauses. While it might be attractive to limit ticagrelor's use to patients without histories of sick sinus syndrome, second or third degree AV block, recurrent dizziness, history of loss of consciousness, syncope, advanced COPD or sleep apnea, the reduced frequency of cardiac arrest outweighs these other concerns.

Renal Function Effects

No signals for renal toxicity were identified during non-clinical development and phase I clinical studies. In the phase 2 studies, all treatment arms had increases in serum creatinine levels throughout the trial. However, when looking at frequency of categorical changes, i.e., > 30% to ≤ 50% increase, or >100% increase in serum creatinine; there was a trend toward a somewhat greater and earlier categorical increase in serum creatinine in the ticagrelor treatment groups compared to the clopidogrel treatment group. Most patients in the small placebo group also had categorical increases in serum creatinine by week 8. Since renal impairment carries high morbidity and mortality and is an independent predictor of cardiovascular mortality and a co-morbidity in patients with cardiovascular disease, the findings of categorical changes in renal function were explored thoroughly in PLATO.

The PLATO protocol specified that laboratory testing (clinical chemistry and hematology) should be tested at visit one (randomization), visit two (one month), visit three (3 months), visit four (6 months) and visit six (end of treatment at 12 months ± 10 days). The protocol allowed for safety laboratory monitoring to be discontinued if the data and safety monitoring board (DSMB) decided that testing was no longer required. As specified in the protocol, the DSMB decided that patients randomized on or before January 31, 2008 would continue to have safety laboratory testing (hematology and chemistry) during the course of the study in accordance with the study plan. Patients who were randomized on or after February 1, 2008 did not have safety laboratory testing (hematology and chemistry) after Visit 1 (Randomization).

For interpreting the results, it is important to know that while the mean baseline creatinine values were normal, the mean eGFR-MDRD values were below 90 cc/min. Therefore, most of the patients enrolled in PLATO had a baseline of chronic renal insufficiency. In Table 18, there are fewer Visit 1 values than Visit 2 values which indicates that ~ 250 patients in each treatment group had missing baseline values. There were fewer measurements at Visit 5 because it was an unscheduled visit. The 30-day follow-up visit was done off-drug. Table 18 shows that mean serum creatinine increased with both drugs, but the magnitude of the increase was slightly higher with ticagrelor (by 0.01 – 0.05 mg/dL, which is a minimal difference. The shift table for mean serum creatinine values did not add cause for concern, and neither did the mean eGFR data or shift tables. The mean serum creatinine values trended toward a greater increase while on treatment with ticagrelor and then stabilized or came down slightly in the recovery period. A substudy looking at absolute changes of cystatin C, a biomarker of renal function, showed that both treatment arms had 20 -25% mean increases from baseline. The mean changes were driven by small changes in the majority of patients as opposed to large changes in a minority of patients. However, as can be seen in Table 19, mean changes in creatinine tend to obscure the effects of ticagrelor on renal function. One can

readily see from Table 19 that there is a trend toward higher percentages of ticagrelor-treated patients who developed creatinine increases between 30 and 50% and between 50 and 100%. One must keep in mind that there is a large amount of missing data because patients randomized after February 1, 2008 did not have safety laboratory values collected after Visit 1 (as prespecified in the protocol at the discretion of the DSMB) and because some patients missed a baseline value or the timepoint of the baseline value was not recorded properly. My concern is that the missing data might contribute to an underestimation of the negative effect of ticagrelor on renal function.

Table 18: Sponsor's Analysis Summary statistics for serum creatinine by visit and treatment group – PLATO safety laboratory analysis set

Visit schedule[a]		Ticagrelor		Clopidogrel	
		N	Mean creatinine mg/dL Mean (SD)	N	Mean Creatinine mg/dL Mean (SD)
Visit 1	Index Event	4641	0.98 (0.31)	4624	0.98 (0.32)
Visit 2	1 mo	4901	1.06 (0.35)	4870	1.04 (0.32)
Visit 3	3 mo	4494	1.05 (0.33)	4496	1.03 (0.33)
Visit 4	6 mo	4022	1.05 (0.33)	3998	1.04 (0.32)
Visit 5	9 mo	229	1.08 (0.33)	222	1.03 0.25)
Visit 6	12 mo	3652	1.07 (0.41)	3643	1.04 (0.31)
	30 day follow-up	3595	1.06 (0.37)	3545	1.05 (0.34)

Source: Modified from Table 87, PLATO study report NDA 22-433, p. 315.

Table 19: Sponsor's Analysis: Greatest change from baseline to maximum serum creatinine value while on-treatment – safety data laboratory set

Criteria	Ticagrelor 90 mg bd N=4031	Clopidogrel 75 mg od N=4035
Change in serum creatinine (baseline to maximum value)		
Creatinine increase >100%	35 (0.9%)	34 (0.9%)
Creatinine increase >50% to 100%	300 (7.4%)	237 (5.9%)
Creatinine increase >30% to 50%	692 (17.2%)	588 (14.6%)
Creatinine increase 0 to <30%	2632 (65.3%)	2750 (68.2%)
Decrease	372 (9.2%)	426 (10.6%)
Missing data	1579	1547

Source: PLATO study report, Table 89, p. 317.

Mechanism of Renal Function Changes

The mechanism of increased serum creatinine with ticagrelor treatment is unknown. Adenosine infusion directly into the renal arteries of dogs that were salt-depleted resulted in a change in renal hemodynamics (decreased efferent arteriolar resistance but unchanged afferent arteriolar resistance) and led to decreased GFR, filtration fraction, sodium excretion and renal venous renin. It is possible that ticagrelor which indirectly increases serum levels of adenosine may indirectly increase serum creatinine and decrease GFR through this mechanism (H Tagawa and A. Vander, Effects of Adenosine Compounds on Renal Function and Renin Secretion in Dogs, Circulation Research, Vol 26, March 1970, p. 327-338).

Renal Deaths and Adverse Events

Four patients randomized to ticagrelor died from renal-related AEs. Six patients randomized to clopidogrel died from renal-related AEs.

Overall, according to the sponsor's analysis, there were 80 (0.8%) patients receiving treatment with ticagrelor reported 1 or more renal-related SAEs while on and off treatment. Of the clopidogrel treatment group, there were 67 (0.7%) patients with renal-related SAEs. The frequency of SAEs of renal failure acute, renal failure and renal failure chronic were the same in both treatment groups. Six SAEs related to hematuria accounted for most of the small increase in renal related SAEs on ticagrelor compared to clopidogrel. There were no imbalances in renal transplantation or dialysis between the treatment groups.

However, in the subgroup of patients with baseline eGFRs of <30cc/min/1.73m^2 one can see a large differences in the frequency of renal failure depending on treatment arm. 13.6% of ticagrelor-treated patients with baseline eGFRs of <30cc/min/1.73m^2 developed renal failure while only 0.1% of ticagrelor-treated patients with eGFRs > 90 cc/min/ 1.73 m^2 were reported to have renal failure. Also when comparing treatment groups, in the subgroup of patients with baseline eGFRs less than 30 cc/min/1.73m^2 , there were more than twice as many who had renal failure events in the ticagrelor group than in the clopidogrel group [12/88 (13.6%) vs. 5/93 (5.4%)]. It is also important to note that irrespective of treatment group, patients over 75 years of age had an increased incidence of renal failure (18-19% compared to patients under 65 years of age (0.3 -0.4%).

Interestingly, there were fewer renal-related SAEs that lead to permanent discontinuation from PLATO in the ticagrelor treatment arm compared to the clopidogrel treatment arm, [4(0.0%) compared to 8(0.1%), respectively]. It is reassuring that more than half of the renal-related SAEs in both treatment groups resolved while patients were still on treatment. If the renal-related SAEs had been related solely to the drug, recovery would probably not have occurred.

Overall, more ticagrelor-treated patients developed renal AEs [449 (4.9%) in the ticagrelor treatment group compared to 345 (3.8%) in the clopidogrel-treatment group]. The most frequent preferred terms (occurring in order of descending frequency) for renal-related AEs while on treatment were hematuria, renal failure, increased creatinine and acute renal failure.

All other preferred term AEs (renal impairment, renal failure chronic, proteinuria, oliguria or nephropathy) occurred in less than 0.5% of the patients.

Figure 12 shows the KM plot for time to first renal-related AE. Percentages presented in this figure represent the event rate at 12 months. The ticagrelor treatment group shows an increase in the percentage of patients with at least 1 renal-related AE. The analysis of the time to first event was significantly different between treatment groups (HR 1.31 [95% CI 1.14, 1.50]), and the 2 curves appear to separate early and become parallel within 90 to 120 days. The majority of this separation is evident by Day 60.

Figure 12: Kaplan-Meier plot of time to first renal-related AE – safety analysis set
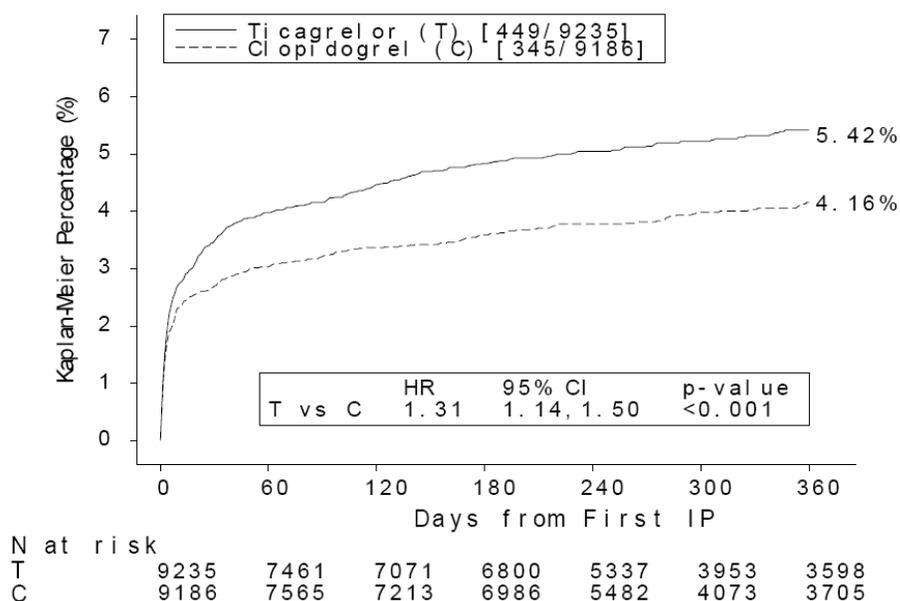
Source: PLATO study report, p. 305

As shown in Table 20, the frequencies of renal related AEs, renal function AEs, and > 50% increases in serum creatinine were higher in ticagrelor-treated patients who were on ARBs > 50% of study days compared to ticagrelor-treated patients who didn't receive ARBs >50% of study days. This was true for the clopidogrel-treated patients but the change in frequency of adverse renal events was not as marked. If the hemodynamic mechanism proposed earlier is accurate, it would stand to reason that ARBs would worsen renal function in ticagrelor-treated patients and it may be prudent to avoid them during treatment. While ACE inhibitor use (not shown) increased the frequency of creatinine increase > 50%, they did not change the frequency of renal AEs for the worse.

Table 20: Sponsor's Analysis: Frequencies of >50% elevation of creatinine, renal-related AEs, renal function AEs by use of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) by treatment

Concomitant ACEI or ARB use >50% of study days	Renal outcome	ticagrelor	clopidogrel	Concomitant ACEI or ARB use >50% of study days	ticagrelor	clopidogrel
ACEI USE: YES	Total at risk for >50% creatinine increase	2721 (100%)	2763 (100%)	ACEI USE: NO	752 (100%)	744 (100%)
	Creatinine increase >50%	228 (8.4%)	187 (6.8%)		51 (6.8%)	37 (5.0%)
	Total at risk for a renal-related AE	6056 (100.0%)	6059 (100.0%)		1874 (100.0%)	1883 (100.0%)
	Renal related AE	249 (4.1%)	206 (3.4%)		95 (5.1%)	58 (3.1%)
	Total at risk for renal function AE	6056 (100%)	6059 (100%)		1874 (100%)	1883 (100%)
	Renal function AE	119 (2.0%)	82 (1.4%)		56 (3.0%)	39 (2.1%)
ARB USE: NO	Total at risk for >50% creatinine increase	511 (100%)	508 (100%)	ARB USE: NO	3300 (100%)	3322 (100%)
	Creatinine increase >50%	57 (11.2%)	36 (7.1%)		251 (7.6%)	212 (6.4%)
	Total at risk for a renal-related AE	1127 (100.0%)	1126 (100.0%)		7634 (100.0%)	7585 (100.0%)
	Renal related AE	73 (6.5%)	48 (4.3%)		333 (4.4%)	265 (3.5%)
	Total at risk for renal function AE	1127 (100%)	1126 (100%)		7634 (100%)	7585 (100%)
	Renal function AE	51 (4.5%)	31 (2.8%)		166 (2.2%)	111 (1.5%)

Source: reformatted Table 4, PLATO renal report, p.15. The reason for smaller at risk population for >50% creatinine increase is that patients randomized after February 1, 2008 did not have safety laboratory values collected after Visit 1 (as determine by the DSMB) and because some patients missed a baseline value or the timepoint of the baseline value was not recorded properly.

