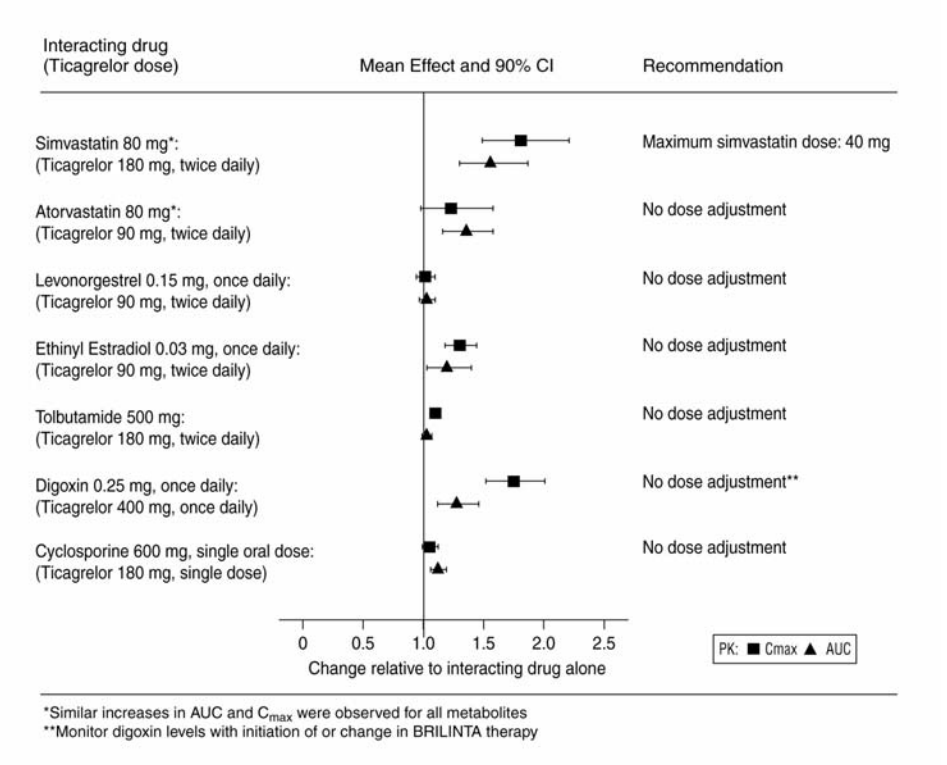
**Figure 7 – Impact of BRILINTA on the pharmacokinetics of co-administered drugs**




### 12.5 Pharmacogenetics

In a genetic substudy cohort of PLATO, the rate of thrombotic CV events in the BRILINTA arm did not depend on CYP2C19 loss of function status.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). 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 twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis

Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

# 14 CLINICAL STUDIES

## 14.1 Acute Coronary Syndromes and Secondary Prevention after Myocardial Infarction

**PLATO**

PLATO was a randomized double-blind study comparing BRILINTA (N=9333) to clopidogrel (N=9291), both given in combination with aspirin and other standard therapy, in patients with acute coronary syndromes (ACS), who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. The study's primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke.

Patients who had already been treated with clopidogrel could be enrolled and randomized to either study treatment. Patients with previous intracranial hemorrhage, gastrointestinal bleeding within the past 6 months, or with known bleeding diathesis or coagulation disorder were excluded. Patients taking anticoagulants were excluded from participating and patients who developed an indication for anticoagulation during the trial were discontinued from study drug. Patients could be included whether there was intent to manage the ACS medically or invasively, but patient randomization was not stratified by this intent.

All patients randomized to BRILINTA received a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Patients in the clopidogrel arm were treated with an initial loading dose of clopidogrel 300 mg, if clopidogrel therapy had not already been given. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at investigator discretion. A daily maintenance dose of aspirin 75-100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment. Patients were treated for at least 6 months and for up to 12 months.

PLATO patients were predominantly male (72%) and Caucasian (92%). About 43% of patients were >65 years and 15% were >75 years. Median exposure to study drug was 277 days. About half of the patients received pre-study clopidogrel and about 99% of the patients received aspirin at some time during PLATO. About 35% of patients were receiving a statin at baseline and 93% received a statin sometime during PLATO.

Table 6 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint. Separate secondary endpoint analyses are shown for the overall occurrence of CV death, MI, and stroke and overall mortality.

