CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s000

OFFICE DIRECTOR MEMO

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	July 20, 2011
Proprietary Name / Established (USAN) Name	Brilinta™/ticagrelor
Dosage Forms / Strength	90 mg Tablets
Approved Indication(s)	This new drug application provides for the use of Brilinta (ticagrelor) 90 mg tablets to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis. (1) BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily.
Action:	Approval

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	Manizheh Siahopoushan, PharmD
OSE/DRISK	Cyntha LaCivita, PharmD
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 large outcome trial intended to support approval: PLATO, a comparison of ticagrelor and clopidogrel in patients with acute coronary syndrome (ACS). There are no outstanding chemistry, toxicology, or clinical pharmacologic issues. Like all platelet inhibitors, ticagrelor causes bleeding, which can be serious; major non-CABG bleeds were slightly more common on ticagrelor. Intracranial bleeds were infrequent but more common on ticagrelor and more likely to be fatal (11 vs 1), but overall fatal bleeding rates were similar on both drugs. The main issue, raised by the finding of a marked difference in results by region, and 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, which overall showed clear superiority to clopidogrel, provided evidence that ticagrelor is effective in the population for which it is intended, people living in the United States, and the extent to which regional differences in the dose of aspirin used explain the observed regional difference in outcome.

Ticagrelor is an oral ADP receptor antagonist (P2Y12 receptor). Unlike the approved P2Y12 antagonists, clopidogrel, prasugrel, and ticlopidine, the binding and effect on platelets of ticagrelor is reversible, a potentially valuable property for patients who need surgery (ADP receptor antagonists can cause serious bleeding in surgical patients), although it actually reduces the needed delay for surgery 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 once daily dosing for clopidogrel and prasugrel. At the dose studied it provides greater inhibition of ADP stimulated platelet aggregation than clopidogrel (over 80% compared to an 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 poor metabolizers and it can be blocked by 2C19 inhibitors, such as omeprazole.

The effectiveness of ticagrelor was demonstrated by the PLATO study, which compared ticagrelor with clopidogrel. It was intended to show greater effectiveness of ticagrelor on the endpoint of major adverse cardiovascular events (MACE): cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

II. Overall Study Results - PLATO

PLATO was a large double-blind randomized multi-regional trial comparing the effects of clopidogrel (300 mg loading plus 75 mg daily thereafter) with ticagrelor (180 mg loading dose plus 90 mg bid) in a broad population of people with acute coronary syndrome [including ST-segment elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA).; Final determinations of diagnosis were made during the study, so the diagnoses were not known at randomization and could not be used for stratification] on the rate of Major Adverse Cardiovascular Events (MACE). Plans for patient management (invasive, medical), were elicited at the time of randomization but were not used for stratification, although they could have been.

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 treatment with a thienopyridine in ACS (at least if CABG is not planned). Enrollment of patients with ACS already receiving clopidogrel and allowing early use of clopidogrel would also have the potential to remove some of the potential advantage of the more rapid

anti-platelet effect of ticagrelor, an advantage that would probably be more apparent in a clinical trial setting than under usual (real world) conditions of use.

Aspirin was a required concomitant treatment unless contraindicated, with dose chosen by the investigator; 75-100 mg was recommended as the maintenance dose after a larger loading dose (160-500 mg, but 325 mg preferred), and 325 mg post-stenting was allowed.

It is apparent that there are many potential subgroups of interest, apart from demographic, concomitant illness, and concomitant therapy. To name a few:

- Final diagnoses (STEMI, NSTEMI, UA)
- Planned invasive vs medical management
- Pre-randomization use of clopidogrel or not
- Early vs late PCI
- Region
- Aspirin dose

Study endpoints were assessed by an Independent Central Adjudication Committee and their endpoint assessments were the planned study endpoints. Investigators also provided assessments of endpoints and Dr. Marciniak has carried out analyses of these, noting that they were numerically different from the adjudicated endpoints 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. Dr. Stockbridge has addressed this issue, and I agree with his conclusions. I note also that these differences would not affect the striking effect on overall mortality

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 MI (20.5%), PCI (13%), CABG (6%); hypertension (65-66%) and diabetes (25%); and use of concomitant medications, including ACEIs (30.5%), statins (35.5%), beta-blockers (36.5%) PPIs (14%). The population was predominately male (71.5%) and Caucasian (92%).

PLATO results are shown in the following table:

	Ticagrelor n = 9333	Clopidogrel n = 9291	HR	P-value
Primary Composite of CV death, NFMI, NF Stroke	864 (9.3%)	1014 (10.9%)	0.84 (0.77, 0.92)	0.0003
	499 (5.3%)	589 (6.3%)	0.84	
Components of primary endpoint:	249 (2.7%)	332 (3.6%)	0.74	
NFMI (not silent)	116 (1.2%)	93 (1.0%)	1.24	
CV Death				
NF Stroke				

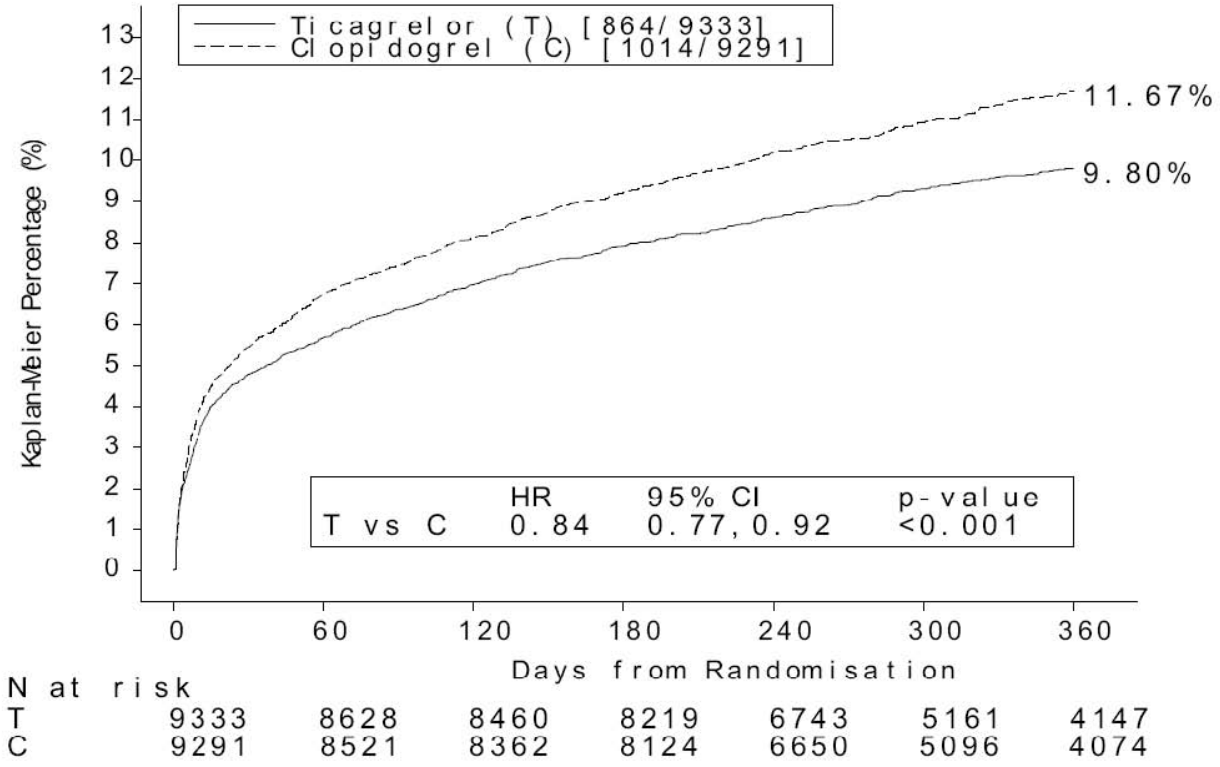
[K-M estimates shown in labeling are slightly different from the rates shown above but show essentially the same effect.]