Because of the renal safety concern, I was interested in knowing if there was any difference in the effectiveness of ticagrelor by baseline eGFR. While the numbers are very small, ticagrelor may not be more effective or possibly worse than clopidogrel in patients with markedly reduced renal function at beginning of treatment. See Table 21.

Table 21: # events (from composite efficacy endpoint) by stage of chronic kidney disease by treatment

eGFR (CG)	N	Ticagrelor # events/n	Clopidogrel # events/n	HR	95%CI
<15	16	6/8 (75%)	1/8 (20%)	12	1.38, 104
<30	262	39/119 (36%)	50/143 (40%)	0.97	0.64, 1.47
<60	3,847	308/1887 (18%)	390/1960 (22%)	0.8	0.69, 0.93
<90	11,558	650/5770 (12%)	757/5788 (14%)	0.86	0.77, 0.95

*365 day KM%
Source: R. Fiorentino, Clinical Reviewer

I was also interested in knowing if the degree of renal disease correlated with increased death. As one would expect, the frequency of death worsened with worsening degrees of baseline renal function in both groups. There were only 15 patients in the study with eGFR < 15 cc/min. 4/4 that were in the ticagrelor treatment group died, whereas 11/11 in the clopidogrel treatment group did not die. This is a disturbing observation. However, the numbers are too low to make any conclusion about ticagrelor and risk of dying when there is baseline renal failure. Post-marketing data will be useful to elucidate this issue.

Also, as discussed in the bleeding section, patients with eGFR ≤30 cc/minute in PLATO had a calculated relative risk of major bleeding of 2.5 if they were on ticagrelor.

In summary, there was an increased frequency of patients that had extreme decreases in eGFR (>30% -100%) in the ticagrelor group as compared to the clopidogrel group. There was no difference between the treatment groups in frequency of deaths or discontinuations for renal AEs. However, there were more renal AEs and renal SAES in the ticagrelor-treated patients compared to the clopidogrel-treated patients that was greatly magnified in patients with preexisting stage 4 renal insufficiency.

Ticagrelor-treated patients with eGFR less than 30 are at higher risk for endpoint events, renal failure, all-cause death and major bleeds. It may be wise to limit the use of ticagrelor in this patient population.

Elevated Uric Acid

Increases in serum uric acid with ticagrelor were first observed in the phase 2 studies DISPERSE and DISPERSE2 and later confirmed in PLATO (approximately 15% mean increase from baseline for ticagrelor-treated patients vs. approximately 7.5% for clopidogrel-treated patients). The degree of uric acid elevation from baseline went from a mean of 15.4 % to 7.3% by the 30-day follow-up after stopping ticagrelor. No mean decrease was seen in the uric acid levels in the clopidogrel-treated patients at the 30-day follow-up visit. Relatively few of all treated patients experienced AEs that were potentially related to uric acid elevation (2.1% of the ticagrelor treated patients and 1.8% of the clopidogrel treated patients. Gout, the most frequently occurring uric acid-related AE, occurred in 0.6% of patients in both treatment groups. There was no difference between groups in incidence of nephrolithiasis. The only difference in AEs between the treatment groups was hyperuricemia (0.5% vs. 0.2%). 2.5% of patients on ticagrelor who crossed the clinically relevant threshold for hyperuricemia (7.0 mg/dL in men and > 6.0 mg/dL in women) developed gout and 2.2% of clopidogrel-treated patients who crossed the threshold developed gout. There were 4 patients in the ticagrelor group that developed a gout/hyperuricemia SAE compared to 2 in the clopidogrel group

The data do not support an association between ticagrelor treatment and gout-related events. Having an elevated serum uric acid level does not reliably predict if the patient has gout or will develop gout, so routine monitoring of serum uric acid levels during ticagrelor treatment should not be indicated (Logan et al, Serum uric acid in acute gout, Ann Rheum Dis 1997, p. 696-7).

<u>Mechanism of Elevation of Uric Acid</u>

It is known that adenosine blocks uric acid transport channel activity. (M Rafey et al, Uric acid transport, Curr Opin Nephrol Hypertens 12:511-6, 2003 Lippincott Williams & Wilkins). Since ticagrelor increases adenosine by interfering with erythrocyte reuptake, it is proposed that this is the mechanism by which uric acid levels increase in ticagrelor-treated patients.

Hormonally Mediated Effects

It was observed in preclinical rat studies that there were uterine carcinomas and benign hepatocellular adenomas after high exposure to ticagrelor.

There was no clinical evidence from the phase 1 and 2 clinical studies that treatment with ticagrelor in humans increased the risk of developing cancer, and more specifically gynecological cancer.

In Table 22, one can see that vaginal bleeding when counted as an AE was not common and there was little difference between treatment groups. There were very few SAEs or discontinuation from vaginal bleeding event. While there was a ticagrelor-treated patient who was diagnosed with endometrial adenocarcinoma on the 14th day of treatment, a causal relationship in this particular case is not possible.

Table 22: AEs that might be hormonally related

Category of possibly hormonally related AE	Ticagrelor 90 mg bd N= 9235	Clopidogrel 75 mg QD N= 9186	RR
	n(percent)	n(percent)	
Vaginal bleeding	22 (0.24)	17 (0.19)	1.3
Breast tenderness/ pain	8 (0.09)	6 (0.04)	2.3
Gynecomastia	15 (0.16)	3 (0.03)	5.3
Breast Cancer	4 (0.03)	10 (0.03)	1
Prostate enlargement, mass, or disorders	39 (0.12)	40 (0.12)	1.2
BPH	10 (0.11)	8 (0.09)	1.2
Prostate cancer	13 (0.13)	12 (0.12)	1.1
Cervical/uterine tumor	5 (0.05)	5 (0.05)	1
Cervical/uterine malignancy	0 (0)	0 (0)	
Erectile Dysfunction	43 (0.5%)	50 (0.8%)	0.625
Decreased Libido	5 (0.1%)	1 (0.1%)	1
Sexual Dysfunction	3 (0.0%)	11 (0.2%)	0

Some patients may be listed in more than one category

IOf greater concern than the vaginal bleeding was the isolated increased frequency of gynecomastia in the ticagrelor-treated patients. It is well known that gynecomastia is hormonally mediated. Drugs may cause gynecomastia by increasing estrogen effects as is the case with digitalis, by decreasing testosterone effects as is the case with spironolactone or increasing prolactin levels as is the case with some antipsychotic medications. There were 17 patients who developed gynecomastia on ticagrelor and 3 patients who developed gynecomastia on clopidogrel. The RR for developing gynecomastia was 5.3 in PLATO.

A Kaplan-Meier curve was generated from the 17 ticagrelor patients with gynecomastia, breast, mass or swelling of breast and the 3 clopidogrel patients with gynecomastia (Figure 13). This graphically demonstrates that the onset of gynecomastia was early and there was a steady rate of new cases. The difference in frequency of gynecomastia between groups was statistically significant (log-rank = 0.0016).

Figure 13: K-M: Gynecomastia (17 of men with gynecomastia or breast swelling or breast mass in ticagrelor group), 3 of men with gynecomastia in the clopidogrel group)

Source: Dr. Thomas Marciniak from his secondary clinical review

There was no increase in breast cancer during PLATO and no increase in any other hormonally related adverse event aside from gynecomastia. The mechanism for the development of gynecomastia is unknown. Many patients in this trial were on spironolactone. In fact, most of the narratives of gynecomastia reported that the patients were also taking spironolactone. Since this is a randomized trial, one would expect equal spironolactone exposure in both treatment groups. Perhaps ticagrelor causes gynecomastia in patients that have other predisposing conditions for gynecomastia.

My assessment is that in the absence of a biologically plausible mechanism for the increased frequency of gynecomastia in ticagrelor-treated patients, and in the absence of any other hormonally mediated effect differences between treatment groups, one can not draw any firm conclusions about the increased frequency of gynecomastia observed in the ticagrelor group. Nevertheless, gynecomastia should be a labeled adverse effect.

Hepatic Effects

There was 1 patient in the ticagrelor arm that died of metastatic hepatic cancer. In the clopidogrel arm, 3 died of hepatic related events. One died of metastatic hepatic cancer, one of hepatic failure and one of hepatic neoplasm.

A total of 8 patients in the ticagrelor group and 13 patients in the clopidogrel group met enzymatic criteria for potential Hy's Law (ALT or AST level of >3xULN, a total bilirubin level of >2xULN, and an ALP <2xULN concurrently) with abnormal tests occurring at anytime during the study. Two (<0.1%) patients in the ticagrelor treatment group and 1 (<0.1%) patient in the clopidogrel treatment group met enzymatic laboratory criteria for potential Hy's Law concurrently while on treatment. Both of the Hy's law cases in the ticagrelor arm occurred soon after starting drug and resolved spontaneously. It is not likely that their enzymes increased as a result of ticagrelor exposure. More likely the enzyme abnormalities were secondary to circulatory changes at the onset of their ACS. The descriptions of the two ticagrelor-treated patients that met Hy's law criteria are in Appendix B.

There were no differences between groups in mean levels of liver enzymes throughout the course of the trial. There were initial elevations of aspartate aminotransferase (AST) and alanine transaminase (ALT) followed by normalization in both treatment groups, likely reflecting the underlying index event rather than an effect of the study drug. There were no clinically relevant changes over time in alkaline phosphatase or bilirubin levels.
Similar trends were seen in patients with and without baseline hepatic disorders. For the most part, there were no differences between treatment groups in terms of frequency of liver enzyme elevations above prespecified cut offs such 2 or 3 times the upper limit of normal. However, bilirubin elevation to 1.5 or 2.0 X elevation of normal occurred more frequently in the ticagrelor treatment group. There were 68 (0.74%) patients that were on ticagrelor and 39 (0.1%) patients that were on clopidogrel that met the criterion of a bilirubin elevation of 1.5X normal. There were 25 (0.3%) ticagrelor treated patients and 10 (0.1%) clopidogrel-treated patients, respectively, that had bilirubin elevations that were 2X normal levels. This difference between groups in bilirubin elevations was not reflected by an increase in hepatobiliary AEs or serious AEs.

There was a low frequency of hepatic AEs in PLATO. There were no differences between groups in the frequency of hepatic AEs (1.7% for both treatment groups). For hepatic SAEs, ticagrelor was slightly better than clopidogrel (0.1% for ticagrelor and 0.2% for clopidogrel.

There is no evidence to suggest that ticagrelor is hepatotoxic in humans.

Neurological System Effects

In PLATO, certain neurological events, particularly, intracranial bleeding events were adjudicated by a neurologist. The intracranial bleeding results were reviewed by the ICAC in a blinded fashion. It can be seen in Table 23 that there are a couple of categories of neurologically-related AEs that were more commonly seen in the ticagrelor treatment group, namely, thrombotic and hemorrhage (all) stroke [124 (1.34%) vs. 103 (1.12%) for ticagrelor-treated and clopidogrel-treated patients, respectively] and focal weakness [17 (0.18%) vs. 11 (0.12%) for ticagrelor-treated and clopidogrel-treated patients, respectively.