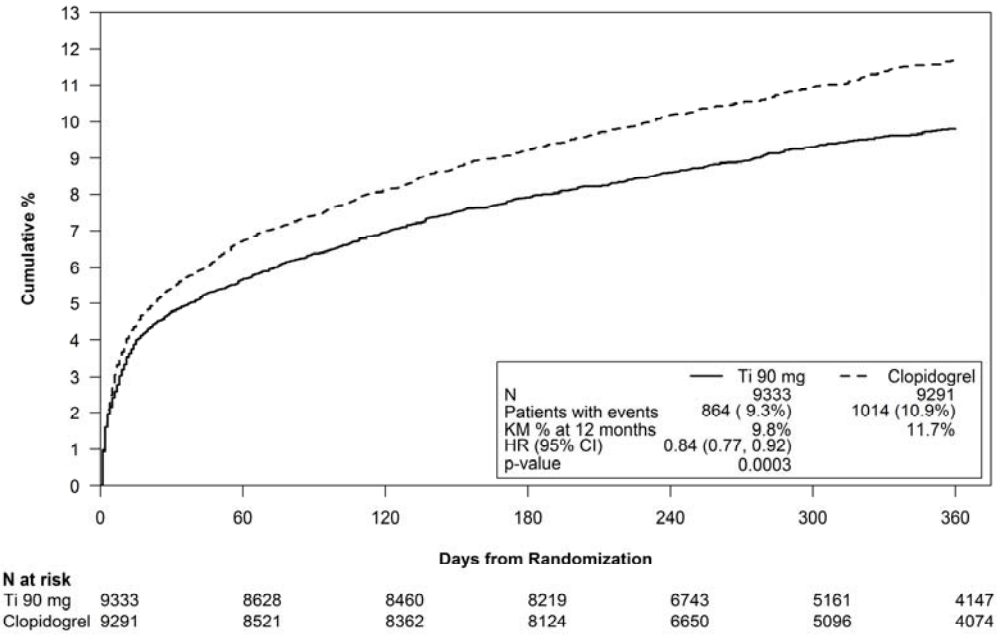
**Table 6 – Patients with outcome events (KM%)(PLATO)**

| | BRILINTA[1] N=9333 | Clopidogrel N=9291 | Hazard Ratio (95% CI) | *p*-value |
|---|---|---|---|---|
| Composite of CV death, MI, or stroke | 9.8 | 11.7 | 0.84 (0.77, 0.92) | 0.0003 |
| CV death | 2.9 | 4.0 | 0.74 | |
| Non-fatal MI | 5.8 | 6.9 | 0.84 | |
| Non-fatal stroke | 1.4 | 1.1 | 1.24 | |
| Secondary endpoints[2] | | | | |
| CV death | 4.0 | 5.1 | 0.79 (0.69, 0.91) | 0.0013 |
| MI[3] | 5.8 | 6.9 | 0.84 (0.75, 0.95) | 0.0045 |
| Stroke[3] | 1.5 | 1.3 | 1.17 (0.91, 1.52) | 0.22 |
| All-cause mortality | 4.5 | 5.9 | 0.78 (0.69, 0.89) | 0.0003 |

1. Dosed at 90 mg bid.
2. Note: rates of first events for the components CV Death, MI and Stroke are the actual rates for first events for each component and do not add up to the overall rate of events in the composite endpoint.
3. Including patients who could have had other non-fatal events or died.

The Kaplan-Meier curve (Figure 8) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke in the overall study.