The components of the primary endpoint were analyzed sequentially (see following table) as secondary endpoints, with significant effects shown on CV death and NFMI, but not NF stroke. Technically, failure on the stroke endpoint would terminate the sequential analysis, but the overall survival effect, significant

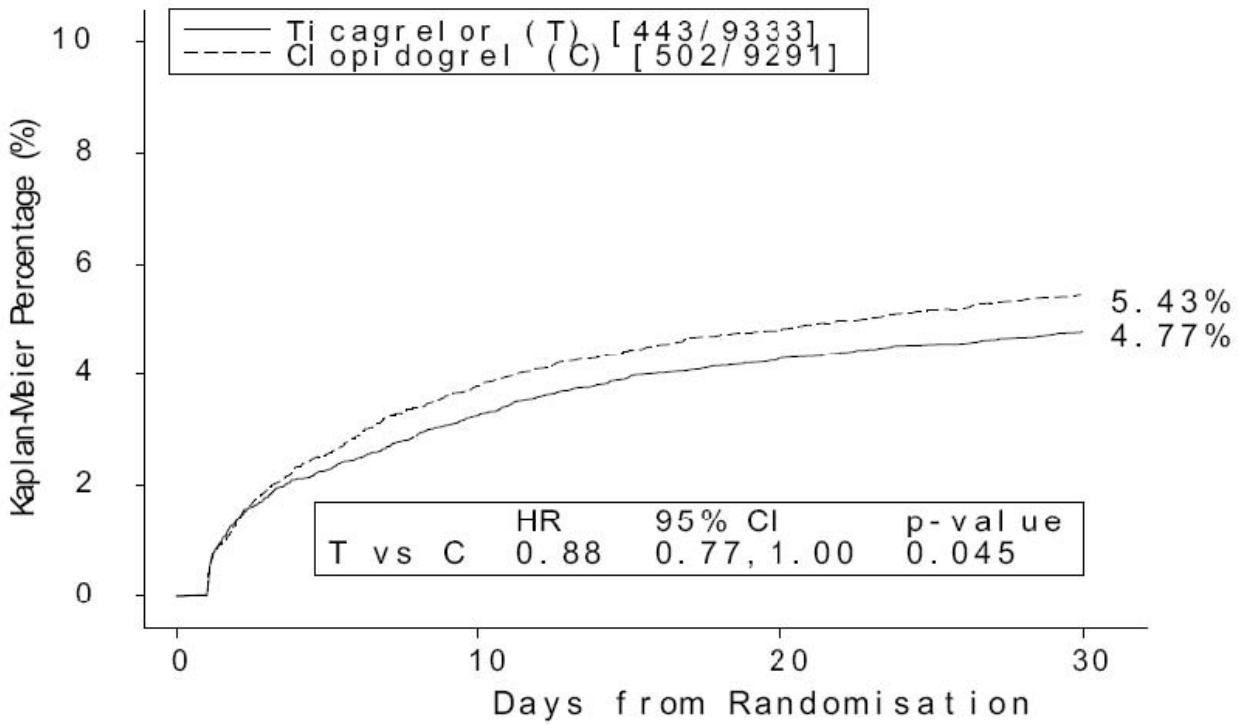
at p=0.0003, is hard to ignore. That effect, of course, is driven predominately by the effect on CV death (about 85% of the deaths).

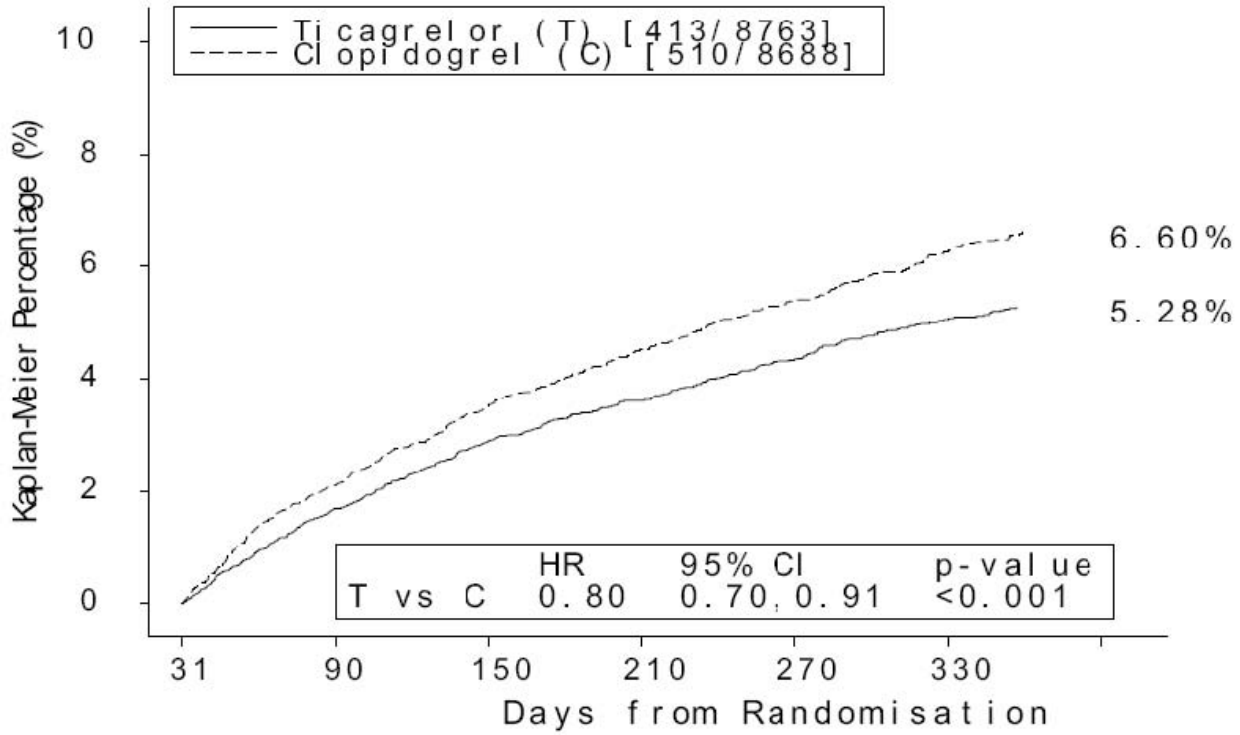
	Ticagrelor n = 9333	Clopidogrel n = 9291	HR	P-value
NFMI	504 (5.4%)	593 (6.4%)	0.84 (0.75, 0.95)	0.0045
CV Death	353 (3.8%)	442 (4.8%)	0.79 (0.69, 0.91)	0.0013
Stroke	125 (1.3%)	106 (1.1%)	1.17 (0.91, 1.52)	0.22
Overall mortality	399 (4.5%)	506 (5.4%)	0.78	0.0003

The K-M curve for the primary composite endpoint 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. The CV death curve shows a similar pattern. It has become common practice to compare early and later results. The 0-30 and 31-360 day curves and the landmark table following the curves, show a modest early advantage and a growing benefit over time.