Table 23: Neurological AEs

AE Category (renamed)	ticagrelor 90 mg bd N=9235	clopidogrel 75mg od N=9186	RR	95% CI
Dimentia	4 (0.04%)	12 (0.13%)	0.33	(0.11, 1.03)
Encephalopathy	27 (0.29%)	22 (0.24%)	1.22	(0.7, 2.14)
Focal weakness	17 (0.18%)	11 (0.12%)	1.54	(0.72, 3.28)
Gait disturbance, Fall	53 (0.57%)	66 (0.72%)	0.8	(0.56, 1.15)
Headache, migraine	640 (6.93%)	578 (6.29%)	1.1	(0.99, 1.23)
Hypotonia, Hypertonia	22 (0.24%)	24 (0.26%)	0.91	(0.51, 1.62)
Malaise, Fatigue, Weakness, Somnolence	552 (5.98%)	570 (6.21%)	0.96	(0.86, 1.08)
Neuropathy, Paresthesia, Hypoaesthesia, Numbness, Neuralgia	227 (2.46%)	230 (2.5%)	0.98	(0.82, 1.18)
Nonsustained ventricular tachycardia, SVT, unspecified Ventricular tachycardia	193 (2.09%)	191 (2.08%)	1.01	(0.82, 1.23)
Seizures	13 (0.14%)	16 (0.17%)	0.81	(0.39, 1.68)
Stroke/TIA	147 (1.59%)	137 (1.49%)	1.07	(0.85, 1.34)
Thrombotic or Hemorrhagic Stroke	124 (1.34%)	103 (1.12%)	1.2	(0.92, 1.55)
Thromoembolic event	63 (0.68%)	53 (0.58%)	1.18	(0.82, 1.7)
Transient Ischemic Attact	26 (0.28%)	38 (0.41%)	0.68	(0.41, 1.12)
Tremor	28 (0.3%)	21 (0.23%)	1.33	(0.75, 2.33)

Figure 14 is a K-M time to event analysis that clearly shows the increased frequency and time to event for hemorrhagic stroke events in the ticagrelor-treated patients. In Figure 15, one can see that the ticagrelor group also had a higher frequency of all stroke events.

Figure 14: K-M: Hemorrhagic Stroke

K-M: Hemorrhagic Stroke

log rank p = 0.13

Group	Number failed	Number censored
AZD6140 BD	22	9213
CLOPIDOGREL 75 MG OD	13	9173
Combined	35	18386

Figure 15: K-M: Stroke

K-M: Stroke

log rank p = 0.22

| Group	Number failed	Number censored
AZD6140 BD	123	9112
CLOPIDOGREL 75 MG OD	104	9082
Combined	227	18194
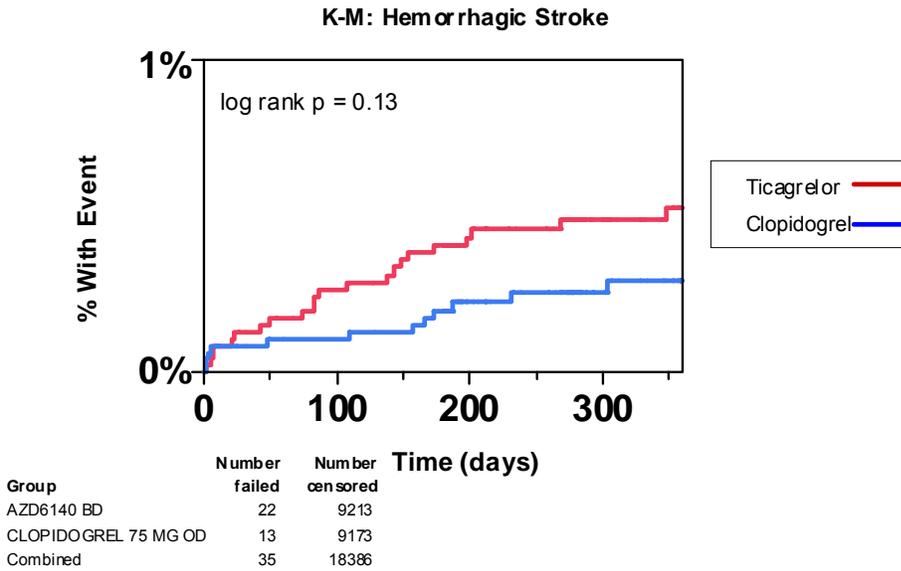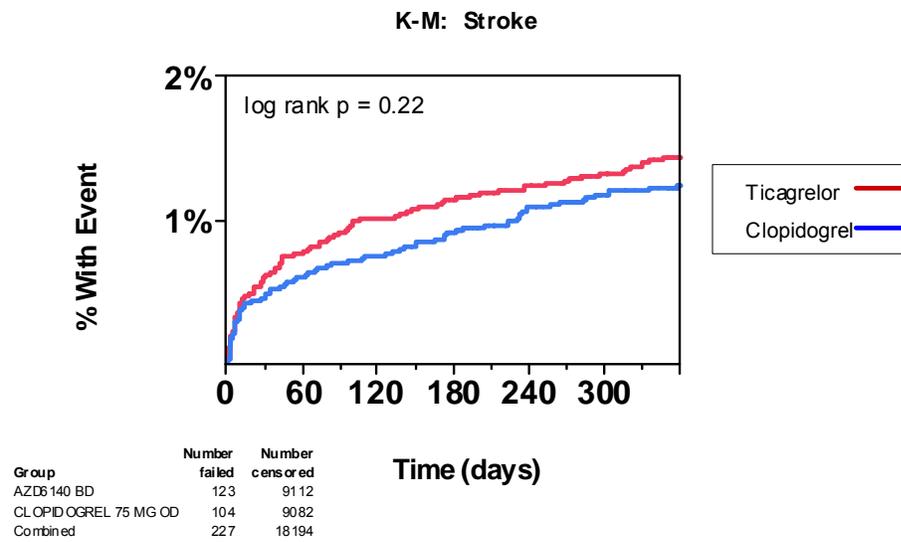
Table 24 shows the higher frequency of major/life-threatening intracranial hemorrhagic bleeds and fatal hemorrhagic bleeds in the ticagrelor group. Most notable is that the ticagrelor treatment group had 11 fatal intracranial bleeds compared to the 1 fatal intracranial bleed in the clopidogrel treatment group.

Table 24: Intracranial Bleeds

Characteristic	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N =9186	RR
Number (percent) of Major Fatal/ Life-threatening Intracranial Bleeds	27 (26 patients) (0.3)	14 (0.15)	2
Fatal Events	11 (0.12)	1 (0.0)	
Out of the Hospital Events	17 (0.19)	10 (0.11)	1.73
Average days to bleed	161	160.9	

Modified from table in PLATO safety report, p.3541

Hemorrhagic stroke is a concerning safety signal. There will need to be a warning about risk of all stroke and hemorrhagic stroke in the label

Neoplasms

There were no concerning findings with regard to neoplasms. See Section 7.6.1 for a detailed analysis.

7.4   Supportive Safety Results

7.4.1   Common Adverse Events

Table 25 displays the most common AEs by descending frequency of the sponsor's preferred terms that occurred in ≥ 2% of the patients. The most common AE was dyspnea in 12% of patients. While headache, cough, dizziness, nausea, atrial fibrillation and so on down the list were common, the only AEs with standout differences between treatment groups were dyspnea, epistaxis, contusion, and hematoma. This analysis supports the previous sections on the important AEs associated with ticagrelor.

Table 25: Sponsor analysis: PLATO: Common AEs by descending frequency of preferred terms by treatment that occurred in ≥ 2% of the patients

Preferred Term	ticagrelor 90mg bd	clopidogrel 75mg od
Dyspnea	1104 (12.0%)	598 (6.5%)
Headache	600 (6.5%)	535 (5.8%)
Epistaxis	558 (6.0%)	308 (3.4%)
Cough	452 (4.9%)	427 (4.6%)
Dizziness	418 (4.5%)	355 (3.9%)
Nausea	397 (4.3%)	346 (3.8%)
Atrial fibrillation	390 (4.2%)	418 (4.6%)
Contusion	357 (3.9%)	187 (2.0%)
Hypertension	353 (3.8%)	363 (4.0%)
Non-cardiac chest pain	344 (3.7%)	306 (3.3%)
Diarrhea	342 (3.7%)	304 (3.3%
Back pain	329 (3.6%)	301 (3.3%)
Hypotension	300 (3.2%)	306 (3.3%)
Fatigue	295 (3.2%)	296 (3.2%)
Chest pain	288 (3.1%)	323 (3.5%)
Bradycardia	269 (2.9%)	270 (2.9%)
Pyrexia	266 (2.9%)	261 (2.8%)
Vomiting	234 (2.5%)	215 (2.3%)
Cardiac failure	214 (2.3%)	236 (2.6%)
Edema peripheral	211 (2.3%)	228 (2.5%)
Hematoma	203 (2.2%)	122 (1.3%)
Constipation	202 (2.2%)	237 (2.6%)
Anxiety	200 (2.2%)	170 (1.9%)
Pain in extremity	196 (2.1%)	211 (2.3%)
Post procedural hemorrhage	192 (2.1%)	180 (2.0%)
Dyspepsia	185 (2.0%)	168 (1.8%)
Urinary tract infection	184 (2.0%)	161 (1.8%)
Ventricular tachycardia	184 (2.0%)	193 (2.1%)
Asthenia	181 (2.0%)	191 (2.1%)

Source: p. 85 in Clinical Summary of Safety, PLATO

As a sensitivity analysis, I renamed verbatim terms into my own broader group terms. The frequencies of AEs by these broader terms are included in Table 26. A lower rank means a higher relative risk. "Bleed, Hematoma" rose to the top of the list. Nevertheless, there were no

findings that differed substantially from the sponsor's analysis other than what has already been covered in this review.

Table 26: Common AEs in order of decreasing frequency by treatment for AEs occurring ≥ 2% of the time

Category	ticagrelor 90 mg bid N=9235	clopidogrel 75 mg od N=9186	RR	95% CI	RANK
Bleed, Hematoma	3312 (35.86%)	2564 (27.91%)	1.28	(1.23, 1.34)	31
Muscle pain, Musculo-skeletal pain, Back pain	1913 (20.71%)	1833 (19.95%)	1.04	(0.98, 1.1)	75
Infection	1488 (16.11%)	1438 (15.65%)	1.03	(0.96, 1.1)	87
Arrhythmia	1349 (14.61%)	1330 (14.48%)	1.01	(0.94, 1.08)	94
Dyspnea	1345 (14.56%)	803 (8.74%)	1.67	(1.53, 1.81)	8
Gastroduodenal Disorder, Helicobacter Pylori	1333 (14.43%)	1230 (13.39%)	1.08	(1, 1.16)	67
Subcutaneous hemorrhage, Ecchymosis, Hematoma	1292 (13.99%)	811 (8.83%)	1.58	(1.46, 1.72)	12
Flu, Cold, Cough, Sore throat, Rhinitis, Hoarseness, Laryngeal disease	947 (10.25%)	882 (9.6%)	1.07	(0.98, 1.17)	70
PCI -related Bleed or Hematoma	924 (10.01%)	711 (7.74%)	1.29	(1.18, 1.42)	29
Noncardiac or unspecified Chest pain,	911 (9.86%)	904 (9.84%)	1	(0.92, 1.09)	99
Surgical, Post-surgical bleed/hematoma	821 (8.89%)	843 (9.18%)	0.97	(0.88, 1.06)	120
Lower Gastrointestinal disorders	806 (8.73%)	786 (8.56%)	1.02	(0.93, 1.12)	90
Coronary Artery Bypass Graft Bleed	748 (8.1%)	748 (8.14%)	0.99	(0.9, 1.1)	101
Supraventricular arrhythmia	688 (7.45%)	659 (7.17%)	1.04	(0.94, 1.15)	75
Headache, migraine	640 (6.93%)	578 (6.29%)	1.1	(0.99, 1.23)	60
Nausea, Vomiting	622 (6.74%)	539 (5.87%)	1.15	(1.03, 1.28)	48
Vertigo, Dizziness, Giddiness	603 (6.53%)	536 (5.83%)	1.12	(1, 1.25)	53
Epistaxis	574 (6.22%)	325 (3.54%)	1.76	(1.54, 2.01)	5
Acute and Chronic Heart failure, Cardiac asthma, Cardio-pulmonary heart failure, Diastolic	555 (6.01%)	576 (6.27%)	0.96	(0.86, 1.07)	122
Malaise, Fatigue, Weakness, Somnolence	552 (5.98%)	570 (6.21%)	0.96	(0.86, 1.08)	122
Bacterial infection	506 (5.48%)	492 (5.36%)	1.02	(0.91, 1.15)	90
Hypertension Increase, Crisis, Unstable Blood Pressure	490 (5.31%)	522 (5.68%)	0.93	(0.83, 1.05)	133
Viral Infection	466 (5.05%)	415 (4.52%)	1.12	(0.98, 1.27)	53