**Figure 8 – Time to first occurrence of CV death, MI, or stroke (PLATO)**



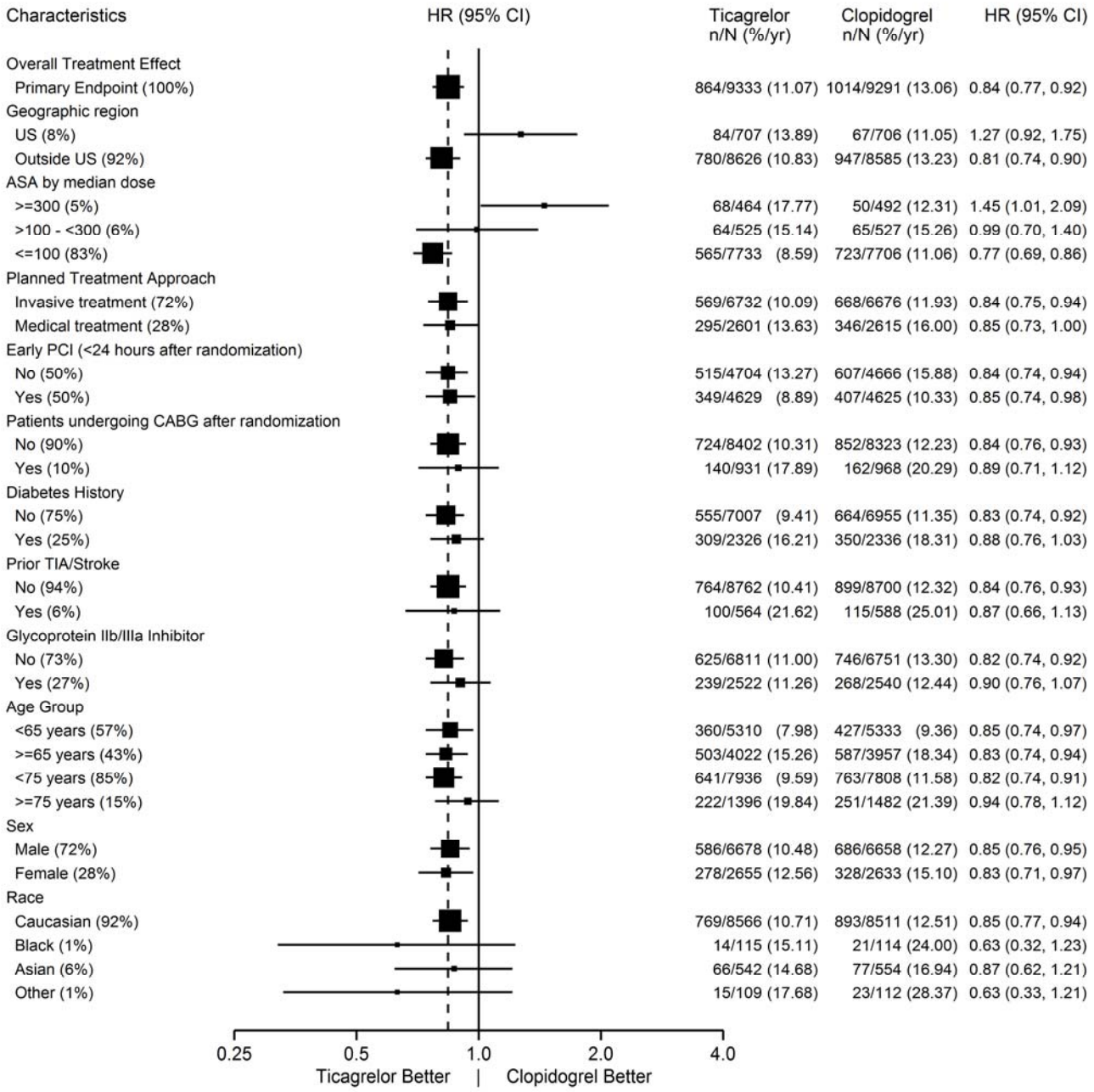

The curves separate by 30 days [relative risk reduction (RRR) 12%] and continue to diverge throughout the 12 month treatment period (RRR 16%).

Among 11289 patients with PCI receiving any stent during PLATO, there was a lower risk of stent thrombosis (1.3% for adjudicated "definite") than with clopidogrel (1.9%) (HR 0.67, 95% CI 0.50-0.91; *p*=0.009). The results were similar for drug-eluting and bare metal stents.

A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Some of these are shown in Figure 9. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two exceptions: a finding of heterogeneity by region and a strong influence of the maintenance dose of aspirin. These are considered further below.

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization determinations (e.g., aspirin maintenance dose, use of PCI).