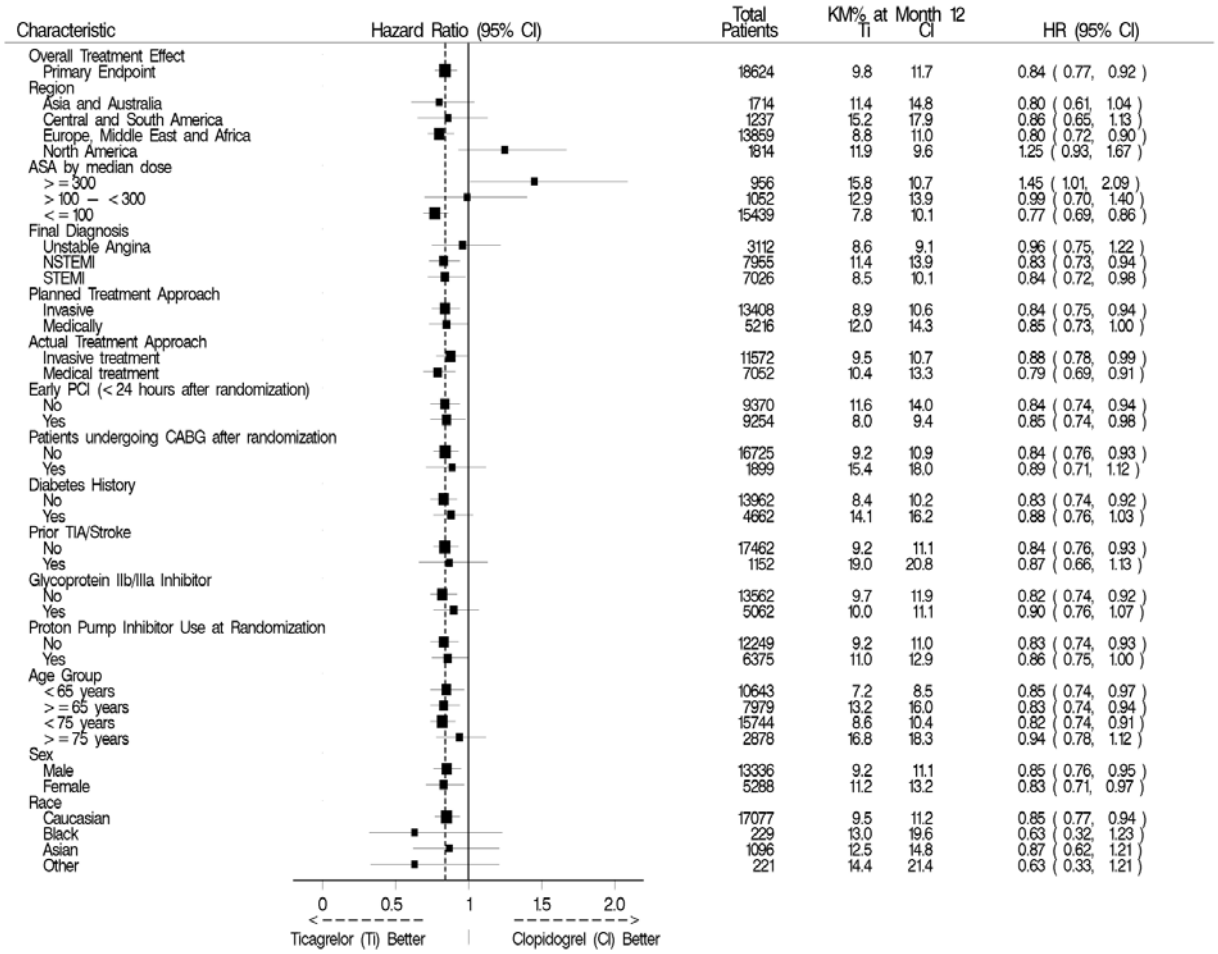

Ticagrelor (T) [443/9333]
Clopidogrel (C) [502/9291]
Kaplan-Meier Percentage (%)
0
2
4
6
8
10
5.43%
4.77%
HR 95% CI p-value
T vs C 0.88 0.77, 1.00 0.045
0
10
20
30
Days from Randomisation


Ticagrelor (T) [413/8763]
Clopidogrel (C) [510/8688]
Kaplan-Meier Percentage (%)
0
2
4
6
8
10
6.60%
5.28%
HR 95% CI p-value
T vs C 0.80 0.70, 0.91 <0.001
31
90
150
210
270
330
Days from Randomisation

Landmark Analysis

Ticagrelor			Clopidogrel			
Primary Endpoint	n	events	n	events	HR	P-value
1-30 days	9333	443 (4.7%)	9291	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 large number of subsets, most based on baseline characteristics, 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. Some of the subsets that are not actually baseline, but were determined during the study (generally very early), include final diagnosis (important because effect appeared smaller in the unstable angina group), actual management (as opposed to planned management), aspirin maintenance dose, and use of PCI early or ever. The following figure shows hazard ratios and KM rates for MACE for many subgroups. [Figure is taken from approved labeling].



The forest plots show great consistency, with two major exceptions, a distinctly poorer result in North America (mainly US, some Canada), and in patients receiving a high dose of aspirin (> 300 mg). A few other differences were also apparent (smaller effect in patients with a diagnosis of unstable angina).

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 provided in publications and the growing number of forest plots in approved labeling demonstrate.

A. Index ACS event

The effect of ticagrelor seemed to be greater in the STEMI/NSTEMI patients than in the UA patients. (Note, of course, that in PLATO, ticagrelor is compared with an active drug; although we do not have a non-inferiority analysis for unstable angina, the lack of an advantage cannot be taken as evidence of no effect). The table shows overall event rates, not K-M calculations.

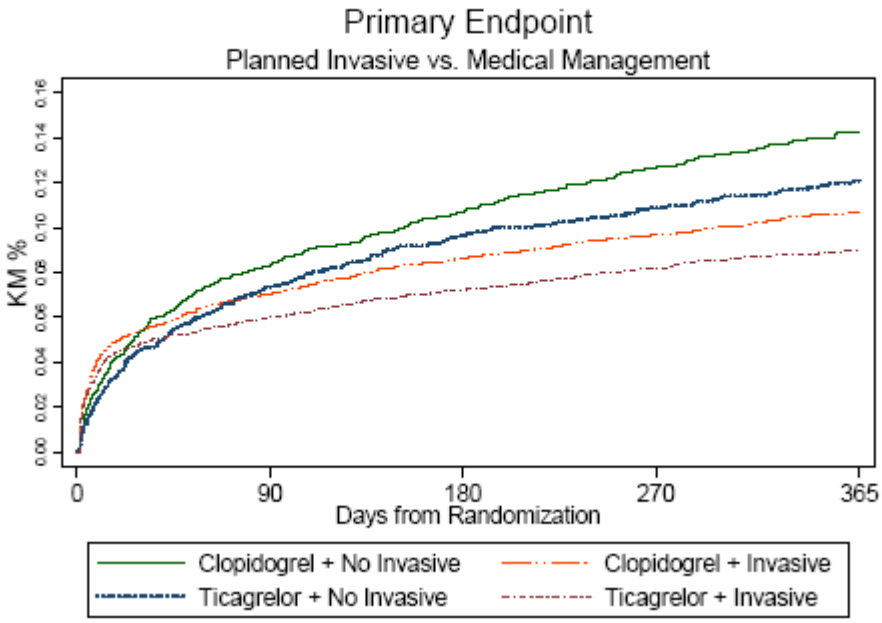
		Ticagrelor	Clopidogrel	HR
	N	Events (%)	Events (%)	
STEMI	7026	281/3496 (8.0%)	337/3530 (9.51%)	0.84 (0.72, 0.98)
NSTEMI	7955	432/4005 (10.8%)	510/3950 (12.9%)	0.83 (0.73, 0.94)
UA	3112	124/1549 (8.0%)	132/1563 (8.4%)	0.96 (0.75, 1.22)

B. Planned Invasive Management

	N	Ticagrelor	Clopidogrel	HR
Invasive 13,408	13,408	569/6732 (8.5%)	668/6676 (10.0%)	0.84 (0.75, 0.94)
Medical 5216	5,216	295/2601 (11.3%)	346/2615 (13.2%)	0.85 (0.73, 1.00)

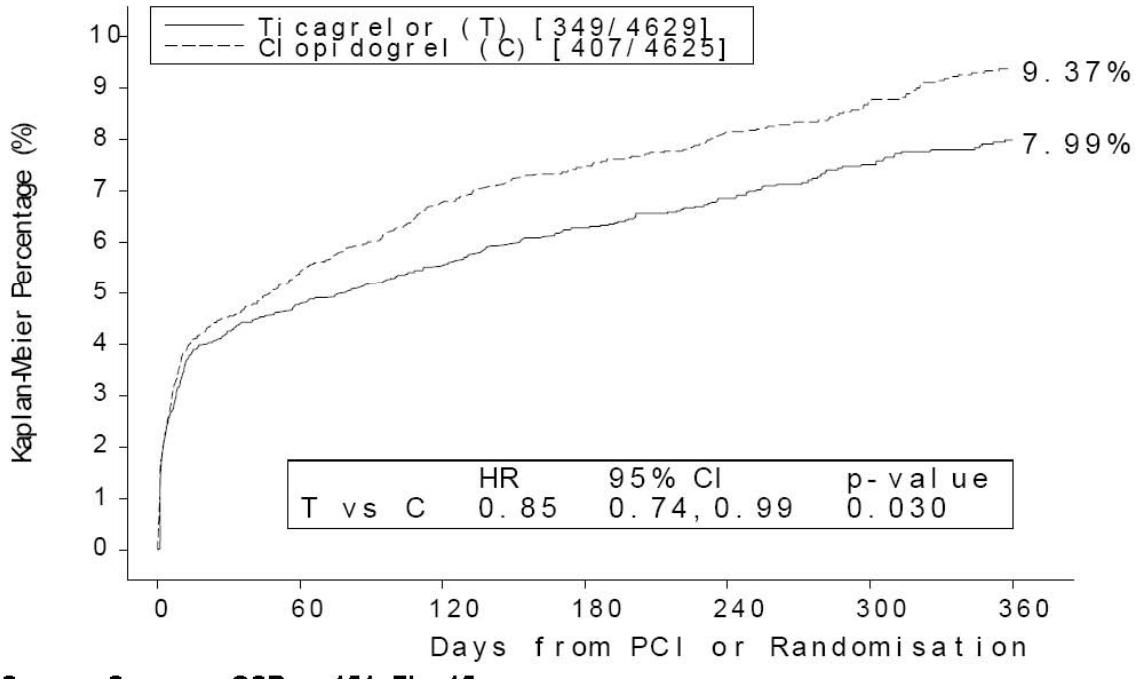
Although overall results were similar, it appeared that much of the late advantage of ticagrelor was in the medically managed patients. (fig 8)

Figure 8. KM Curve: Planned Invasive vs. Medical Management



Results were similar in patients who actually had early PCI within 24 hours of randomization.