Category	ticagrelor 90 mg bid N=9235	clopidogrel 75 mg od N=9186	RR	95% CI	RANK
Atrial fibrillation	447 (4.84%)	455 (4.95%)	0.98	(0.86, 1.11)	116
Renal dysfunction, Polyuria, Anuria/oliguria, Incontinence	444 (4.81%)	362 (3.94%)	1.22	(1.07, 1.4)	35
Bradycardia	398 (4.31%)	369 (4.02%)	1.07	(0.93, 1.23)	70
Diarrhea	382 (4.14%)	339 (3.69%)	1.12	(0.97, 1.29)	53
Ventricular Arrhythmia	375 (4.06%)	415 (4.52%)	0.9	(0.78, 1.03)	140
Tachycardia	357 (3.87%)	358 (3.9%)	0.99	(0.86, 1.15)	101
Hypotension, Hypovolemic shock, Hypovolemia	353 (3.82%)	350 (3.81%)	1	(0.87, 1.16)	99
Anxiety and Agitation, Abnormal dreams, Stress, Agression	342 (3.7%)	279 (3.04%)	1.22	(1.04, 1.42)	35
Fever	331 (3.58%)	318 (3.46%)	1.04	(0.89, 1.2)	75
Gastrointestinal/ Anal bleed	327 (3.54%)	255 (2.78%)	1.28	(1.09, 1.5)	31
Anemia	315 (3.41%)	291 (3.17%)	1.08	(0.92, 1.26)	67
Edema (non-central, non-facial, non generalized)	306 (3.31%)	320 (3.48%)	0.95	(0.82, 1.11)	128
Accident, non-surgical/ procedural Trauma, Fracture	302 (3.27%)	255 (2.78%)	1.18	(1, 1.39)	42
Rash, Erythema	302 (3.27%)	296 (3.22%)	1.01	(0.87, 1.19)	94
Increased cholesterol, Decreased HDL, Increased lipids	282 (3.05%)	254 (2.77%)	1.1	(0.93, 1.31)	60
Hematuria	242 (2.62%)	195 (2.12%)	1.23	(1.02, 1.49)	34
Bronchopneomonia and Pneumonia, Pneumonitis	233 (2.52%)	245 (2.67%)	0.95	(0.79, 1.13)	128
Neuropathy, Paresthesia, Hypoaesthesia, Numbness, Neuralgia	227 (2.46%)	230 (2.5%)	0.98	(0.82, 1.18)	116
Sleep disorder	226 (2.45%)	230 (2.5%)	0.98	(0.82, 1.17)	116
Dyspnea on Exertion	224 (2.43%)	160 (1.74%)	1.39	(1.14, 1.7)	19
Constipation	220 (2.38%)	250 (2.72%)	0.88	(0.73, 1.05)	146
Electrolyte disorder	207 (2.24%)	220 (2.39%)	0.94	(0.78, 1.13)	131
Nonsustained ventricular tachycardia, SVT, unspecified Ventricular tachycardia	193 (2.09%)	191 (2.08%)	1.01	(0.82, 1.23)	94

When sorting my recategorized AEs by relative risk, there were several differences between treatment groups as shown in Table 27. Most of the AEs that are in this table and not in the common AEs ≥ 2% table include very few numbers of patients and there is little reason to be concerned about a drug related effect. The relatively high frequency of gynecomastia led to the initiation of further analysis which was discussed in a previous section.

Table 27: PLATO: Common AEs in order of descending relative risk by treatment

Category	ticagrelor N=9235	clopidogrel N=9186	RR	95% CI
Gynecomastia	15 (0.16%)	3 (0.03%)	4.97	(1.44, 17.17)
Leukemia	5 (0.05%)	2 (0.02%)	2.49	(0.48, 12.81)
Neutropenia	6 (0.06%)	3 (0.03%)	1.99	(0.5, 7.95)
Intracranial hemorrhage or subdural or other hematoma	32 (0.35%)	18 (0.2%)	1.77	(0.99, 3.15)
Epistaxis	574 (6.22%)	325 (3.54%)	1.76	(1.54, 2.01)
Angioedema	14 (0.15%)	8 (0.09%)	1.74	(0.73, 4.15)
Acidosis	12 (0.13%)	7 (0.08%)	1.71	(0.67, 4.33)
Dyspnea	1345 (14.56%)	803 (8.74%)	1.67	(1.53, 1.81)
Colonic Polyp, mass or cancer	20 (0.22%)	12 (0.13%)	1.66	(0.81, 3.39)
Infectious endocarditis, Myocarditis, Mediastinitis	15 (0.16%)	9 (0.1%)	1.66	(0.73, 3.79)
Acute psychosis, Hallucinations, Delusions	21 (0.23%)	13 (0.14%)	1.61	(0.81, 3.21)
Subcutaneous hemorrhage, Ecchymosis, Hematoma	1292 (13.99%)	811 (8.83%)	1.58	(1.46, 1.72)
Retroperiotoneal hematoma or hemorrhage	14 (0.15%)	9 (0.1%)	1.55	(0.67, 3.57)
Focal weakness	17 (0.18%)	11 (0.12%)	1.54	(0.72, 3.28)

Since there was only one dose of ticagrelor in the study, in order to look for a dose relationship for adverse events, I constructed a table (Table 28) that ordered the AEs (as I renamed them) by frequency by weight quintile. Quintile 1 is the lowest weight quintile and the quintile 5 is the highest weight quintile. The more negative the slope, the higher the likelihood that there is a dose relationship between the dose of drug and the adverse event category. I included in the table the most negative slopes and the most positive slopes to provide an idea about which AEs were or were not "dose related". In this analysis it appeared that gastroduodenal disorder, helicobacter pylori was highly "dose related". It appears that spontaneous bleeding and stroke were "dose related", while CABG bleeds, and arrhythmias were not. Dyspnea appeared to not be dose related by this analysis. However, the other evidence that exists to the contrary is more persuasive.

Table 28: Weight Relationship to AEs

Weight quintile (1 is lowest weight, 5 is highest weight)	1	2	3	4	5	slope (ticagrelor)	slope (clopidogrel)
ADVERSE EVENT							
Gastroduodenal Disorder, Helicobactor Pylori	18.65%	14.91%	13.58%	11.97%	12.62%	-15.00799	-9.857502
Bleed, Hematoma	36.25%	37.99%	36.13%	36.87%	32.14%	-9.347137	-5.753074
Nausea, Vomiting	8.70%	7.05%	6.66%	4.80%	6.14%	-7.361829	-8.858698
Subcutaneous hemorrhage, Ecchymosis, Hematoma	15.61%	14.27%	13.84%	13.44%	12.72%	-6.609833	-2.303132
Lower Gastrointestinal disorders	9.85%	9.45%	8.08%	8.81%	7.45%	-5.437616	-5.097829
PCI -related Bleed or Hematoma	11.34%	9.40%	10.09%	10.84%	8.16%	-4.915925	-2.530668
Anemia	4.97%	3.23%	3.01%	3.05%	2.61%	-4.905543	-4.942243
Hypotension, Hypovolemic shock, Hypovolemia	5.22%	4.17%	3.01%	3.05%	3.59%	-4.38474	-2.47548
Thrombotic or Hemorrhagic Stroke	1.99%	1.82%	1.16%	0.90%	0.71%	-3.481181	-1.396592
Constipation	3.28%	2.35%	2.32%	2.26%	1.63%	-3.391441	-2.96964
Cerebrovascular disease	2.49%	2.35%	1.58%	1.41%	1.31%	-3.299701	-2.445994
Stroke/TIA	2.24%	2.00%	1.27%	1.24%	1.09%	-3.054531	-2.307457
Diarrhea	4.72%	5.11%	3.12%	4.01%	3.75%	-3.043555	-3.459322
Vertigo, Dizziness, Giddiness	7.16%	6.69%	6.71%	5.65%	6.36%	-2.644468	0.608463
pulmonary heart failure, Diastolic dysfunction, Pulmonary	6.61%	5.52%	6.87%	5.76%	5.22%	-2.547007	-5.559518
Gastrointestinal/ Anal bleed	4.13%	3.64%	3.28%	3.90%	2.77%	-2.452637	0.244136
cardiogenic shock	2.44%	1.76%	1.22%	1.92%	1.20%	-2.322371	-3.272686
Valvular and Chordae abnormalities, murmurs	1.69%	1.53%	1.74%	0.85%	0.98%	-2.103555	-0.864023

Weight quintile (1 is lowest weight, 5 is highest weight)	1	2	3	4	5	slope (ticagrelor)	slope (clopidogrel)
ADVERSE EVENT							
Arrhythmia	12.98%	16.44%	13.79%	15.02%	15.17%	2.963531	5.676285
Ventricular Arrhythmia	2.93%	4.46%	4.23%	4.18%	4.62%	3.092144	2.213403
Viral Infection	4.03%	5.05%	4.97%	6.04%	5.33%	3.594145	4.385027
Dyspnea on Exertion	1.24%	2.76%	2.69%	2.20%	3.37%	3.69878	0.249861
Surgical, Post-surgical bleed/hematoma	7.26%	9.98%	8.14%	10.28%	9.08%	3.936201	-0.900987
Gout and Hyperuricemia	0.85%	1.35%	1.27%	1.86%	2.61%	4.042323	3.186416
Coronary Artery Bypass Graft Bleed	6.36%	8.98%	7.55%	9.49%	8.43%	4.629023	-0.02552
Infection	15.76%	14.86%	15.64%	17.00%	17.24%	5.088566	2.720359
Muscle pain, Musculo-skeletal pain, Back pain	18.45%	20.73%	20.18%	21.29%	23.27%	10.20925	9.057196
Dyspnea	12.08%	13.80%	14.58%	15.08%	17.51%	12.129	0.484967

7.4.2 Laboratory Findings

According to the Summary of Clinical Safety, hemoglobin, hematocrit, white blood cells and differentials, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), creatinine, glucose, and uric acid were collected in PLATO and the 4 Phase II studies.

Electrolytes

Because of the nonclinical observation of a possible mineralocorticoid effect for ticagrelor, I was interested in analyzing the changes in serum potassium. No serum electrolytes were measured in PLATO. The sponsor provided data from the Phase 2 study, DISPERSE2 I examined mean changes and outliers for potassium and sodium. For potassium, in all treatment groups the mean values increased by 0.1 to 0.3 meq/L but there were no differences between groups. There were very few outliers, mostly in the hyperkalemia range (> 5.5 meq/L) compared to the hypokalemia range (<3.5 meq/L) but there was no difference in frequency between treatment groups . If using more conservative cut points than what the sponsor chose, such as > 4.8 meq/L, there still were no apparent differences between groups. For sodium, there was a mean change from baseline of 0-2 meq/L and no differences between treatment groups. There were hardly any outliers (> 152 meq/L or < 132 meq/L). Even when using more conservative outlier measures for sodium than what the sponsor chose (>142 meq/L or <135 meq/L), while there was a greater frequency of outliers, there was no apparent difference between treatment groups.

I created an AE term called "electrolyte disorders". There was no difference between treatment groups in prevalence of patients having this event in PLATO [207 (2.24%) vs. 220(2.39%) in ticagrelor arm and clopidogrel arm, respectively].

Complete Blood Count

A very small percentage of patients experienced clinically important shifts in hematologic parameters (hemoglobin, white blood cells and platelet counts) and there were no treatment differences in these shifts throughout the study. For hemoglobin, 5% of ticagrelor-treated and 4% of clopidogrel-treated patients had a decrease from normal to low (AstraZeneca threshold of 11.5 g/dL for males or 10.5 g/dL for females). For white blood cells, 0.1% of the ticagrelor-treated and 0.2% of the clopidogrel-treated patients crossed the lower limit of the AstraZeneca threshold of 3×10^9 /L. For platelets, 0.1% of the ticagrelor-treated and 0.4% of the clopidogrel-treated patients crossed the lower limit of the AstraZeneca threshold of 100,000. Mean values for blood cells throughout treatment were also similar. In the phase 2 studies, there was no relationship between dose and changes to any component of the CBC. Thrombocytopenia does not appear to be a safety concern for ticagrelor.

Urinalysis

No urinalysis tests were measured in PLATO. This is disconcerting because the only studies that measured urinalyses were the small phase I studies and DISPERSE, the ticagrelor phase 2 dose-finding study that enrolled 146 male and 54 female patients, aged 34 to 84 years, with documented atherosclerotic disease. The overall mean exposure was only 27.9 days.
The data from the dose finding study, DISPERSE, revealed no worrisome findings. Particularly when one considers the creatinine categorical shifts seen more prominently in the ticagrelor-treatment group and accompanied by more renal AEs, it would have been worthwhile to have a better view of the urinalysis findings in PLATO with its larger target population and longer exposure.

Liver Enzymes

See discussion on hepatic effects in section 7.3.5 Submission Specific Primary Safety Concerns

7.4.3 Vital Signs

Pulse, systolic blood pressure and diastolic blood pressure were measured in PLATO and all Phase 2 studies. Additionally, PLATO measured waist circumference. The OFFSET, RESPOND and other pharmacodynamic studies also included respiratory rate and oral temperature. I evaluated the vital sign data from PLATO and OFFSET.