**Figure 9 – Subgroup analyses of (PLATO)**




Note: The figure above presents effects in various subgroups most of which are baseline characteristics and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Regional Differences

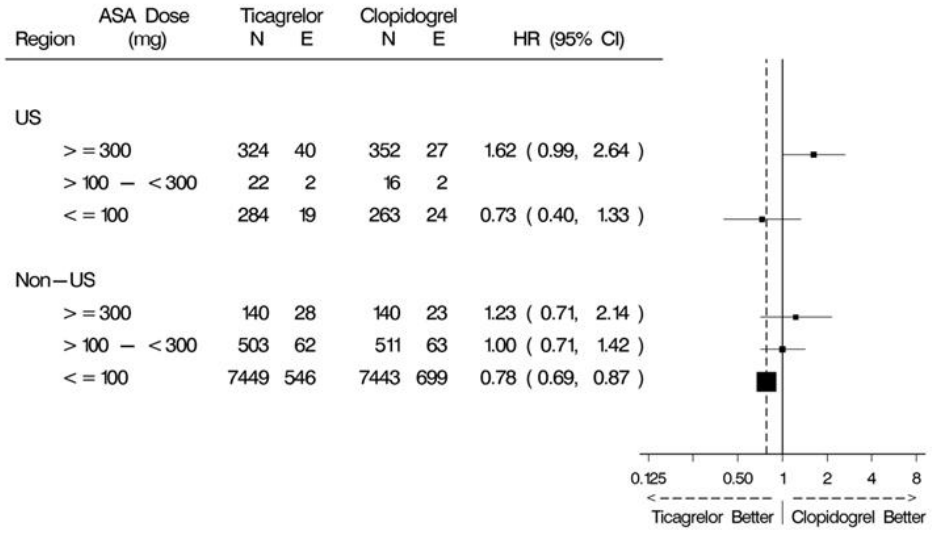
Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison is statistically significant ($p$=0.009), and the same trend is present for both CV death and non-fatal MI. The individual results and nominal $p$-values, like all subset analyses, need cautious interpretation, and they could represent chance findings. The consistency of the differences in both the CV mortality and non-fatal MI components, however, supports the possibility that the finding is reliable.

A wide variety of baseline and procedural differences between the US and non-US (including intended invasive *vs.* planned medical management, use of GPIIb/IIIa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see if they could account for regional differences, but with one exception, aspirin maintenance dose, these differences did not appear to lead to differences in outcome.

Aspirin Dose

The PLATO protocol left the choice of aspirin maintenance dose up to the investigator and use patterns were different in US sites from sites outside of the US. About 8% of non-US investigators administered aspirin doses above 100 mg, and about 2% administered doses above 300 mg. In the US 57% of patients received doses above 100 mg and 54% received doses above 300 mg. Overall results favored BRILINTA when used with low maintenance doses (≤100 mg) of aspirin, and results analyzed by aspirin dose were similar in the US and elsewhere. Figure 10 shows overall results by median aspirin dose. Figure 10 shows results by region and dose.

**Figure 10 – CV death, MI, stroke by maintenance aspirin dose in the US and outside the US (PLATO)**




Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary endpoint, CV death and non-fatal MI.

Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA.

**PEGASUS**

The PEGASUS TIMI-54 study was a 21162-patient, randomized, double-blind, placebo-controlled, parallel-group study. Two doses of ticagrelor, either 90 mg twice daily or 60 mg twice daily, co-administered with 75-150 mg of aspirin, were compared to aspirin therapy alone in patients with history of MI. The primary endpoint was the composite of first occurrence of CV death, non-fatal MI and non-fatal stroke. CV death and all-cause mortality were assessed as secondary endpoints.

Patients were eligible to participate if they were ≥50 years old, with a history of MI 1 to 3 years prior to randomization, and had at least one of the following risk factors for thrombotic cardiovascular events: age ≥65 years, diabetes mellitus

requiring medication, at least one other prior MI, evidence of multivessel coronary artery disease, or creatinine clearance <60 mL/min. Patients could be randomized regardless of their prior ADP receptor blocker therapy or a lapse in therapy. Patients requiring or who were expected to require renal dialysis during the study were excluded. Patients with any previous intracranial hemorrhage, gastrointestinal bleeding within the past 6 months, or with known bleeding diathesis or coagulation disorder were excluded. Patients taking anticoagulants were excluded from participating and patients who developed an indication for anticoagulation during the trial were discontinued from study drug. A small number of patients with a history of stroke were included. Based on information external to PEGASUS, 102 patients with a history of stroke (90 of whom received study drug) were terminated early and no further such patients were enrolled.