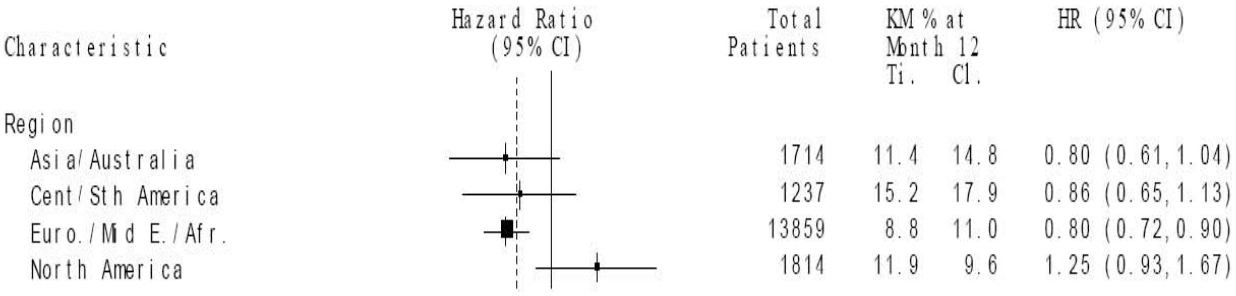
Figure 9. Kaplan-Meier plot of primary clinical endpoint events for patients intended to have invasive management who received PCI within 24 hours



C. Regional Differences

As has been apparent from the beginning of the review, the principal issue with PLATO is the regional difference, i.e., a distinctly poorer result in North America than in the rest of the world (OUS) and the United States (US) in particular, an obvious concern for a drug intended for use in the US population, and the related issue of whether the difference is explained by differences in aspirin use in US and OUS settings. Regional results for the primary endpoint are shown in the following figure and US/OUS results are shown in the table.

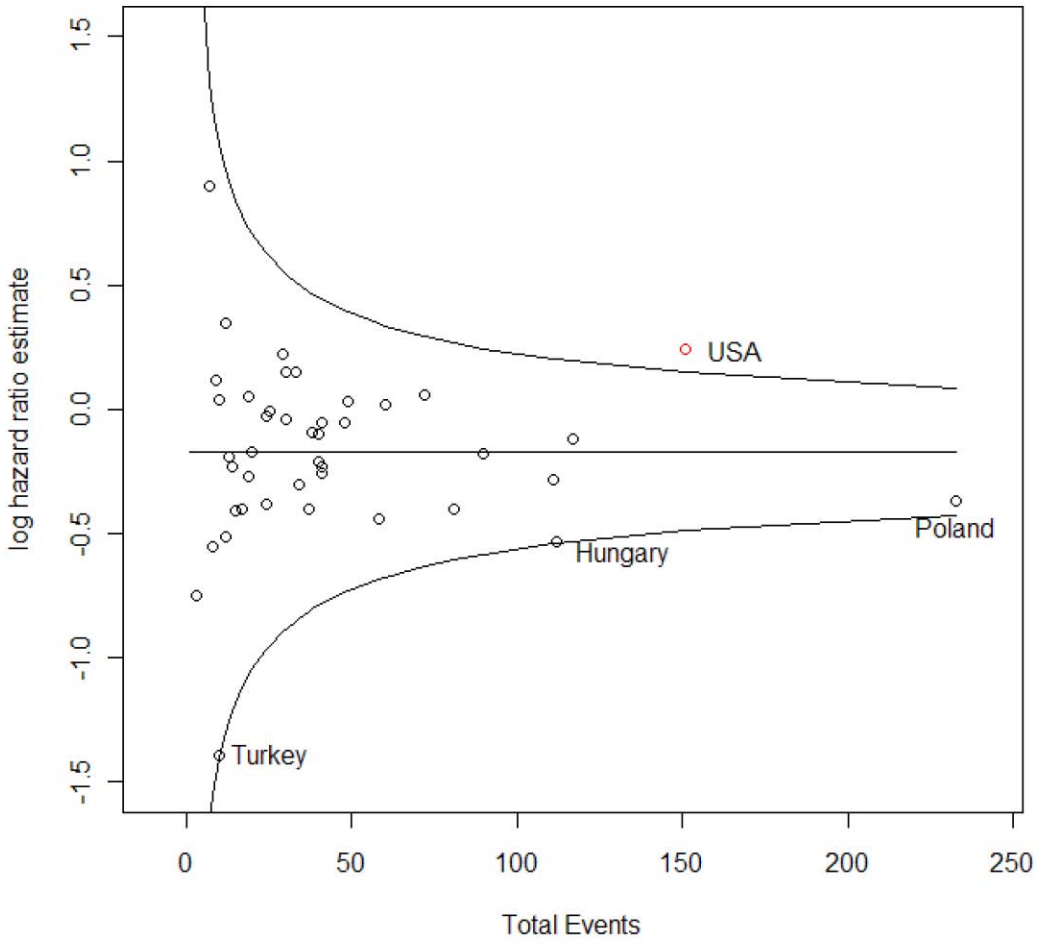
Figure 20 Forest Plot: Results by Region (K-M)



	Ticagrelor	Clopidogrel	HR	P
Overall n = 18,624	864/9333 (9.8%)	1014/9291 (11.7%)	0.84 (0.77, 0.93)	< 0.0003
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

Country by country results are shown in a funnel plot

Figure 6 Funnel Plot



Only the US result is actually outside the approximate 95% confidence interval boundary, although Hungary, Poland and Turkey are close (but in a favorable direction). 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," which is not nominally statistically significant, probably should not be over-interpreted. What is clear, however, is that there is strong evidence of heterogeneity of the results, with an overall region-treatment heterogeneity (p = 0.045) and, more pertinently, a US/non-US heterogeneity of about p = 0.009. It is also noteworthy that the poor result in the US was present for both NFMI and CV

death, shown in the following table, which would be surprising if the US/OUS difference were random. Again, of course, the numbers of events are small.

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

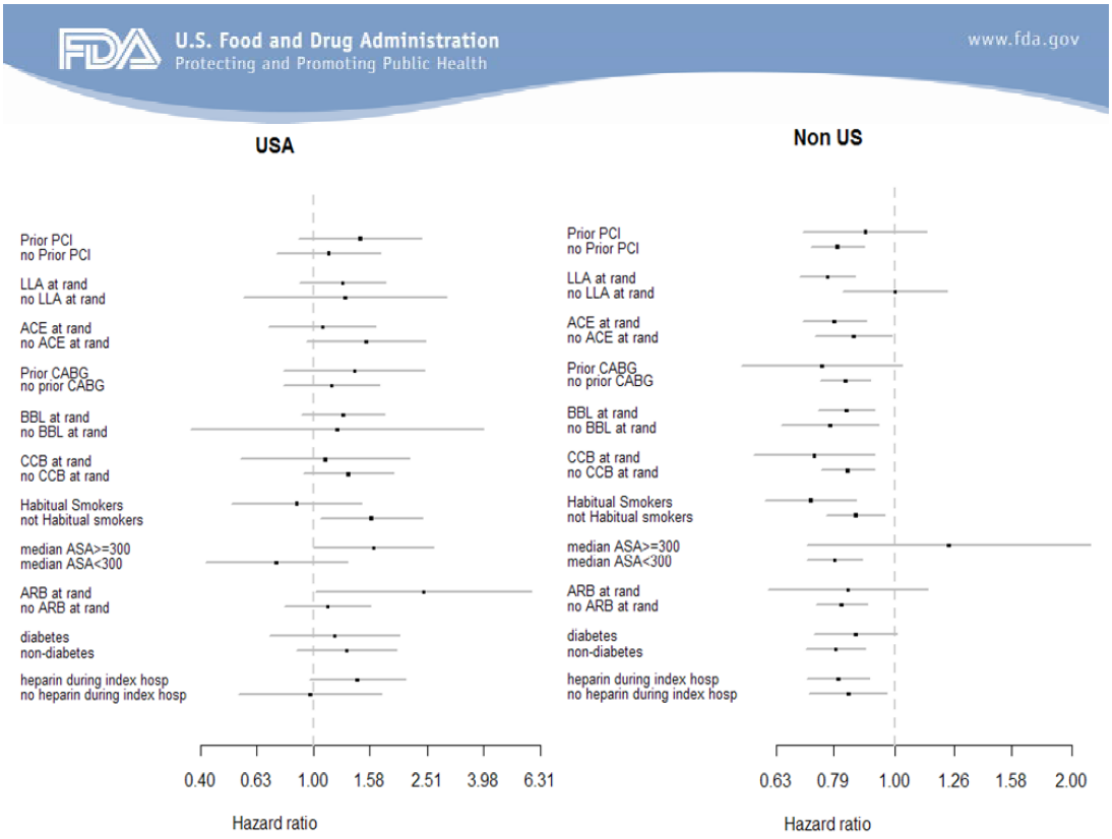
The OUS/US difference has been the subject of intense scrutiny. There have been found to be many baseline differences between the US and OUS population [(greater weight in US; different distribution of index events (67.3% NSTEMI in US vs 40.8% OUS and 15.7% STEMI in US vs 39.6% OUS, and UA 10.1% in US vs 17.3 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 (most from Dr. Zhang's 6/29/10 review, which included dozens of such covariates in her table 6 and continuous variables in her table 7. I have shown below only those with reasonably large regional differences. Her 8/31/10 review examined potential interactions between aspirin dose and other factors. In general aspirin dose was not very different in these various subgroups, although early PCI patients received somewhat higher doses on average.