In PLATO, the changes in heart rate and blood pressure were examined by mean changes, shift tables that used reasonable prespecified thresholds, and absolute increases or decreases. There were some overall changes as described below but the changes were similar between treatment groups. Therefore, there are no changes to vital signs that appear to be related to ticagrelor.

Heart Rate
For heart rate, there was a drop of approximately 8 beats per minute in mean heart rate between Visit 1 and Visit 2. Approximately 5% of patients experienced a decrease in heart rate that crossed the AstraZeneca extended reference range (50 beats/min). Approximately 1.5% of patients experienced an increase that crossed the AstraZeneca extended reference range (100 beats/min). Bradycardia was more likely than tachycardia. This observation may have been related to changes in other medications and also to stabilization after the acute phase.

Blood Pressure
For both diastolic and systolic blood pressure there was a small reduction in mean values between Visit 1 and Visit 2 of approximately 6 mmHg, and no further reduction thereafter. At all visits, 4% and 1% of patients crossed the prespecified upper limit threshold of high systolic blood pressure (160 mmHg) and high diastolic blood pressure (100 mmHg), relative to the previous visit, respectively. There was only a 1% and 1% frequency of decreased systolic (less

than 100 mmHg) and diastolic blood pressure (less than 60 mmHg) relative to the previous visit, respectively. Patients were more likely to develop systolic hypertension (defined by sponsor as > 160 mmHg) than systolic hypotension (defined by sponsor as <100 mmHg) by the sponsor's prespecified standards (4% vs. 1%). Patients had low prevalence of either diastolic hypertension (defined by sponsor as >100 mmHg) or hypotension (defined by sponsor as <60 mmHg), (1% for both).

Waist circumference
There were no changes in mean waist circumference in both treatment groups.

7.4.5   Special Safety Studies/Clinical Trials

APPENDIX B: HOLTER Substudy for exploration of ventricular pauses

A thorough QT study (D5130C00037) was conducted. Ticagrelor was evaluated for effects on QTc interval at a single 900 mg oral dose, compared to placebo, using moxifloxacin as a positive control, in healthy volunteers age 18 to 45 years. The conclusion was reached that there was no cardiac ventricular repolarization effect with ticagrelor and no apparent ticagrelor plasma concentration-related increases in the QTc interval.

In phases 1 and 2, ventricular pauses and adverse events related to bradycardia were observed with ticagrelor, including in a few individual healthy volunteers.   Observations of cardiac arrhythmias from Phase I and II studies include the following examples:

- In a Phase I single ascending dose study (CSR D5130C00049), a healthy volunteer experienced 2 long periods of sinus and ventricular arrest (the longer of these 2episodes was approximately 11 seconds), high-grade AV block, and ventricular escape rhythm associated with syncope as well as nausea and vomiting following ingestion of a 1260 mg single dose of ticagrelor, a 14-fold multiple of the maintenance dose in PLATO.

- In the Phase I Thorough QT study (CSR D5130C00037), during prolonged telemetry, episodes of AV block were observed for 1 healthy volunteer. These were recorded 1 to 1.5 hours post dose, and again approximately 70 hours post dose. The ticagrelor dose given was 900 mg. The ECG changes included first-degree AV block and second-degree AV block with Wenckebach phenomenon, and episodes of 2 to 3 non-conducted P waves superimposed on more pronounced sinus bradycardia and sinus arrhythmia. No pauses >5 seconds occurred, and the QRS complexes were narrow. The volunteer was asymptomatic during these episodes.

- The Phase II study DISPERSE2 examined the safety and tolerability of ticagrelor for up to 12 weeks in patients who had non-ST elevation ACS events. In total, 990 patients were randomized into 3 groups: 1) ticagrelor 90 mg bd; 2) ticagrelor180 mg bd; or 3)

clopidogrel 75 mg od. In DISPERSE2 there was a dose-related association of ticagrelor treatment with an increased occurrence of ventricular pauses ≥2.5 seconds detected on Holter ECG recordings obtained during the first week after the index hospitalization. The incidence was 4.4% for clopidogrel, 5.6% for ticagrelor 90 mg bd, and 9.9% with ticagrelor 180 mg bd. Most of these pauses were asymptomatic and due to sinus node arrest or sinoatrial (SA) block, although a few were due to AV block. In the few cases associated with symptoms, no clear relationship existed between these symptoms and the time of administration of study therapy. A variety of potentially confounding clinical factors prevented a clear assessment of causality.

The sponsors decided to conduct a Holter substudy as part of PLATO to further elucidate the relationship between ticagrelor and ventricular pauses as well as other arrhythmias.

In this section, I will review the Holter substudy (D5130C05262) and observations during the main body of the PLATO trial related to cardiac arrhythmias and arrhythmia related symptoms.The primary variable of interest was the occurrence of ventricular pauses ≥3 seconds. Secondary variables included longer lengths of pauses, other bradycardic episodes, heart rate (HR), atrial (supraventricular) tachyarrhythmias, and ventricular arrhythmias.

Holter monitoring was initiated at or shortly after the administration of first dose of study drug and continued for up to 7 days following randomization. For those patients who had Holter monitoring during the initial hospitalization, repeat monitoring was performed during Visit 2 when possible. These were done on an outpatient basis with recordings of up to 7 days duration. The recording during Visit 1 was performed to capture pauses during the acute phase when patients are at the greatest risk of ischemia-related arrhythmias and because this was the same time frame when increased pauses were observed in DISPERSE2. After unblinding of the data, the sponsor decided not to analyze the Holters of patients who were not on treatment at Visit 2. This choice was appropriate because there were very few patients that fell into this category (3.8%) and because presence or lack of findings in this group of patients would tend to obfuscate rather than clarify differences between the two treatment groups. A much larger concern was that approximately 1/3 of the patients in each treatment group had no Visit 2 monitoring, for mostly "unknown" reason or premature discontinuation of study drug. Nevertheless, the results of the Visit 1 Holters were captured in these patients and were included in the study report. This was not an ideal choice, but since the data was available, there was no great cause for concern.

Holter recording during procedures (such as PCI) was left to the investigator's discretion, so some recordings may have continued during PCI while others may have been interrupted during the procedure. Therefore, no specific information was collected about arrhythmias that occurred during procedures. For patients with ventricular pauses ≥10 seconds that occurred less than 5 times during Holter monitoring, there was an additional review of data to ensure that those isolated episodes were not recording artefacts.

The Holter recordings were analyzed centrally using an automated arrhythmia detection program followed by cardiologist review at the ECG core laboratory. The following variables were detected:

- Heart rate (mean, minimum, maximum)
- Ventricular pauses including duration and mechanism (such as absence of ventricular electrical activity ≥3 seconds as a result of SA node pause, atrial fibrillation with slow ventricular response, supraventricular rhythm with high degree A-V block or other mechanism)
- Dropped beats
- Bradycardia defined by at least 4 consecutive beats at a rate ≤ 45 beats per minute
- Atrial fibrillation defined as an ECG finding of supraventricular tachyarrhythmia (SVT) characterized by irregular A-V conduction and absence of regular p waves
- Atrial flutter defined as an ECG finding of SVT characterized by a rapid atrial rhythm (≥ 220 bpm), slower ventricular response, and the presence of atrial flutter waves
- Other SVT
- Non-sustained ventricular tachycardia defined as an ECG finding of ventricular tachycardia lasting < 30 seconds
- Sustained ventricular tachycardia defined as an ECG finding of a ventricular tachycardia that lasts > 30 seconds
- Ventricular fibrillation defined as showing irregular and changing ventricular wave patterns of varying contours and amplitude without discernible QRS complexes

Determination of Sample Size

The target sample size of 2500 for the Holter recordings allowed for a 20% non-completion rate for the second recording so that at least 2000 paired recordings were obtained. With 2000 patients receiving Holter monitoring (1000 per treatment group) at both visits and an expected rate of ventricular pauses of about 5% in the clopidogrel group based on DISPERSE2, the 95% CI for an absolute 5% increase in the ticagrelor group was expected to be an absolute increase of 2.7% to 7.3%.During the study, the number of patients with Visit 1 Holter monitoring was increased by about 20% to ensure that there were enough patients that had paired readings during Visit 1and Visit 2 since the attrition rate between Visit 1 and Visit 2 was higher than expected. This was a reasonable approach.

Study Subjects/ Disposition
In total, 2908 patients were included in the Holter analysis set from 41 of the 43 countries that participated in PLATO.

Four hundred sixty-one of the 862 study centers in PLATO conducted Holter monitoring and had patients included in the Holter analysis set. Although it was intended that all patients at sites with monitoring equipment would have Holter monitoring starting at the beginning of the study, there were some patients not monitored for logistical reasons or as a result of their

medical condition. The sponsor stated that there was no deliberate selection of patients for inclusion. This method of patient selection was reasonable.

Demographics

In Table 29, one can see that the distribution of demographic characteristics was similar between the treatment groups. The maximum weight was higher in the clopidogrel group (175 kg vs. 163 kg) whereas the maximum BMI was higher in the Ticagrelor group (68 vs. 56). Because the means and medians were similar for weight and BMI, there is no cause for concern.

Most of the characteristics were similar in this substudy when compared to the characteristics of the PLATO full analysis set.

Table 29: Demographics for Holter Substudy

Characteristic	Statistic or Category	Ticagrelor 90 mg bd N = 1472	Clopidogrel 75 mg od N = 1436	Total N = 2908
Age (years)	N	1472	1436	2908
	Mean	63.1	63	63
	SD	11.49	11.34	11.41
	Median	64	63	63
	Min	26	25	25
	Max	97	91	97
Sex	Total	1472 (100%)	1436 (100%)	2908 (100%)
	Male	1085 (73.7%)	1052 (73.3%)	2137 (73.5%)
	Female	387 (26.3%)	384 (26.7%)	771 (26.5%)
Weight (kg)	N	1471	1435	2906
	Mean	81.4	80.6	81
	SD	16.63	16.74	16.69
	Median	80	80	80
	Min	41	40	40
	Max	163	175	175
BMI (kg/m2)	N	1468	1430	2898
	Mean	27.9	27.7	27.8
	SD	4.96	5	4.98
	Median	27.3	27.1	27.2
	Min	13	13	13
	Max	68	56	68
Smoking Status	Total	1472	1436	2908
	Non-smoker	514 (34.9%)	515 (35.9%)	1029 (35.4%)
	Ex-smoker	439 (29.8%)	405 (28.2%)	844 (29.0%)
	Habitual smoker	519 (35.3%)	516 (35.9%)	1035 (35.6%)

Source: Holter study report, p. 28, 29

There were numerically fewer patients with persistent ST segment elevation (29.4% of patients in the Holter analysis set) than in the PLATO full analysis set (37.6% total) for both treatment groups combined. This was probably because of the greater urgency of treatment of patients with STEMI and the desire to minimize additional steps prior to intervention.

There was similar use of the various concomitant medications that might affect SA and AV nodal function during Holter monitoring between the groups (Beta-blockers, antiarrhythmics, calcium channel blockers, amiodarone, digoxin, adenosine, dipyridamole and ivabradine, and CYP3A inhibitors).

Results

Exposure

The number of patients with at least 1 dose of study drug during the Visit 1 or Visit 2 Holter monitoring period was similar between treatment groups (1451 in the ticagrelor group and 1415 in the clopidogrel group for Visit 1 and for Visit 2 Holters there were 985 patients in the ticagrelor group and 1006 patients in the clopidogrel group). The high attrition rate between Visit 1 and 2 was not explained but it was similarly high in both groups (approximately 1/3). The reason that only 2/3 of the patients were evaluated in the main analysis is that the sponsor chose to analyze only paired readings.

Main Analysis

The findings as shown in Table 30, were that there was a higher frequency of ventricular pauses ≥ 3 seconds in the ticagrelor as compared to the clopidogrel group, mostly at Visit 1, which occurred during the acute phase of their coronary syndrome. There were more ventricular pauses for both treatment groups during Visit 1 compared to Visit 2, presumably because patients with acute coronary syndrome have a greater susceptibility to arrhythmias. Most pauses were SA node pauses. Although there were fewer overall ventricular pauses ≥ 5 seconds, the same pattern persisted. It is unfortunate that only approximately 2/3 of patients were captured in this analysis. However, this was enough to capture differences between the groups. The relative risk for having a ventricular pause ≥ 3 seconds when treated with ticagrelor compared to when treated with clopidogrel at Visit 1 was 1.743 (1.152 -2.637) but only 1.341 (0.704 – 2.554) at Visit 2.