Patients were treated for at least 12 months and up to 48 months with a median follow up time of 33 months.

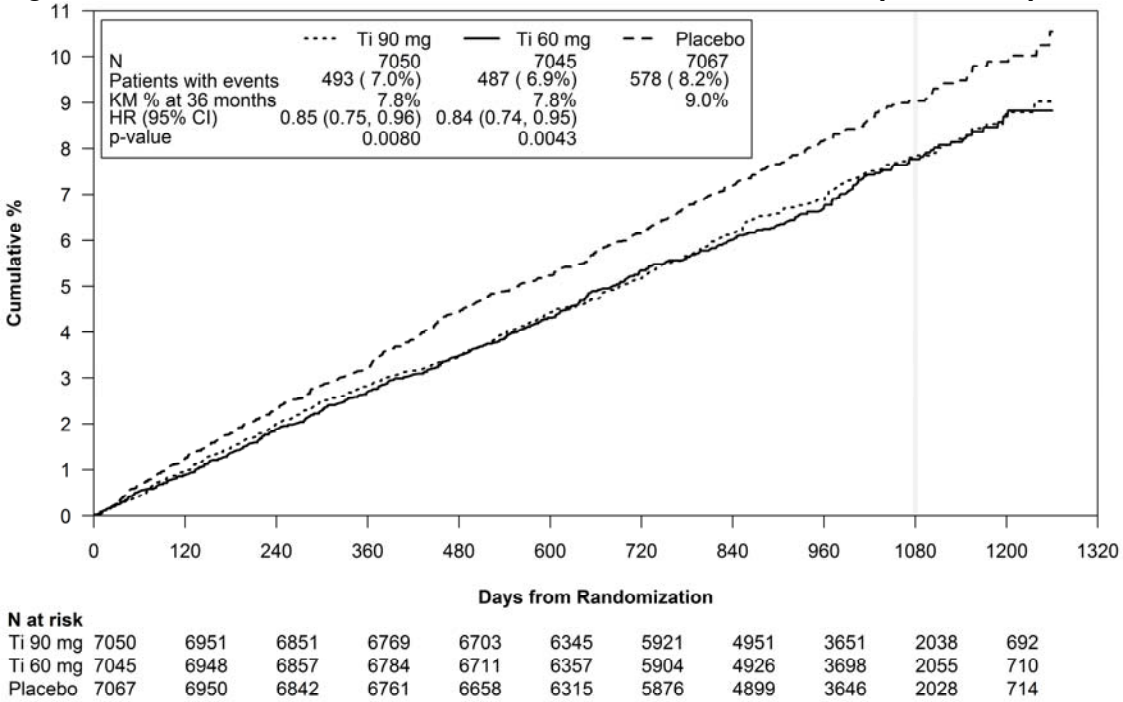
Patients were predominantly male (76%) Caucasian (87%) with a mean age 65 years, and 99.8% of patients received prior Aspirin therapy. See Table 7 for key baseline features.

**Table 7 – Baseline features (PEGASUS)**

| Demographic | % Patients |
|---|---|
| <65 years | 45% |
| Diabetes | 32% |
| Multivessel disease | 59% |
| History of >1 MI | 17% |
| Chronic non-end stage renal disease | 19% |
| Stent | 80% |
| Prior P2Y12 platelet inhibitor therapy | 89% |
| Lipid lowering therapy | 94% |

The Kaplan-Meier curve (Figure 11) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke.

**Figure 11 – Time to First Occurrence of CV death, MI or Stroke (PEGASUS)**




Ti = Ticagrelor BID, CI = Confidence interval; HR = Hazard ratio; KM = Kaplan-Meier; N = Number of patients.

Both the 60 mg and 90 mg regimens of BRILINTA in combination with aspirin were superior to aspirin alone in reducing the incidence of CV death, MI or stroke. The absolute risk reductions for BRILINTA plus aspirin *vs.* aspirin alone were 1.27% and 1.19% for the 60 and 90 mg regimens, respectively. Although the efficacy profiles of the two regimens were similar, the lower dose had lower risks of bleeding and dyspnea.

Table 8 shows the results for the 60 mg plus aspirin regimen *vs.* aspirin alone.