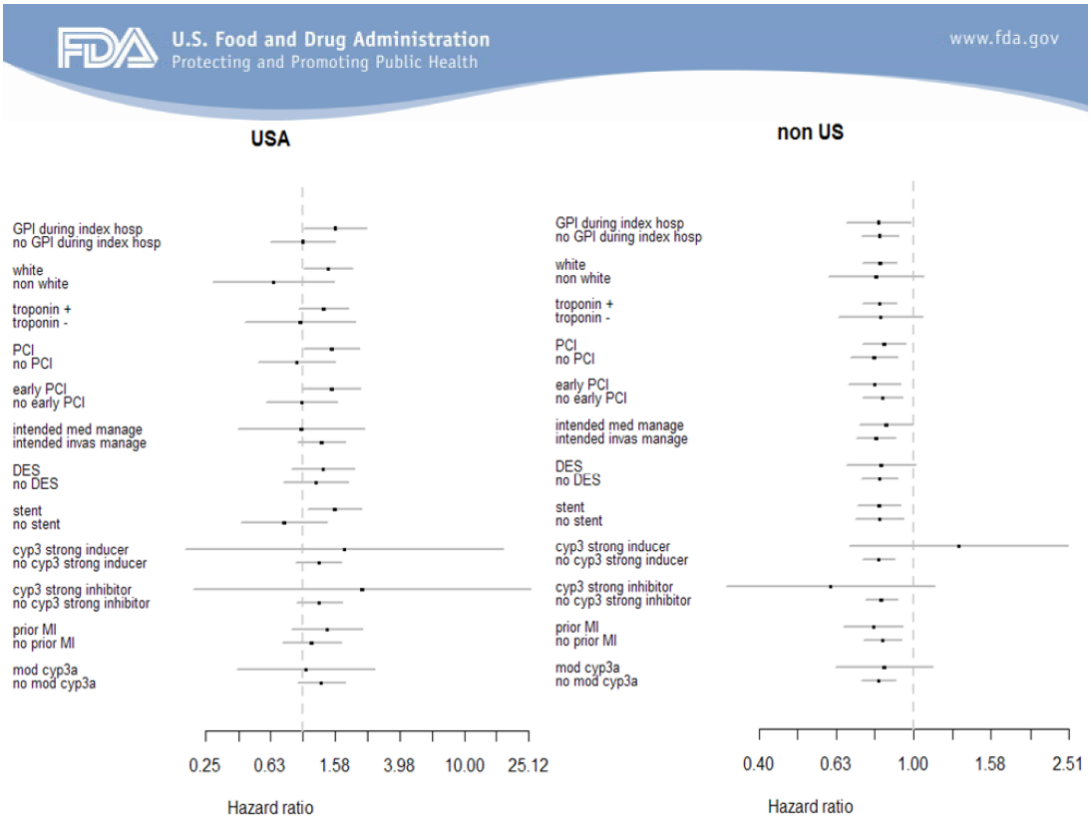
Measure	US n = 1413	OUS n = 17,211
> 12 hr from index event to first dose	63%	46%
Prior MI	27%	20%
Prior PCI	29%	12%
Prior CABG	17%	5%
Intended invasive	94%	70%
Early PCI (< 24 hr)	61%	49%
Diagnosis of Event		
STEMI	16%	40%
NSTEMI	67%	41%
Unstable Angina	10%	17%
Other	7%	2%
Bare Metal Stent	23%	46%
Drug Eluting Stent (DES)	46%	19%
GP IIb/IIIa use	50%	25%
Beta blocker day 1	87%	75%
ASA dose (median) median	325	100
Mean	217	99
Median ASA > 300 mg	44%	1.4%

There are thus clear differences between the US and OUS populations, but both populations had substantial representation of patients with all variables (excepting ASA > 300 mg, which was rare OUS), so that these differences can be examined for their effect on outcome.

The effects on outcome of a wide range of factors in both the US and OUS populations are shown in the following figures from Dr. Zhang's 6/29/10 review.

The only factor that on its face seems to have a consistent (i.e., in US and OUS) important treatment effect (considering factors with relatively narrow CI's), so that a difference in prevalence of the factor might yield an apparent regional difference, is median aspirin dose, where higher doses lead to HR > 1, i.e., favoring clopidogrel, and low doses to HR < 1, i.e., favoring ticagrelor.