For all patients who had Holters (including the 487 patients in the ticagrelor group and 430 patients in the clopidogrel group who had Visit 1 but not Visit 2 recordings), ticagrelor-treated patients had a higher risk of having a ventricular pause ≥ 3 seconds during Visit 1 than clopidogrel-treated patients (RR=1.61 [95% CI 1.14, 2.26]). This corroborative finding made the sponsor's choice to not include patients without paired Holters in the main analysis less objectionable.

Table 30: Arrhythmias at Visit 1 and Visit 2 for patients with paired readings

Characteristic	Statistic or Category	Visit 1		Visit 2	
		Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od
Total Patients	N	964	985	964	985
Duration of Holter Monitoring (Days)	Mean (SD)	6.1 (1.27)	6.0 (1.50)	6.0 (1.59)	5.9 (1.66)
Heart rate (bpm)	Mean (SD)	68.0 (10.52)	67.9 (10.09)	68.1 (10.21)	67.9 (10.22)
Patients with at least 1 bradyarrhythmia		571 (59.2%)	531 (53.9%)	556 (57.7%)	498 (50.6%)
Ventricular pauses ≥ 3 secs		58 (6.0%)	34 (3.5%)	21 (2.2%)	16 (1.6%)
AV node pause ≥3 secs		15 (1.6%)	11 (1.1%)	6 (0.6%)	7 (0.7%)
SA node pause ≥3 secs		43 (4.5%)	22 (2.2%)	17 (1.8%)	11 (1.1%)
Other pause ≥3 secs		4 (0.4%)	4 (0.4%)	0	0
Ventricular pauses ≥5 secs		20 (2.1%)	10 (1.0%)	8 (0.8%)	5 (0.5%)
AV node pause ≥5 secs		6 (0.6%)	5 (0.5%)	2 (0.2%)	1 (0.1%)
SA node pause ≥5 secs		15 (1.6%)	4 (0.4%)	7 (0.7%)	4 (0.4%)
Other pause ≥5 secs		0	2 (0.2%)	0	0
Dropped Beats		321 (33.3%)	298 (30.3%)	288 (29.9%)	262 (26.6%)
Bradycardia		400 (41.5%)	385 (39.1%)	401 (41.6%)	372 (37.8%)
Patients with at least 1 tachyarrhythmia		690 (71.6%)	687 (69.7%)	592 (61.4%)	614 (62.3%)
Supraventricular Tachyarrhythmia		571 (59.2%)	567 (57.6%)	517 (53.6%)	543 (55.1%)
Ventricular Tachyarrhythmia		361 (37.4%)	347 (35.2%)	207 (21.5%)	214 (21.7%)

Source: Holter study report p.37

Risk Factors for Developing Arrhythmias and Pauses

Apparent risk factors for developing ventricular pauses were higher mean weight and BMI if one was in the ticagrelor treatment group only, having a medical history of diabetes for both treatment groups and being on concomitant medications for both treatment groups.

Patients with ventricular pauses ≥3 seconds had a higher mean weight, especially in the ticagrelor group, compared to patients without pauses; the mean weight was 86.1 kg for patients with pauses compared to 81.1 kg for patients without pauses in the ticagrelor-treated group. This pattern was not evident in the clopidogrel-treated group. Mean BMI and BMI groups followed the same patterns in the ticagrelor group only.

Patients with ventricular pauses ≥3 seconds were also more likely to have diabetes in both treatment groups; in the ticagrelor group 28.1% of patients with vs. 23.2% of patients without pauses had diabetes and in the clopidogrel group. 33.9% of patients with pauses vs 25.7% of patients without pauses had diabetes. A numerically higher percentage of patients with ventricular pauses ≥3 seconds in the ticagrelor group compared to clopidogrel, were taking selected concomitant medications such as CYP3A moderate inhibitors, calcium channel blockers, and >1 medication known to predispose patients to arrhythmias. The absolute difference in the number of patients taking these medications was relatively small and unlikely to account for any differences in arrhythmic episodes between treatment groups. These patterns were also observed in patients with ventricular pauses ≥5 seconds.

Ventricular Pauses by Time of Day

There was a numerically higher occurrence of nocturnal pauses with ticagrelor compared to clopidogrel in patients that had 5 or more ventricular pauses of ≥ 3 seconds during Holter monitoring periods. Only 23 and 10 patients tell into this category in the ticagrelor-treatment group and clopidogrel-treatment group, respectively. See Figure 16. If there were fewer than 5 ventricular pauses during the Holter monitoring period, the pattern was not as pronounced. Most of the ventricular pauses were asymptomatic. Increased ventricular pauses at night may be attributable to increased vagal tone during sleep or possibly because of sleep apnea which causes hypoxia. Hypoxia was shown in another AstraZeneca study to increase ticagrelor-induced inhibition of adenosine reuptake in cardiomyocytes, leading to increased interstitial levels of adenosine. One might postulate that hypoxia might cause patients to have more ventricular pauses and therefore, ticagrelor might be best avoided in patients with sleep apnea and advanced COPD.

Figure 16: Patients with 5 or more non-agonal ventricular pauses ≥ 3 seconds by hour of the day
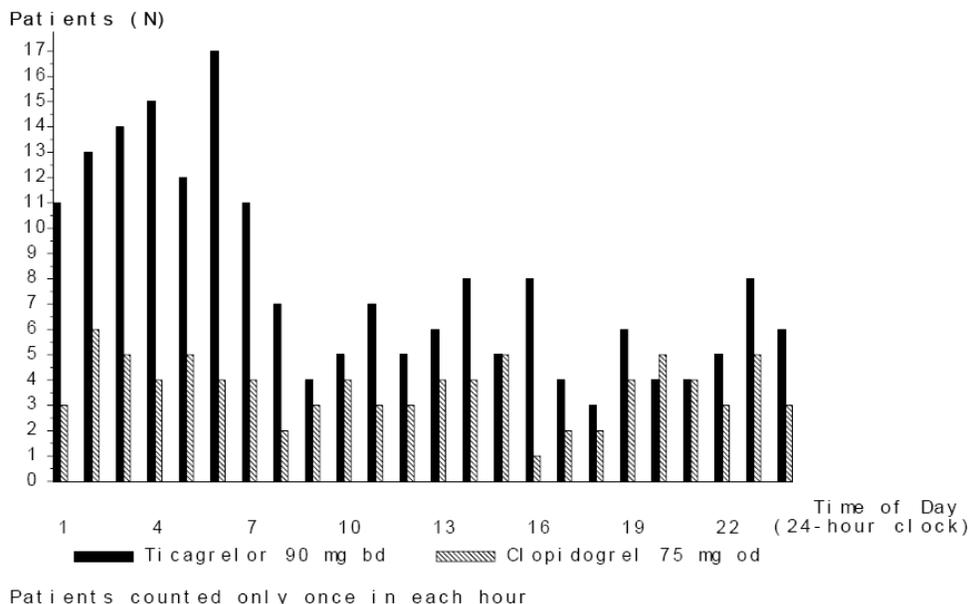
Source: Holter study report p. 46

Proposed Mechanism for Ventricular Pauses

The pathophysiological mechanism for the increase in ventricular pauses with ticagrelor is not known, but the sponsor's hypothesis is that ticagrelor-induced adenosine reuptake inhibition may be playing a role, especially in the setting of ACS, where there may be increased release of adenosine due to ischemia. Adenosine depresses sinoatrial node activity, AV nodal conduction, and ventricular automaticity, and attenuates cardiac stimulatory action of catecholamines and the release of norepinephrine from nerve terminals (Belardinelli andLerman 1991). The sponsor added that other mechanisms may also be involved in addition to an adenosine-mediated effect, e.g., increased vagal tone.

Tachyarrhythmias

Tacharrhythmias were more common during Visit 1 Holters compared to visit 2 Holters (70.7% vs. 61.9%). Additionally there were some numerical differences between the treatment groups that generally trended to worse results for patients treated with ticagrelor. For instance, for Visit 1 Holter, there were 37.4% vs. 35.2% of patients who had ventricular arrhythmias, for ticagrelor and clopidogrel respectively. There were 37.3% vs. 34.9% of patients treated with ticagrelor vs. clopidogrel, respectively, who had non-sustained ventricular tachycardia (NSVT) ≥ 4 seconds and < 30 seconds. There were 59.2% vs. 57.6% of patients treated with ticagrelor vs. clopidogrel, respectively, in Visit 1 Holter who had supraventricular tachyarrhythmia. Contrary to these results, fewer patients treated with ticagrelor had sustained ventricular

tachycardia in the Visit 1 Holter period (0.9% vs. 1.4%) but the numbers were extremely small (9 vs. 14).

Symptoms

As shown in Table 31, the sponsor found no glaring differences in the frequency of the PTs bradycardia, symptomatic or asymptomatic events between treatment groups when looking at the full safety data set. In my analysis of SAEs, there were no substantial differences between treatment groups for the SAE PT of bradycardia.

Table 31: Sponsor's Analysis: Bradycardia in PLATO Safety Analysis Set

Characteristic	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N=9186
Total patients with ≥1 event	435 (4.7%)	400 (4.4%)
Symptomatic event	172 (1.9%)	183 (2.0%)
Bradyarrhythmia	122 (1.3%)	97 (1.1%)
SA node dysfunctiona	33 (0.4%)	32 (0.3%)
AV block II and III	38 (0.4%)	29 (0.3%)
Vasovagal reaction	38 (0.4%)	36 (0.4%)
Other cardiac cause	48 (0.5%)	61 (0.7%)
Other known cause	141 (1.5%)	129 (1.4%)
Unknown/uncertain cause	80 (0.9%)	67 (0.7%)

Source: PLATO study report, p. 283

When looking at the small group of patients in the Holter substudy with pauses ≥ 3 seconds (89 in the ticagrelor group and 62 in the clopidogrel group), there was 1 case of syncope in each treatment group that occurred during the Holter period. Also during the Holter period, 1 patient in the ticagrelor group had dizziness while 2 patients in the clopidogrel group had dizziness.

During the full course of the Holter substudy, patients with pauses ≥ 3 seconds during the Holter period were more likely to experience the following symptoms if they were on ticagrelor: Dizziness, 6 patients on ticagrelor, and syncope (4 patients on ticagrelor:1 patient on clopidogrel). No patients with long pauses had loss of consciousness during the study.

Pacemaker insertion in patients with ventricular pauses ≥5 seconds was generally similar between treatment groups (3 patients [9.4%] in the ticagrelor group and 2 [10.0%] in the clopidogrel group), as were temporary and permanent pacemaker placement. Among all patients in the Holter analysis set, numerically fewer patients in the ticagrelor group had pacemaker placement compared to patients in the clopidogrel group.

Conclusions

This was a well designed study that demonstrated that ticagrelor causes more arrhythmias and pauses than clopidogrel. Since there were more cases of dizziness and syncope in the ticagrelor treatment group, ventricular pauses may be a real safety issue. Nevertheless, in view of the decreased prevalence of cardiac arrest in ticagrelor-treated patients, it is probably best to accept these increases in arrhythmia-related symptoms as part of an acceptable risk-benefit tradeoff.

One limitation of PLATO study is that patients with an increased risk of bradycardic events (eg, no pacemaker and known sick sinus syndrome, second or third degree AV block or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker) were excluded from the study so there is limited information of the effect of ticagrelor on patients with these conditions.

PULMONARY FUNCTION Substudy exploration of dyspnea

In PLATO, a pulmonary function substudy was designed to examine the effect of ticagrelor, 90 mg bd, in comparison to clopidogrel, 75 mg od on pulmonary function in a subset of ACS patients.

The purpose of this substudy was to determine the impact of chronic dosing with ticagrelor, lasting at least 6 months and up to 12 months, on pulmonary function in patients with ACS.

Primary Objective
The primary objective of this pulmonary function substudy was to evaluate the effects of ticagrelor in comparison with clopidogrel on forced expiratory volume in 1 second (FEV_1) after completion of study treatment.

Schema

Figure 17 shows the design of the substudy within the whole PLATO study and the sequence of measurement periods. Pulmonary function tests (PFT) were performed in conjunction with study visits for the PLATO study within the allowable visit windows.