**Table 8 – Incidences of the primary composite endpoint, primary composite endpoint components, and secondary endpoints (PEGASUS)**

| | **BRILINTA[1] + Aspirin N=7045** | | **Aspirin Alone N=7067** | | **HR (95% CI)** | ***p*-value** |
|---|---|---|---|---|---|---|
| | **n (patients with event)** | **KM%** | **n (patients with event)** | **KM%** | | |
| Time to first CV death, MI, or stroke[2] | 487 | 7.8 | 578 | 9.0 | 0.84 (0.74, 0.95) | 0.0043 |
| CV Death[4] | 116 | | 128 | | | |
| Myocardial infarction[4] | 283 | | 336 | | | |
| Stroke[4] | 88 | | 114 | | | |
| Subjects with events at any time CV Death[3 5] | 174 | 2.9 | 210 | 3.4 | 0.83 (0.68, 1.01) | |
| Myocardial infarction[5] | 285 | 4.5 | 338 | 5.2 | 0.84 (0.72, 0.98) | |
| Stroke[5] | 91 | 1.5 | 122 | 1.9 | 0.75 (0.57, 0.98) | |
| All-cause mortality[3] | 289 | 4.7 | 326 | 5.2 | 0.89 (0.76, 1.04) | |

CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; KM = Kaplan-Meier percentage calculated at 36 months; MI = Myocardial infarction; N = Number of patients.