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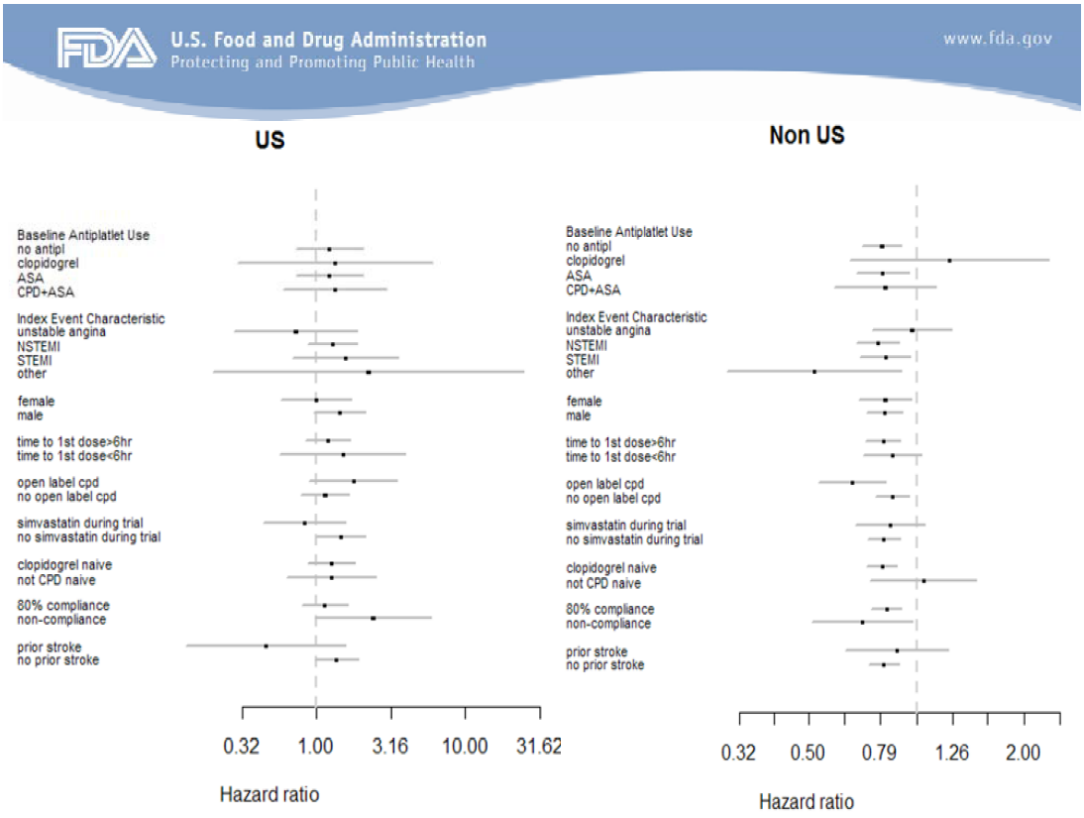
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time to 1st dose<6hr
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no open label cpd
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no simvastatin during trial
clopidogrel naive
not CPD naive
80% compliance
non-compliance
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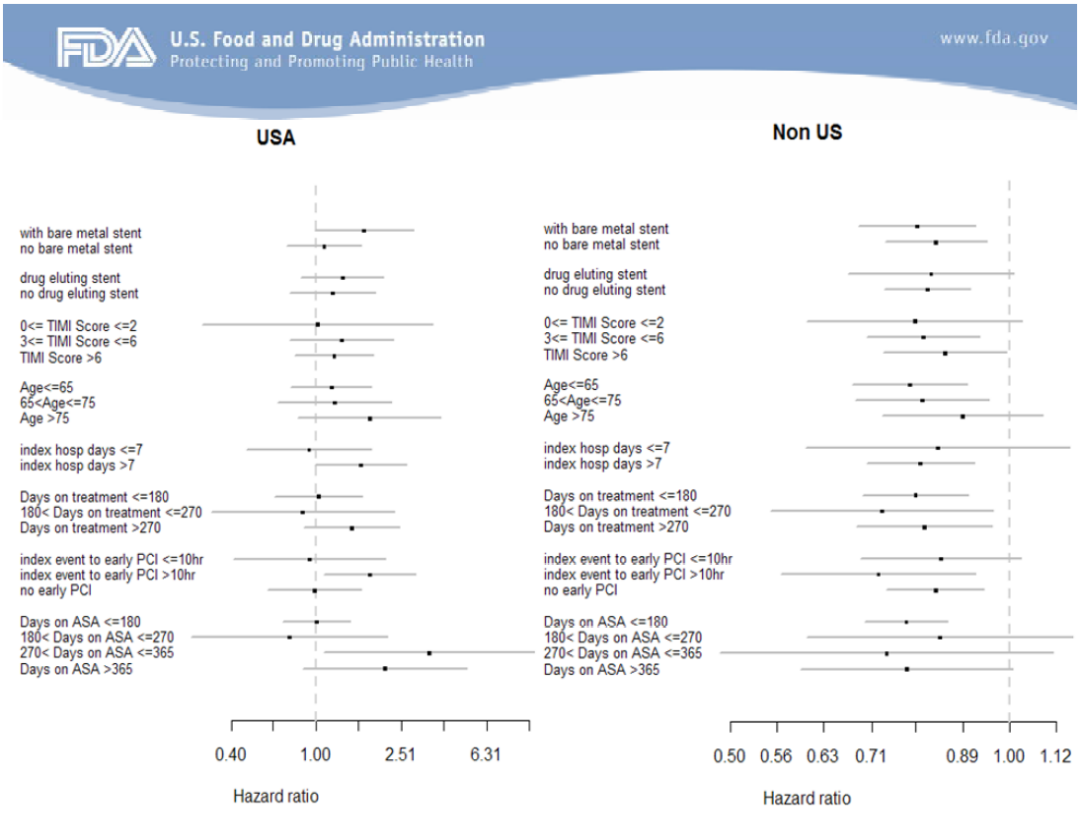
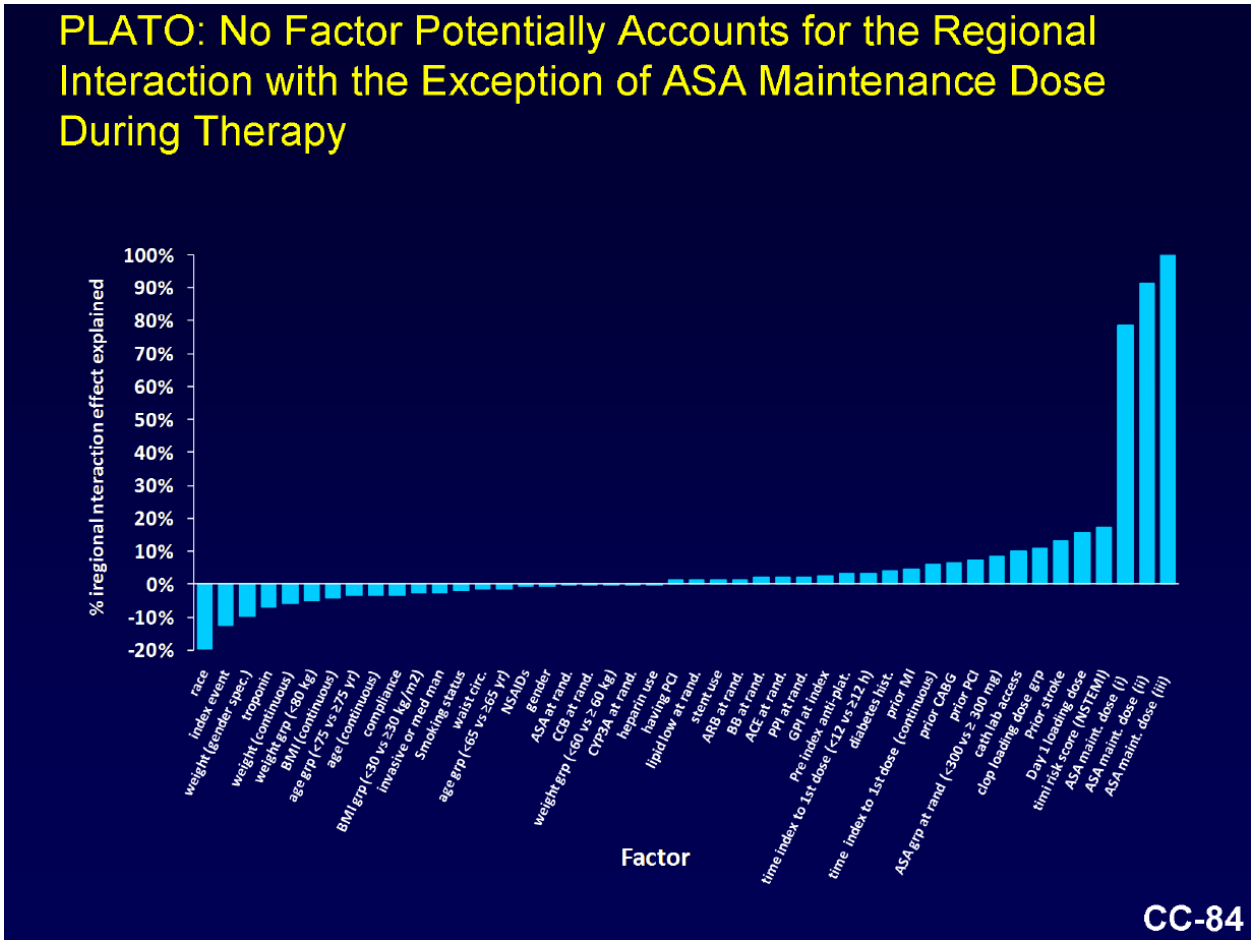
Hazard ratio



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 lack of effect of these covariates on outcome is a figure presented by the sponsor relating many variables to the extent to which they explain the regional interaction. Only aspirin dose seems to do so.