Figure 17: Schema of Pulmonary Function Test Study

PFT (Pulmonary function test)

The following measurements were done in order of measurement:
1. Blood oxygen saturation (SpO_2) using pulse oximetry
2. Lung volumes: functional residual capacity (FRC); total lung capacity (TLC); and residual volume (RV) by plethysmography (mean of 3 values that had values within 5%)
3. Single-breath diffusion capacity for the lungs, measured using carbon monoxide ($DLCO_{SB}$).
4. The hemoglobin was measured within 10 days of the PFT. (average of 2 similar values)
5. Spirometry: forced expiratory volume in 1 second (FEV_1); forced vital capacity (FVC); mean forced expiratory flow between 25% and 75% of the FVC (FEF_{25-75}) before and 20 minutes after a short-acting β_2 agonist e.g. albuterol. (mean of at least 3 values that considered good studies and were free of artifact)

The sponsor's rationale for conducting the PFT studies at the prespecified intervals was because most dyspnea episodes began within the first 30 days of treatment. While this method may capture some patients while they were complaining of dyspnea, it would have been better, in order to increase capture of PFT abnormalities, to also conduct the PFTs at the time of dyspnea episode.

The sponsor eliminated tests that were way out of the norm for that patient and/or had artifactual data. While it is never good to eliminate data, in this case it is reasonable to decrease the erroneous effect that outliers would have on the results. The sponsor also averaged the remaining results as an imputed data point. A concern is that the effect of elimination of data and instead using an average the remaining values as a substitue may have obscured abnormalities and differences between the treatment groups.

Patient Selection

Patients were selected from a subset of centers in a subset of countries participating in the PLATO study (fifteen centers in 5 countries (Czech Republic, Hungary, India, Poland and US)

The sites were required to have access to a pulmonary function test laboratory and to an adequate pool of PLATO participants. These requirements could have introduced a selection bias. The sponsor stated that it was not possible for all sites to participate given "timing and logistical restraints." These constraints were not elaborated upon. All PLATO participants who were eligible at the selected sites were invited to join the substudy. to decrease further selection bias.

Inclusion criteria

1. Patients must have provided written informed consent for the substudy
2. Patients must have been able to perform all the necessary lung function tests

Exclusion criteria

The exclusion criteria were designed to provide a patient population in which PFTs could be used to identify meaningful changes in pulmonary function as a result of treatment with ticagrelor versus clopidogrel.

1. Patients who have discontinued study medication prior to the first Pulmonary Function assessment
2. Patients with advanced lung disease such as chronic obstructive pulmonary disease (to avoid confounding results)
3. Patients with symptomatic Heart Failure
4. Participants whose index event resulted in a coronary artery bypass graft (CABG)

These inclusion and exclusion criteria are reasonable in theory because confounding and excess "noise" will be limited. However, if a patient discontinued for any AE, particularly dyspnea, it would have been very informative to capture that patient's PFT data at time of dyspnea. In fact, the choice to not capture patients with AEs of dyspnea at the time of dyspnea may have obscured an effect of ticagrelor on PFTs.

Disposition

The pulmonary function substudy protocol specified that up to 450 patients would be enrolled in the pulmonary function substudy with the expectation that 250 would complete (125 in each treatment group). As displayed in Table 32, only 199 patients enrolled in the pulmonary function substudy. More than 80% (166 patients in total) completed Visit 102 and more than 70% (147 patients in total) completed Visit 103. Within each visit, the number of patients who remained in the substudy was somewhat better for the clopidogrel group. The difference was mostly accounted for by withdrawal of informed consent. The sponsor provided no information about why patients withdrew consent.

The sponsor stated that the reason for the low enrollment was that the substudy started enrollment late relative to the overall PLATO study. Clearly, this low enrollment would have the impact of obscuring any differences between the treatment groups if they existed.

Table 32: Disposition

Characteristic	Ticagrelor 90 mg bd N = 101	Clopidogrel 75 mg od N = 98
Patients who had Visit 101	101 (100%)	98 (100%)
Patients who had Visit 102	80 (79.2%)	86 (87.8%)
Patients missing Visit 102 (no substudy withdrawal)	4 (4.0%)	1 (1.0%)
Patients with substudy withdrawal after Visit 101 and prior to Visit 102	17 (16.8%)	11 (11.2%)
Adverse Event	2 (2.0%)	1 (1.0%)
Subject Withdrawal of Informed Consent	13 (12.9%)	9 (9.2%)
Safety Concerns	1 (1.0%)	1 (1.0%)
Severe noncompliance	1 (1.0%)	0
Patients who had Visit 103	71 (70.3%)	76 (77.6%)
Patients missing Visit 103 (no substudy withdrawal)	2 (2.0%)	1 (1.0%)
Patients with substudy withdrawal after Visit 102 and prior to Visit 103	12 (11.9%)	10 (10.2%)
Adverse Event	2 (2.0%)	0
Subject Withdrawal of Informed Consent	9 (8.9%)	10 (10.2%
Severe noncompliance	1 (1.0%)	0

Source: PFT substudy report

Demographics

The most significant demographic difference between the PFT Substudy patients and the patient enrolled in PLATO as a whole was the higher percentage of current or x-smokers (62% ticagrelor and 55% clopidogrel). The effect of increased numbers of patients with a history of smoking on the study cannot be known. It may have magnified or obscured a differences in PFTs between the treatment groups.

Results

The sponsor reported that there were no differences observed in any of the measured pulmonary function variables in ticagrelor-treated patients as compared with clopidogrel-treated patients at any time point of assessment. The sponsor also concluded that there was no evidence of changes in lung function over time in patients taking ticagrelor compared to

those taking clopidogrel. The statistical tests, however, were done using mean measurements which may have obscured differences.

There were a few limitations of the study that relate to the study design, execution and analysis.
1. No baseline values (would be hard to do).
2. Outlier data was eliminated and substituted with averages of other data during the study which could obscure differences.
3. High percentage of patients in both treatment groups with h/o current or past smoking (ticagrelor 62%, clopidogrel 55%) which could obscure differences because of preexisting PFT abnormalities
4. Fewer patients than expected enrolled in this substudy.
5. The exposure was 6 months only in most of these patients.
6. Few of the patients had dyspnea, especially unexplained dyspnea at enrollment.
7. PFTs were not done at time of dyspneic episodes
8. The smaller than expected sample size reduced the power for detecting differences between groups.
9. Using mean values reduced the power for detecting differences.

Conclusions

The numerous limitations of this study make it difficult to interpret its results. A higher powered study with more dyspneic patients would be necessary to convince this reviewer that ticagrelor has no effect on PFTs. Additionally, it would be important to have some idea of how patients in the midst of a dyspneic episode perform on their PFTs.

7.4.6 Immunogenicity

There was an increase in angioedema in the ticagrelor arm in the all AE data but this evened out when looking at angioedema SAEs. The numbers are small and there were no other disturbing signs for excessive immunogenicity for ticagrelor. In fact, the term "allergy and hypersensitivity" AEs and SAEs which includes the other categories listed in these tables favors ticagrelor. The AEs and the SAEs for immunologically mediated disorders are listed in a tabular form in Table 33 and in Table 33, respectively.

Table 33: Immunologically mediated AEs from PLATO dataset

AE Category	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N=9186	RR	CI
Anaphylaxis, Anaphylactoid reaction	8 (0.09%)	9 (0.1%)	0.88	(0.34, 2.29)
Allergy, Hypersensitivity	148 (1.6%)	158 (1.72%)	0.93	(0.75, 1.16)
Angioedema	14 (0.15%)	8 (0.09%)	1.74	(0.73, 4.15)
Laryngeal Edema	70 (0.76%)	67 (0.73%)	1.04	(0.74, 1.45)

Table 34: Immunologically mediated SAEs from PLATO dataset

SAE Category	ticagrelor 90 mg bd N= 9235	clopidogrel 75 mg bd N=9186	RR	95% CI
Anaphylaxis, Anaphylactoid reaction	3 (0.03%)	4 (0.04%)	0.75	(0.17, 3.33)
Allergy, Hypersensitivity	7 (0.08%)	18 (0.2%)	0.39	(0.16, 0.93)
Angioedema	3 (0.03%)	4 (0.04%)	0.75	(0.17, 3.33)
Laryngeal Edema	0 (0%)	2 (0.02%)	0	

7.5   Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Exposure-response relationships were established for major and for major + minor bleeding, however the response curve is very shallow.

7.5.2 Time Dependency for Adverse Events

For dyspnea, a time-dependent exposure-response relationship, which was most pronounced at the start of the treatment period, was identified. At visit 1, slightly over 5% of patients had dyspnea (mild to severe), which decreased to <5% at visit 2, > 3% by visit 3, approximately 3% by visit 4 and less than 2% by visit 6. Approximately 10% of patients that had dyspnea dropped out during the study for AEs. However, this would not account for the observed differences.

7.5.3 Drug-Demographic Interactions

The sponsor evaluated safety by different demographic features using data from PLATO. The following demographic categories were evaluated: age, gender, racial origin, BMI, baseline hepatic impairment, baseline renal impairment, or baseline diabetes (all intrinsic factors) and geographic distribution, smoking status, and concomitant medication use (extrinsic factor).

Age
The frequency of AEs, SAEs, and DAEs increased with age regardless of treatment group. The percentage of patients reporting AEs increased with increasing age in both treatment groups.

Gender
In PLATO, women on ticagrelor tended to have more AEs, including SAEs, DAEs and deaths than men. Only for overall adverse events during treatment was there a difference between the treatment groups. For overall AEs, women did not have more events than men when they were treated with clopidogrel. This observed difference is probably has no clinical significance.

Race
There were few patients that were not Caucasian. There were only 222 patients that were Black, 1081 that were "Oriental" (which does not include those of Indian and southwest Asian descent, only Chinese and Japanese) and 219 that were "Other". While there were some numerical differences among racial groups, the small patient counts make it more likely that these findings were the result of chance.

Of note, there was 40% greater exposure to ticagrelor in Japanese compared to Caucasians shown in an 8 day phase 1 study (for both Cmax and AUC). The maximum dose of ticagrelor was 300 mg bd. Despite these differences, the 36 healthy male Japanese volunteers that enrolled in this study generally tolerated ticagrelor well. No healthy volunteers died during their participation in this study or experienced an SAE. In PLATO, there were only 6 patients of Japanese descent (from Brazil) enrolled. Only two of these were in the ticagrelor treatment group. They were not in the Holter or PFT substudies. Neither of these two patients had a recorded AE.

Renal Insufficiency
As previously stated in section 7.3.5, renal deaths and adverse events, patients with preexisting renal disease with an eGFR of < 30 cc/min are at greater risk for death and major bleeding and do not appear to receive benefit from ticagrelor. Consideration should be given to contraindicating ticagrelor in this population.

Hepatic Impairment
Moderate to severe hepatic impairment were exclusion criteria for PLATO. However, 196 and 217 patients in the ticagrelor treatment group and the clopidogrel treatment group,

respectively, had mild hepatic impairment. From a phase 1 study (D5130C000016), Cmax and AUC of ticagrelor for patients with mild hepatic impairment were found to be12 and 35% higher than matched healthy subjects, respectively. While there were no differences in IPA and no significant difference in plasma binding protein, there was an increase in deaths (3.1% vs. 0.9%), SAEs (20.4% vs. 16.6%) and AEs (84.2% vs. 81.1%) for the ticagrelor-treated hepatically impaired patients compared to the clopidogrel-treated hepatically impaired patients. There were approximately 400 patients with hepatic impairment enrolled. This imbalance in deaths, SAEs and AEs is cause for concern. Ticagrelor should not be administered to patients with hepatic impairment.

Diabetes
Diabetes resulted in more deaths for both treatment groups. Also, there were more urinary tract infections in diabetics in both treatment groups. There were no concerning differences between treatment groups.

BMI
Interestingly there was a lower frequency of death in patients with BMI $\geq$ 30 for both treatment groups despite an increased risk for dyspnea. There were no concerning differences between treatment groups.

Smoking
An unexpected finding was that for both treatment groups the number of patients with DAEs and SAEs was lower among habitual smokers compared to those patients who were not habitual smokers. The number of deaths was lower in ticagrelor-treated habitual smokers (1.3%) compared to ticagrelor treated patients who were not habitual smokers (2.9%). Regardless of smoking habits, fewer ticagrelor-treated patients died, compared to clopidogrel-treated patients (habitual smokers [1.3% vs 2.6%, respectively]; not habitual smokers [2.9% vs 3.4%, respectively])

7.5.4   Drug-Disease Interactions

As discussed in section 7.3.5, patients with preexistent stage 4 and 5 renal insufficiency were more vulnerable to developing worsening renal insufficiency and more vulnerable to bleeding.

Patients with baseline hepatic dysfunction are at a higher risk for death, SAEs and AEs.

7.5.5   Drug-Drug Interactions

Coadministration of ticagrelor with CYP3A inducers results in increasing its clearance by 110%. Examples of CYP3A inducers are rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital. For this reason, ticagrelor may be less effective in patients on these medications.