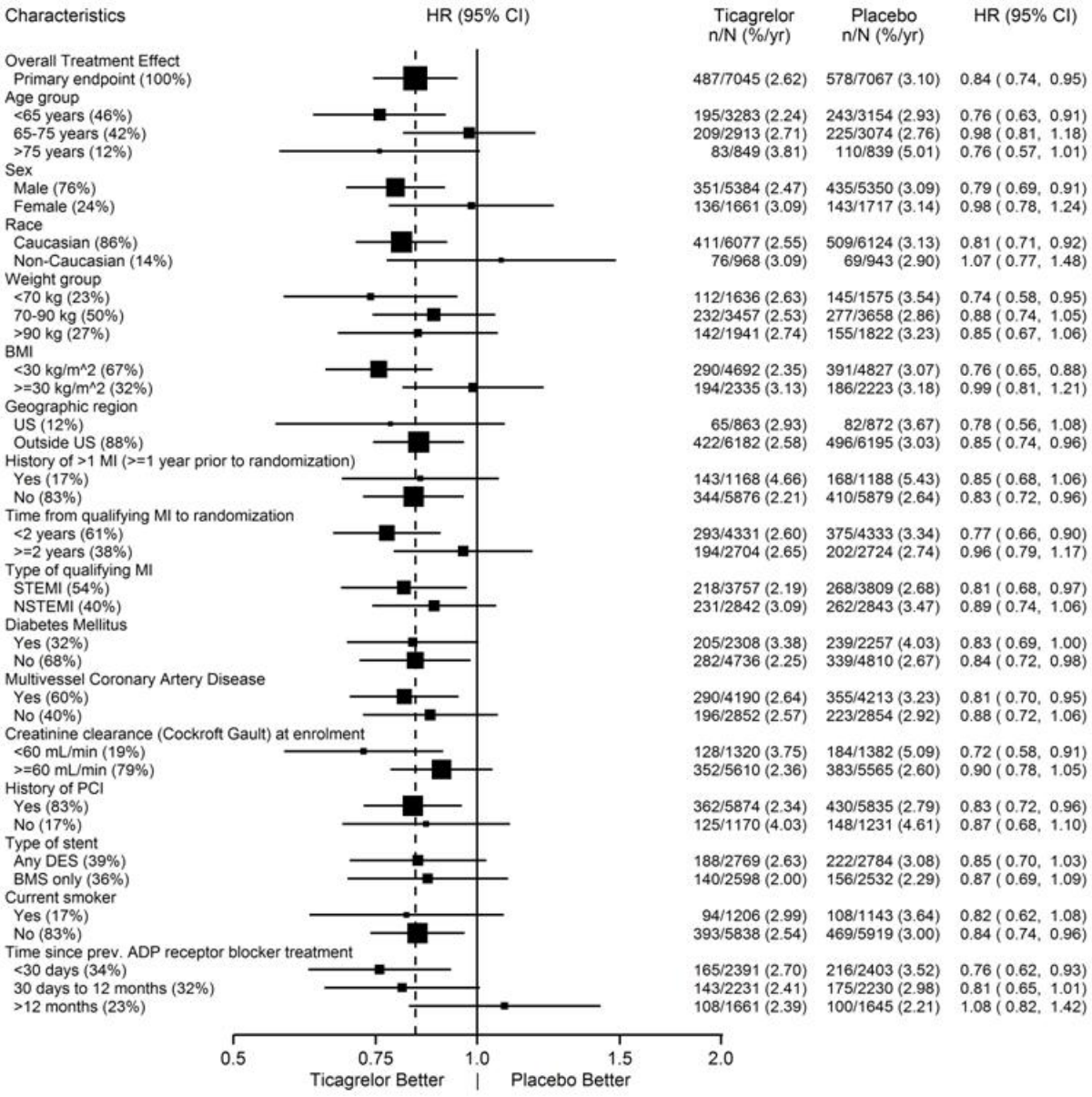
[1] 60 mg BID

[2] Primary endpoint
[3] Secondary endpoints
[4] For the components, the first-occurring component of the composite is included.
[5] The number of first events for the components CV Death, MI and Stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

In PEGASUS, the RRR for the composite endpoint from 1 to 360 days (17% RRR) and from 361 days and onwards (16% RRR) were similar.

The treatment effect of BRILINTA 60 mg over aspirin appeared similar across most pre-defined subgroups, see Figure 12.

**Figure 12 – Subgroup analyses of ticagrelor 60 mg (PEGASUS)**




Note: The figure above presents effects in various subgroups all of which are baseline characteristics and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

# 16 HOW SUPPLIED/STORAGE AND HANDLING

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet with a “90” above “T” on one side:

Bottles of 14 – NDC 0186-0777-28
Bottles of 60 – NDC 0186-0777-60
100 count Hospital Unit Dose – NDC 0186-0777-39

BRILINTA (ticagrelor) 60 mg is supplied as a round, biconvex, pink, film-coated tablet with a “60” above “T” on one side;

Bottles of 60 – NDC 0186-0776-60
Blister of 14 – NDC 0186-0776-94

**Storage and Handling**

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room temperature].

# 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

Advise patients daily doses of aspirin should not exceed 100 mg and to avoid taking any other medications that contain aspirin.

Advise patients that they:

- Will bleed and bruise more easily
- Will take longer than usual to stop bleeding
- Should report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

Advise patients to contact their doctor if they experience unexpected shortness of breath, especially if severe.

Advise patients to inform physicians and dentists that they are taking BRILINTA before any surgery or dental procedure.

BRILINTA® is a trademark of the AstraZeneca group of companies.

**Distributed by: AstraZeneca LP, Wilmington, DE 19850**

**MEDICATION GUIDE**

**BRILINTA® (brih-LIN-tah)**

**(ticagrelor) Tablets**

**What is the most important information I should know about BRILINTA?**

BRILINTA is used to lower your chance of having a heart attack or dying from a heart attack or stroke **but BRILINTA (and similar drugs) can cause bleeding that can be serious and sometimes lead to death.** In cases of serious bleeding, such as internal bleeding, the bleeding may result in the need for blood transfusions or surgery. While you take BRILINTA:

- you may bruise and bleed more easily
- you are more likely to have nose bleeds
- it will take longer than usual for any bleeding to stop

Call your doctor right away, if you have any of these signs or symptoms of bleeding while taking BRILINTA:

- bleeding that is severe or that you cannot control
- pink, red or brown urine
- vomiting blood or your vomit looks like “coffee grounds”
- red or black stools (looks like tar)
- coughing up blood or blood clots

**Do not stop taking BRILINTA without talking to the doctor who prescribes it for you.** People who are treated with a stent, and stop taking BRILINTA too soon, have a higher risk of getting a blood clot in the stent, having a heart attack, or dying. If you stop BRILINTA because of bleeding, or for other reasons, your risk of a heart attack or stroke may increase.

Your doctor may instruct you to stop taking BRILINTA 5 days before surgery. This will help to decrease your risk of bleeding with your surgery or procedure. Your doctor should tell you when to start taking BRILINTA again, as soon as possible after surgery.