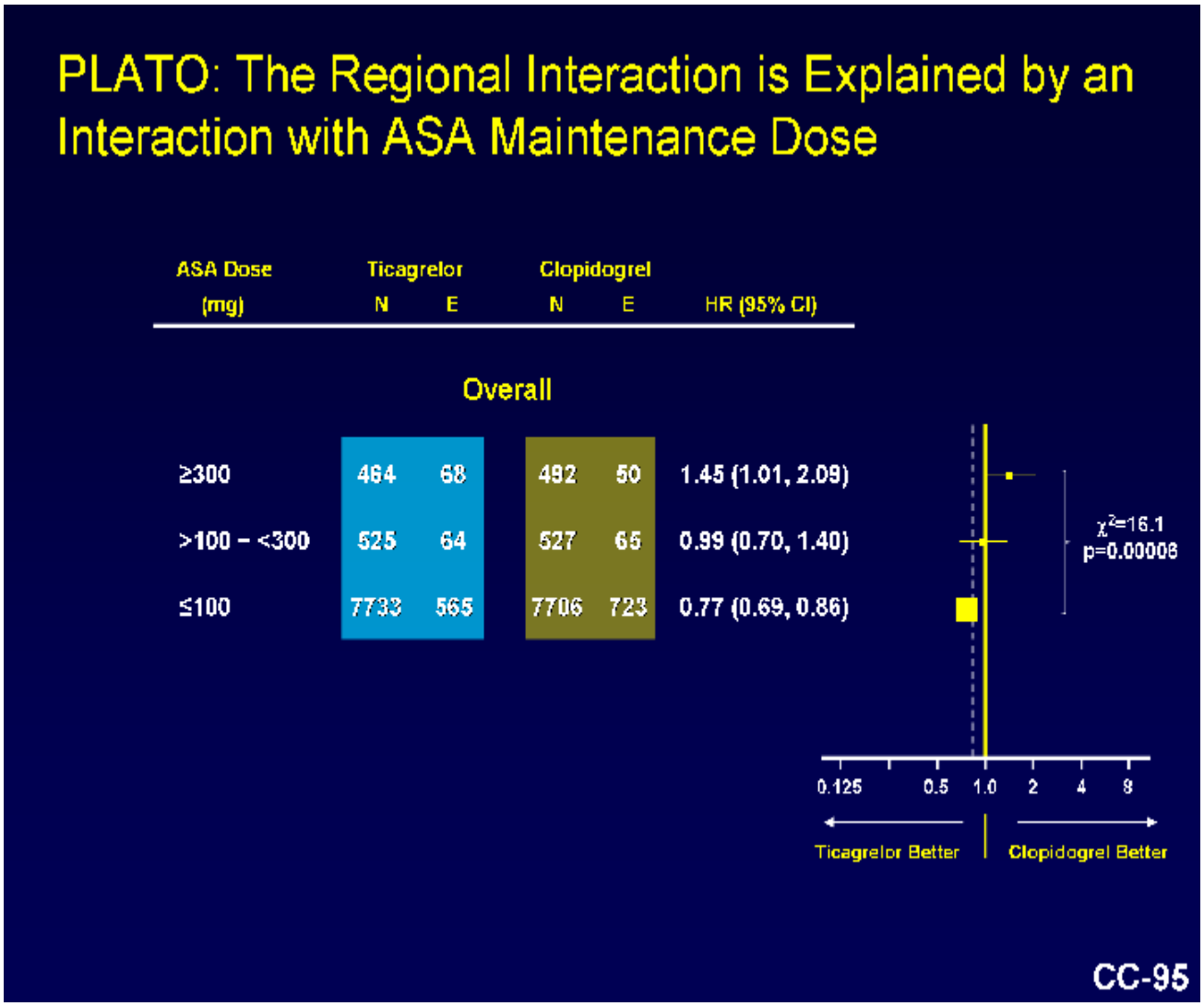


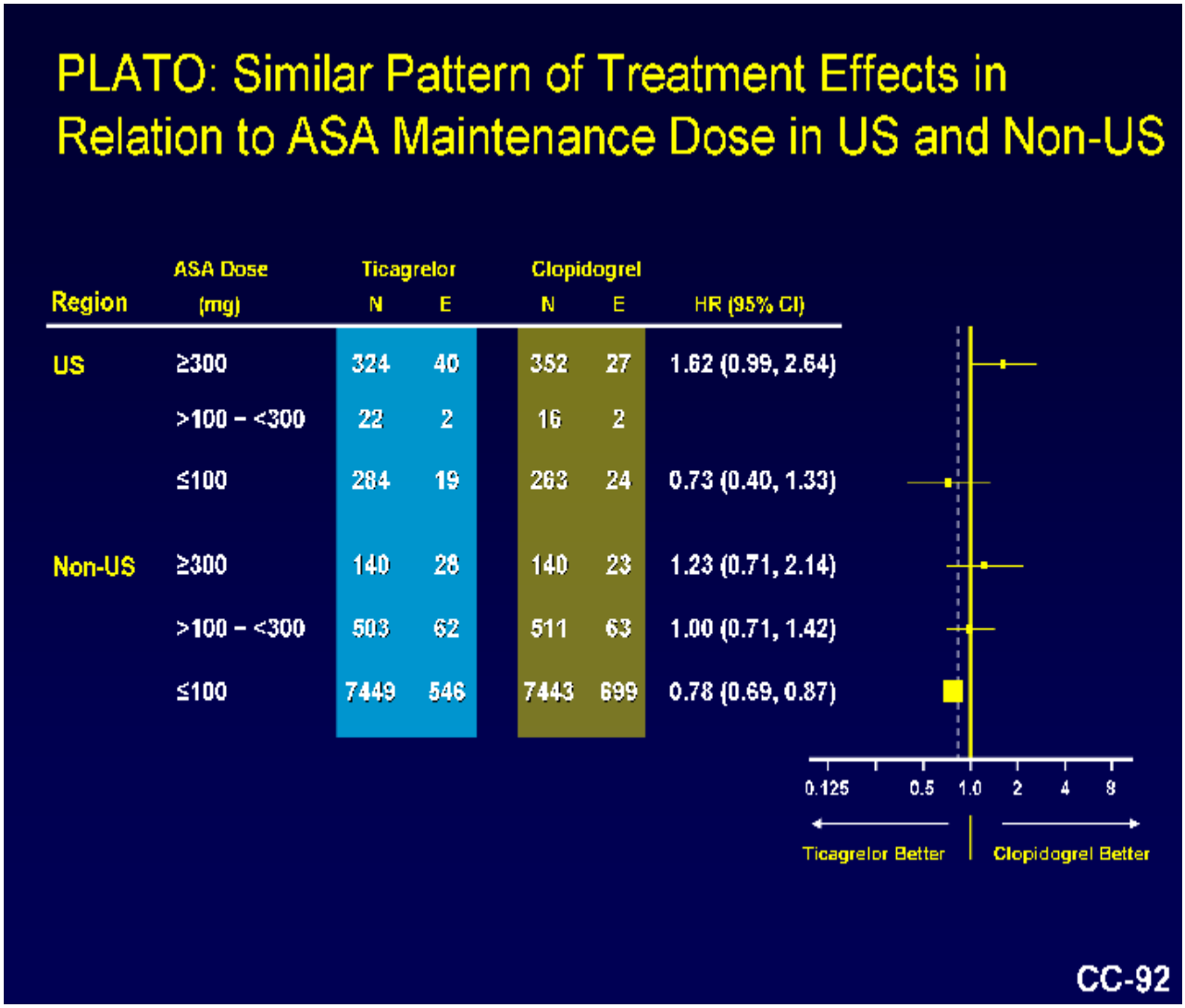
D. Effect of aspirin dose

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) and in response to our CR letter explored a variety of ways of characterizing the aspirin maintenance dose for each patient. Results were similar for the methods that ignored the day 1 dose and used mean or median values. The sponsor's conclusion was that the aspirin dose explained essentially all of the regional disparity.

The overall results of the study show a strong interaction with dose, with a graded relationship to dose that has a very high level of statistical significance (p=0.00006) in an analysis using a proportional hazards model with 3 terms: log median ASA dose, treatment, and the interaction between the 2 variables. Other interaction analyses are not as extreme but strongly indicate that higher aspirin doses led to a smaller effect of ticagrelor.

The overall results presented by the sponsor are shown in the following table. A similar analysis by region in the subsequent table shows that the difference related to aspirin dose was present in both US and OUS.





US results in the ≤ 100 mg ASA group are very similar to the OUS low dose results and results for ASA ≥ 300 mg are uniformly adverse, favoring clopidogrel both in the US and OUS. Results for the two components of the primary endpoint are shown in the following table.

		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 their face, showing great similarity for both components of the composite endpoint between US and OUS results once patients are divided into high and low aspirin

dose. Just as the fact that the US/OUS difference in effect was seen for both CV death and NFMI supported the credibility of the regional subset finding, the observation that the high dose/low dose aspirin difference is apparent for both endpoints strengthens the aspirin observation. Because there was uncertainty as to just how ASA dose was defined in the sponsor's analysis, our CR letter, dated December 15, 2010, asked that aspirin dosing be explored fully and validated and the sponsor reported their analysis in the response to the CR letter.