Ticagrelor appears to be a weak activator of CYP3A5 which means that the bioavailability of drugs that are metabolized by CYP3A5 may be decreased when the drugs are coadministered. Examples of drugs metabolized by ticagrelor are midazolam, cyclosporine, nifedipine, testosterone, progesterone and androstenedione.

Ticagrelor is also a weak CYP3A4 inhibitor and causes decreased metabolism of simvastatin, atorvastatin, and estradiol. A study was done (D5130C00042) that evaluated the potential interaction between ticagrelor 90mg bd and Nordette®, a monophasic oral contraceptive (0.03 mg ethinyl estradiol plus 0.15 mg levonorgestrel) in 20 healthy female subjects of childbearing potential. Coadministration of ticagrelor and ethinyl estradiol/levonorgestrel resulted in increases in ethinyl estradiol exposure (30% in Cmax and 20% in AUC), but had no effect on levonorgestrel plasma levels. Low progesterone concentrations were seen throughout the luteal phase, suggesting that ovulation did not occur and that ticagrelor should not interfere with the effects of oral contraceptives.

Ticagrelor is also a weak inhibitor of P-gp, making it important to monitor digoxin levels in clinical practice.

Concomitant medications with an identified potential for interaction were simvastatin, atorvastatin, digoxin and diltiazem. Drug classes selected as they are commonly co-prescribed in ACS patients were statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), proton-pump inhibitors (PPI) and beta blockers. Ticagrelor-treated patients were divided into those who received the drug (or class of drug) for >20% of their time on ticagrelor treatment compared with those who received them ≤20% of their time on ticagrelor treatment (including those for whom the data are missing). Astra-Zeneca did an analysis where they looked at patients by whether or not they had been on these individual drugs by the prespecified criteria. According to the sponsor, none of these drugs when administered concomitantly with ticagrelor caused increased or decreased frequencies of any particular AEs by PT. By my analysis I saw numerical increases in relative risk for certain AEs in the ticagrelor arm for patients on CYP3A4 inhibitors at time of admission when compared to the patients not on CYP3A4 inhibitors at time of admission but the numbers were too small to draw any conclusions. Since there were so few patients on digoxin and diltiazem, the analysis may have made the chances of finding a difference between groups very small. Conversely, the same thing holds true for statins and beta blockers because most of the patients were on these medications during the study and so few did not take the medications. Additionally, when tested, there were no pharmacodynamic interactions between ticagrelor and heparin, enoxaparin, aspirin and desmopressin.

In vitro, ticagrelor and/or AR-C124910XX were shown to moderately inhibit CYP2C9 activities. In a clinical pharmacology study, however, concomitant administration of ticagrelor with tolbutamide, a representative CYP2C9 substrate did not affect the PK parameters of tolbutamide and its primary metabolite, 4-hydroxytolbutamide (Study D5130C00051), which suggest that ticagrelor is not a CYP2C9 inhibitor *in vivo* and unlikely to alter the metabolism of drugs such as warfarin and tolbutamide whose metabolism is mediated via CYP2C9

7.6.1   Human Carcinogenicity

The lifetime carcinogenicity study in rats with ticagrelor showed an increased incidence in uterine adenocarcinoma, a slight increase in hepatic adenomas, and one case of hepatocellular carcinoma. To provide perspective, the effected rats received 180 mg/kg/day of ticagrelor. Daily AUC exposures to ticagrelor in rats given 180 mg/kg/day are 29-fold higher than human AUC exposures following 90 mg bd and exposure to the main active metabolite AR-C124910 following exposure of 180 mg/kg/day are 24-fold higher than the clinical AUC exposures to the metabolite. No increases in tumor incidences were observed in the mouse carcinogenicity study where exposures to ticagrelor and the metabolite were comparable to those seen in rats. Toxicity studies up to a year in duration in marmosets have not shown any uterine proliferative changes.   Ticagrelor and the active metabolite ARC124910 are not mutagenic in the Ames test and mouse lymphoma assay, and ticagrelor was not active in the rat micronucleus test (the metabolite was not tested in the rat micronucleus test).

In PLATO, deaths due to cancer overall were similar between treatment groups, (ticagrelor 15, 0.2%; clopidogrel 17, 0.2%) regardless of the presence or absence of a neoplasm at baseline. The frequency of patients with solid malignant tumors was 72(0.78%) for ticagrelor and 79 (0.86%) for clopidogrel. When examining frequencies of specific types of malignancies separately (hematologic, lymphoma, gastrointestinal, ovarian, prostate, testicular, hepatobiliary, respiratory system, skin, breast or CNS neoplasms), I found no concerning differences between the treatment groups.

In PLATO, the overall occurrence and patterns of benign and non-benign neoplasms were similar in both treatment groups for the extent of patient follow-up. Patients with histories of non-benign neoplasms had numerically fewer cases of reported neoplasm at any time during follow-up [23 (5.7%) for ticagrelor and 31 (7.8%) for clopidogrel].

7.6.2 Human Reproduction and Pregnancy Data
Animal studies did not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition, or postnatal development. Ticagrelor had no effect on male or female fertility.

The safety of ticagrelor in Humans during pregnancy or lactation has not been established. Limited clinical data on exposure to ticagrelor during pregnancy are available and none on lactation.

Despite enrollment criteria to prevent fetal exposure to ticagrelor, there was 1 documented exposure during pregnancy. A 38-year-old woman became pregnant during the study. The pregnancy continued post-study period, at which time she delivered a healthy female full-term baby.

While it is not known whether ticagrelor is excreted in human milk, studies in rats have shown that ticagrelor and its active metabolite are excreted in mammary milk.

Ticagrelor should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the fetus.

The use of ticagrelor during breastfeeding is not recommended.

7.6.3 Pediatrics and Assessment of Effects on Growth

There were no pediatric patients enrolled.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

A total of 27 cases of overdose (16 in the ticagrelor group and 11 in the clopidogrel group) with study drug, defined as a patient who received more than the dose at once per the clinical study protocol, were reported to the AstraZeneca Patient Safety group. None of these overdose cases were reported with any apparent associated AEs. All except one of these overdoses were related to accidental medication errors.

In addition, there were 7 cases of overdose (5 in the ticagrelor group and 2 in the clopidogrel group) with concomitant medications during the study treatment period. There were 2 SAEs of overdose in patients in the ticagrelor group (one with chlordiazepoxide as an attempted suicide and one with a narcotic overdose with oxycodone) and none in the clopidogrel group. The 2 SAEs in the ticagrelor group were attempted suicide with chlordiazpoxide and narcotic overdose with oxycodone.

There is currently no known antidote to reverse the effects of ticagrelor, and it is likely because of its high level of protein binding that it is not dialyzable. The main concern with a ticagrelor overdose would be a bleeding event. The label should alert the physician and patients of this potential concern.

9 Appendices

Appendix A: <u>Deaths in N.A. in Ticagrelor group from day 119 – 180.</u>

E5490005: 56 y/o Caucasian man with h/o habitual alcohol and tobacco use presented to hospital on [REDACTED] (b) (6) with new-onset cardiac ischemic symptoms, including dyspnea and angina, and with persistent ST elevation ≥ 1 mm) ≥ 20 min on ECG, h/o carotid stenosis (≥ 50%), S/P h/o cerebrovascular revascularization 1997, family h/o coronary heart disease. Physical examination on admission was unremarkable with normal vital signs. Diagnosis: STEMI. Procedure during hospitalization: urgent percutaneous coronary revascularization with stent. Discharged from hospital [REDACTED] (b) (6) [REDACTED]. AEs during hospitalization: non-sustained ventricular tachycardia, vasospasm, headache. No bleeding was reported at Visit 2 on March 2, 2007, and at Visit 3, on May 17, 2007, Date of death was [REDACTED] (b) (6). Cause of death: myocardial infarction. Patient was **non-compliant with medication following discharge.**

Medications during hospitalization:
Nitrogylcerin, Maalox, Lidocaine, Donnatol, Lopressor, Morphine, Aspirin, Benadryl, Darvocet, Lipitor, Enalpril, Dilaudid, Protonix, Lisinopril, Heparin
Aggrastat

E1602058: 71 y/o Caucasian woman with prior h/o MI, presented on [REDACTED] (b) (6) with cardiac ischemic symptoms at rest ≥ 10 minutes, new bundle branch block and T wave inversion. Patient reported that she was a nonsmoker, had h/o chronic obstructive pulmonary disease (COPD) and experienced dyspnea at baseline. Diagnosis: NSTEMI. The patient had a coronary angiography on [REDACTED] (b) (6). Ejection fraction was 30 - 39%. EF was measured as 50% 9 days later. Treatment with ticagrelor was interrupted on [REDACTED] (b) (6) for a non-bleeding adverse event (COPD exacerbation which required hospitalization). Date restarted was [REDACTED] (b) (6). The patient also missed one dose of ticagrelor on June 20, 2008 and then refused to take it from June 21, 2008 until June 25, 2008. The patient's last visit was on July 3, 2008. According to the case report form, she was compliant with her medications after June 26, 2008. On [REDACTED] (b) (6), the patient died at home of cardio-pulmonary arrest (secondary to COPD according to the sponsor). Autopsy was not performed. This death was counted as non-vascular.

Concomitant medications: raberpazole, temazepam, advair, tylenol with codeine #3, atrovent, ventolin, lipitor, synthroid, Spireva, alendronate, altace, nitroglycerin, metoporolol, atacand, lasix, B12, gravol, milk of magnesia, solumedrol, avelox, pentaspan, amoxil, diamox, aspirin 81 mg, enoxaparin, .

E1601008: 76 y/o obese Caucasian man with h/o hypercholesterolemia, DM type II, peripheral artery disease and peripheral neuropathy, presented to the hospital on [REDACTED] (b) (6) [REDACTED] with ischemic symptoms and elevated cardiac enzymes. Diagnosis: NSTEMI.

He had a PCI with stent. One bare metal stent was placed. On his follow up visits the patient was reported to be compliant with his medication. On ░░░░░ (b) (6) the patient developed dyspnea and a respiratory infection. ░░░░░ (b) (6), the patient was in the ICU for 12 days for a malignant left pleural hemorrhagic effusion and a major bleed with dyspnea. On ░░░░░ (b) (6), the patient discontinued drug. On ░░░░░ (b) (6), the patient died.

E1621011: 72 y/o non-smoking Causasian woman with h/o hypertension and schizophrenia presented on ░░░░░ (b) (6) with cardiac ischemic symptoms and elevated cardiac enzymes. Diagnosis: NSTEMI. The investigational product was prematurely and permanently stopped on ░░░░░ (b) (6) after a non-urgent CABG of her left main and LAD which resulted in a peri-operative STEMI. No antiplatelet therapy was given post surgery in the hospital where she was operated. The patient was hospitalized on ░░░░░ (b) (6) for congestive heart failure. The patient died on ░░░░░ (b) (6), cause unknown.

E5250001: 59 y/o Caucasian man with h/o prior PCI, smoking and hypercholesterolemia presented on ░░░░░ (b) (6) with ischemic symptoms, persistent ST elevation ≥ 1 mm and elevated cardiac enzymes. Diagnosis: STEMI. On presentation he had diastolic hypertension (135/101 mmHg), obesity (137 kg), and rales and S3 heart sound. On coronary angiography, his EF was <30%. He had a drug eluting stent placed. The patient was compliant with treatment. The patient died of sudden death on ░░░░░ (b) (6), presumably of a vascular event.

Appendix B: Hy's Laws Cases

One was a 67-year old man who was diagnosed with STEMI and who had no known history of liver disease had liver enzymes on day 1 of the study that were abnormal [(ALT 68 IU/L, AST 182 IU/L, ALP 42 IU/L, total bilirubin 2.7 mg/dL], drawn 20 minutes after administration of investigational product (ticagrelor). These values were consistent with the enzymatic laboratory criteria of Hy's Law at Visit 1 only, and normal the remainder of the study duration (392 days) while on study medication. It is likely that this elevation in liver enzymes was not related to ticagrelor because of the normal follow-up laboratory values and the short interval between drug administration and enzyme elevation.

One was a 67 year old woman who was diagnosed with unstable angina pectoris without ECG changes, but with elevated CK-MB. She developed elevated liver enzymes (ALT 770 IU/L, AST 800 IU/L, ALP 185 IU/L, Total bilirubin 2.7 mg/dL) 10 minutes after administration of ticagrelor. The enzymes were normal with the exception of one abnormal ALT value (177) 96 days later, for the remainder of the study. It is also likely in this case that the elevation in liver enzymes was not related to ticagrelor because of the normal follow-up laboratory values and the short interval between drug administration and enzyme elevation.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

MELANIE J BLANK
06/28/2010