**Taking BRILINTA with aspirin**

BRILINTA is taken with aspirin. Talk to your doctor about the dose of aspirin that you should take with BRILINTA. You should not take a dose of aspirin higher than 100 mg daily because it can affect how well BRILINTA works. Do not take doses of aspirin higher than what your doctor tells you to take. Tell your doctor if you take other medicines that contain aspirin, and do not take new over-the-counter medicines with aspirin in them.

**What is BRILINTA?**

BRILINTA is a prescription medicine used to treat people who:

- have had a heart attack or severe chest pain that happened because their heart was not getting enough oxygen.

BRILINTA is used with aspirin to lower your chance of having another serious problem with your heart or blood vessels, such as heart attack, stroke, or blood clots in your stent. These can be fatal.

Platelets are blood cells that help with normal blood clotting. BRILINTA helps prevent platelets from sticking together and forming a clot that can block an artery.

It is not known if BRILINTA is safe and effective in children.

**Who should not take BRILINTA?**

**Do not take BRILINTA if you:**

- have a history of bleeding in the brain
- are bleeding now
- are allergic to ticagrelor or any of the ingredients in BRILINTA. See the end of this Medication Guide for a complete list of ingredients in BRILINTA.

**What should I tell my doctor before taking BRILINTA?**

**Before you take BRILINTA, tell your doctor if you:**

- have had bleeding problems in the past
- have had any recent serious injury or surgery
- plan to have surgery or a dental procedure
- have a history of stomach ulcers or colon polyps
- have lung problems, such as COPD or asthma
- have liver problems
- have a history of stroke
- are pregnant or plan to become pregnant. It is not known if BRILINTA will harm your unborn baby. You and your doctor

should decide if you will take BRILINTA.

- are breastfeeding or plan to breastfeed. It is not known if BRILINTA passes into your breast milk. You and your doctor should decide if you will take BRILINTA or breastfeed. You should not do both without talking with your doctor.

Tell all of your doctors and dentists that you are taking BRILINTA. They should talk to the doctor who prescribed BRILINTA for you before you have any surgery or invasive procedure.

**Tell your doctor about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. **BRILINTA may affect the way other** medicines work, and other medicines may affect how BRILINTA works.

Especially tell your doctor if you take:

- an HIV-AIDS medicine
- medicine for heart conditions or high blood pressure
- medicine for high blood cholesterol levels
- an anti-fungal medicine by mouth
- an anti-seizure medicine
- a blood thinner medicine
- rifampin (Rifater, Rifamate, Rimactane, Rifadin)

Ask your doctor or pharmacist if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

**How should I take BRILINTA?**

- Take BRILINTA exactly as prescribed by your doctor.
- Your doctor will tell you how many BRILINTA tablets to take and when to take them.
- Take BRILINTA with a low dose (not more than 100 mg daily) of aspirin. You may take BRILINTA with or without food.
- Take your doses of BRILINTA around the same time every day.
- If you forget to take your scheduled dose of BRILINTA, take your next dose at its scheduled time. Do not take 2 doses at the same time unless your doctor tells you to.
- If you take too much BRILINTA or overdose, call your doctor or poison control center right away, or go to the nearest emergency room.

**If you are unable to swallow the tablet(s) whole**, you may crush the BRILINTA tablet(s) and mix it with water. Drink all the water right away. Refill the glass with water, stir, and drink all the water.

**What are the possible side effects of BRILINTA?**

**BRILINTA can cause serious side effects, including:**

- **See "What is the most important information I should know about BRILINTA?"**
- **Shortness of breath**. Call your doctor if you have new or unexpected shortness of breath when you are at rest, at night, or when you are doing any activity. Your doctor can decide what treatment is needed.

These are not all of the possible side effects of BRILINTA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store BRILINTA?**

- Store BRILINTA at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep BRILINTA and all medicines out of the reach of children.**

**General information about BRILINTA**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BRILINTA for a condition for which it was not prescribed. Do not give BRILINTA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or doctor for information about BRILINTA that is written for health professionals.

**What are the ingredients in BRILINTA?**

**Active ingredient:** ticagrelor

90 mg tablets:

Inactive ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

60 mg tablets:

**Inactive ingredients:** mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, ferric oxide black and ferric oxide red.

**Distributed by: AstraZeneca LP, Wilmington, DE 19850**

For more information call 1-800-236-9933 or go to www.Brilinta.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 09/2015