IV. The Strength of the Aspirin Conclusion

A critical question is whether aspirin can be treated as if it had the critical properties of a baseline characteristic, i.e., was more or less randomly (with respect to the two treatment groups) assigned. In considering subsets in a trial, baseline characteristics, presumably randomly distributed, have long been considered by far the most credible definers of subsets because they cannot be influenced by treatment. In contrast, a subset based on a post-randomization difference raises the concern that the subset does not really represent the characteristic identified in the subset, but some other characteristic that led to the post-randomization difference, and that this other characteristic might be influenced by the drug. That is undoubtedly a valid concern, but the level of concern would depend in part on whether the choice was differentially chosen for the two drugs, e.g., that patients doing badly or having some finding on ticagrelor caused by the drug tended to be moved to 300 mg aspirin, but similar patients on clopidogrel were not. This could lead to a false conclusion that high dose aspirin was the problem when in fact it was what led to use of high dose aspirin that was the problem. It is therefore noteworthy that the aspirin doses used were quite similar in the ticagrelor and clopidogrel groups, indicating that there did not appear to be an effect of ticagrelor that led to the high doses, both within and outside the US. In addition, aspirin dose was generally chosen fairly early, before many events would have occurred. There was in the OUS population evidence that higher risk patients (who had higher event rates) were given higher doses of aspirin, but this was true for both OUS treatment groups and cannot explain the difference in outcome.

There is reason to think ASA dose was in fact chosen based on physician practice and preference, not on any patient observation. Advice on aspirin dose from expert cardiovascular groups in the US in some cases suggests higher maintenance doses, probably explaining the US physicians' choices. Plainly, dose in OUS patients was heavily directed toward the low dose. If aspirin dose in fact represented physician preference, it would have characteristics similar to a baseline characteristic; i.e., it was de facto largely determined before the study because investigators brought in their preferences. It will be difficult to resolve this question to everyone's satisfaction, but it is 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, just as it did in US patients.

Dr. Zhang has examined the effect on outcomes of various ways of calculating ASA dose provided by the sponsor on 1/20/2011 in her 4/28/11 review. Results are discussed by Dr. Stockbridge. The aspirin effect is not as extreme as the analysis shown above but the various analyses using a number of maintenance dose estimates, almost all uniformly support the aspirin effect, generally at $p < 0.01$, sometimes considerably lower. In most cases, again using a variety of ways to choose the aspirin dose, the interaction of treatment with aspirin was stronger than the interaction by region. Dr. Stockbridge finds the aspirin dose interaction "moderately robust." Clearly, robustness depends on the particular analysis but, as noted above, it seems greatly strengthened by the very similar findings for both regions (US/OUS) and for both CV mortality and NFMI. Moreover, the effects of numerous US/OUS differences on the by-region interaction are minimal, leaving no plausible explanation, other than chance, as to why the US/OUS results should differ so markedly.

V. Conclusions

The ticagrelor NDA was presented to the Cardio-Renal Advisory Committee on July 28, 2010. By a 7-1 vote the committee recommended approval.

The Committee members were impressed by the presence of a CV mortality reduction and the overall strength of the study. They, of course, noted the US/OUS disparity, but appeared to believe the disparity most probably represented the play of choice. They clearly did not consider the disparity a deterrent to approval, although there was a wish expressed, fairly strongly, that a follow-on study similar to PLATO would be conducted in a US population, a study whose results would be years away. In discussion at the Advisory Committee, particularly following Dr. Stockbridge's expressed uncertainty as to the ethics of such a trial following approval of ticagrelor in the US, the considerable difficulty of conducting such a trial was recognized. Of interest, the sponsor's consultant, (b) (4), found the ticagrelor results with low dose aspirin very powerful, and by far the best estimate of the effect of ticagrelor (i.e., better than the overall study result) but expressed a wish to see a follow-up study with high dose aspirin.

There was relatively little discussion of the aspirin dosing results and no strong recommendation on use with low dose aspirin was made.

Like all of us who have considered these data, Dr. Stockbridge expresses concern about the US/OUS heterogeneity for a drug intended for a US population. He notes that there has been diligent and prolonged examination of a wide variety of differences between US and OUS patients, including demographic, concomitant medicines, diagnosis, (UA, STEMI, NSTEMI), procedures (stent, drug-eluting stent, early revascularization), without a finding of any difference that accounts for the US/OUS outcome differences, except for the strikingly different pattern of aspirin dosing. He is less impressed than I am by the observation that the US/OUS and aspirin dose heterogeneities are present for both mortality and NFMI because these would be expected to be correlated, but I do not agree with that conclusion.

If the US/OUS differences were in fact the result of chance, i.e., the Advisory Committee view, then there is no reason to expect chance to affect both components of the endpoint similarly, as such a correlation should reflect only the actual effect of the drug, not the effect of chance. That is, a chance difference related to one endpoint (e.g., CV death) would NOT be expected to show up with the other endpoint (NFMI). It is the fact that the US/OUS differences and the aspirin dose differences are present for both endpoints that suggests they are real, not random, considerably strengthening both findings (beyond their nominal p-values for heterogeneity, which do not take into account the impressive similarity of the effects on the components). Dr. Stockbridge is troubled, as we all are, by the lack of a good explanation for high dose aspirin's adverse effect on outcome, although he notes a reasonable basis for thinking aspirin would not add to ticagrelor's effect (this argument would be more persuasive, of course, if we knew aspirin added to the effect of clopidogrel, something widely thought likely but lacking controlled trial data).

Dr. Stockbridge discusses in detail concerns raised by Dr. Marciniak about data quality and investigator vs control adjudication and explains why he does not consider them determinative. I have little to add to his discussion, but would note that his concerns would not appear to apply to a mortality effect, which was a striking finding.

Dr. Stockbridge's lack of complete assurance about the role of ASA on outcome does not cause him to argue against approval, nor against a reasonably strong recommendation that ticagrelor should be used with aspirin doses ≤ 100 mg and I believe there is consistency in this. If the most probable explanation of US/OUS differences is chance, approval of ticagrelor is appropriate and if there is reasonably strong, even if not overwhelming, evidence that a high aspirin dose can undermine that effectiveness, a strong

recommendation to use ASA doses ≤ 100 mg is of obvious importance, as there is no established benefit of the higher ASA dose.

My own view is that the likelihood that the US/OUS difference is chance must be considered, and is surely possible. Major US/OUS differences, presumably the result of chance, have been seen in the past in large trials. The MERIT-HF study of controlled release metoprolol in 4000 heart failures patients showed a 34% reduction in mortality overall, $p < 0.0001$, with an approximately 45% reduction OUS, but no effect at all in the United States, which had 25% of patients. The difference on the primary endpoint however, death plus hospitalization, was much smaller. The difference in mortality was certainly about as striking as the difference in PLATO; a critical difference in that case, however, suggesting chance, was the similarity of the effects of metoprolol on heart failure hospitalization. Nonetheless, I do not believe chance is the most likely explanation of the results. The possibility that the US/OUS populations differed in some critical feature has been fully explored and no baseline or post-treatment factor (other than ASA dose) even weakly explains the difference in outcome and it is hard to think of any genetic, dietary, medical practice, or disease characteristic in the two populations that would lead to such a difference.

Although I consider the likelihood that the US/OUS difference was a chance occurrence, a credible basis for approval of ticagrelor, I believe the evidence that aspirin dose explains the difference is a powerful further basis for approval.

1. The aspirin dose difference, as shown in the last two tables, entirely accounts for the striking US/OUS difference.
2. The 2 main components of the study endpoint, CV death and NFMI, are similarly affected by region and by ASA dose, which argues strongly against the idea that this effect of region and aspirin dose are chance effects.
3. The aspirin effect is present for a variety of ways of counting aspirin maintenance dose. Moreover, uncertainty (noise) about ASA dose should work against the aspirin dose finding.
4. Diligent examination of many other US/OUS difference (all of which might have been characteristics of interest, were represented in both regions, albeit at different rates) showed none that at all explained the US/OUS outcome difference.
5. The aspirin dose-related difference in the overall study, AND in each region, AND for both components of the primary endpoint is impressive, even if there are relatively few patients in some subsets (OUS ASA > 300 mg).

Ticagrelor should be approved for treatment of patients with ACS to reduce the rate of thrombotic cardiovascular events, whether the US/OUS difference represents play of chance or the consequence of differences in aspirin dose in the two regions. If the former, there is perhaps no need to urger lower aspirin dose strongly, but if the aspirin dose effect is reasonably persuasive, even if not considered definitive, a strong recommendation to use maintenance doses ≤ 100 mg is warranted. There is no known harm from selection of this dose and a strong possibility (very strong in my view) that use of higher doses will reduce the beneficial effect of ticagrelor.

The Labeling will note in several places, including a Boxed Warning, that ticagrelor has been studied in combination with aspirin and that maintenance doses above 100 mg appear to decrease its effectiveness. The Boxed Warning for Ticagrelor will also warn about bleeding and the need to keep aspirin dose at or below 100 mg. Post-approval communication efforts and a Medguide will also emphasize these concerns.

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/s/

ROBERT TEMPLE
07/20/2011