



# 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<sub>12</sub> 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<sub>12</sub> 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.

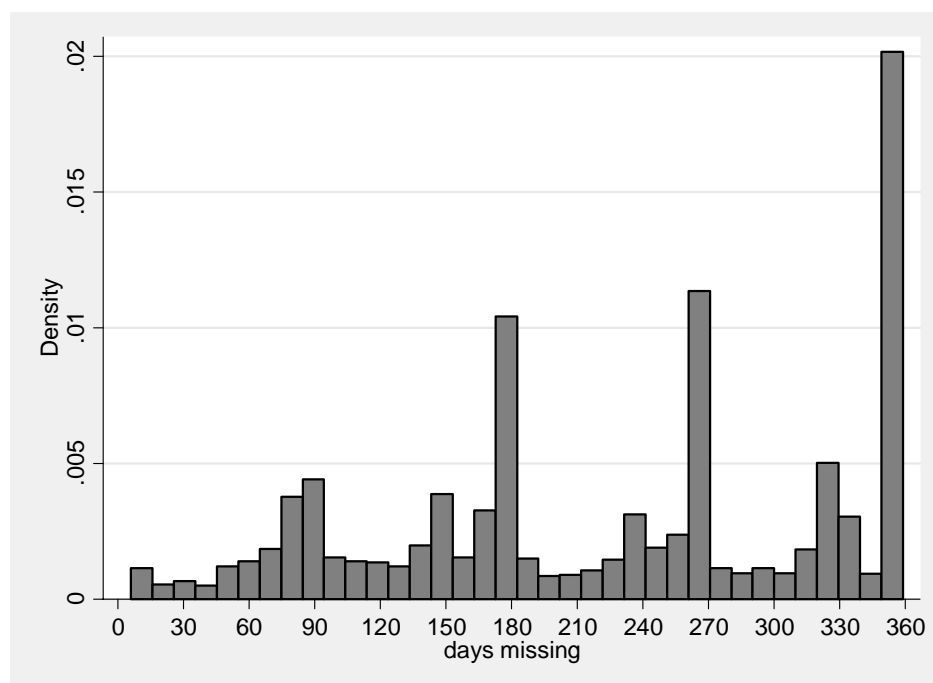
### **PLATO Study Conduct**

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).

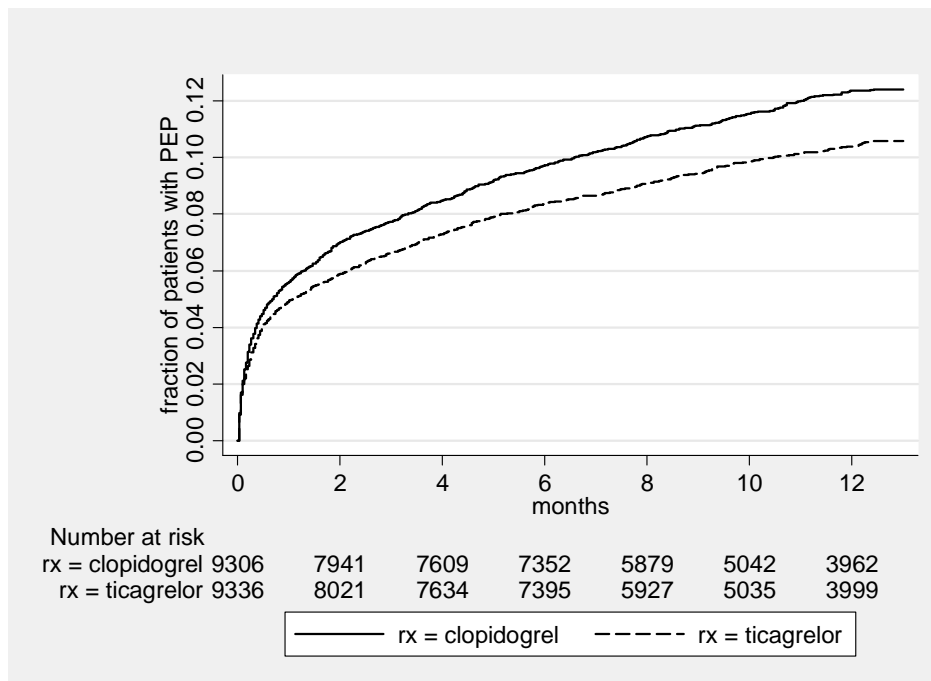
### *Sponsor’s Primary Adjudicated Results*

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., “Quintiles 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.

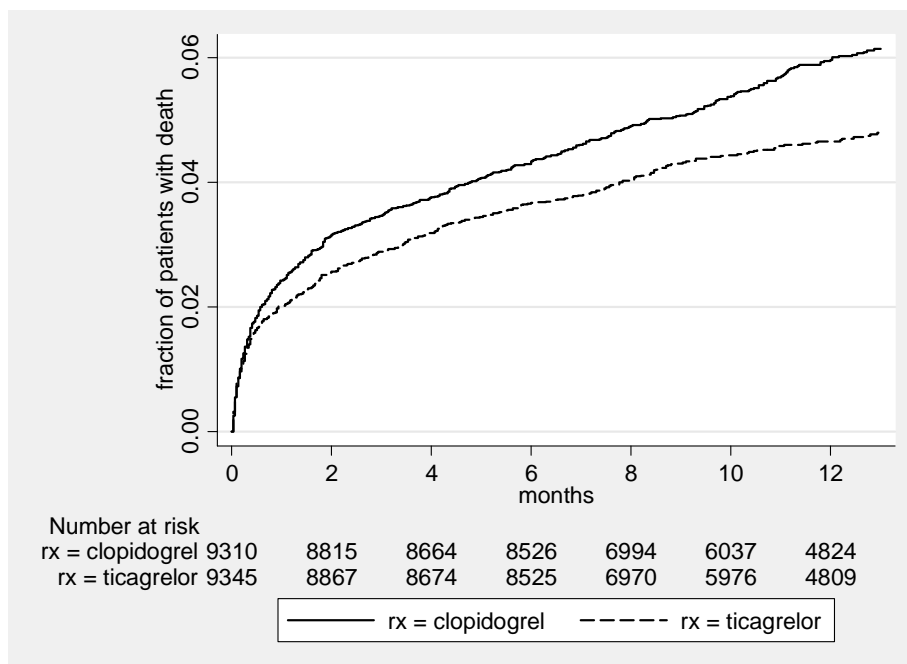
I show the Kaplan-Meier (K-M) plot for the sponsor’s first primary endpoint event (CV death, MI, or stroke - MACE) in Figure 2 and for death in Figure 3.



**Figure 2: Time to Sponsor's First Primary Endpoint Event (MACE)**



**Figure 3: Time to Death from Any Cause**

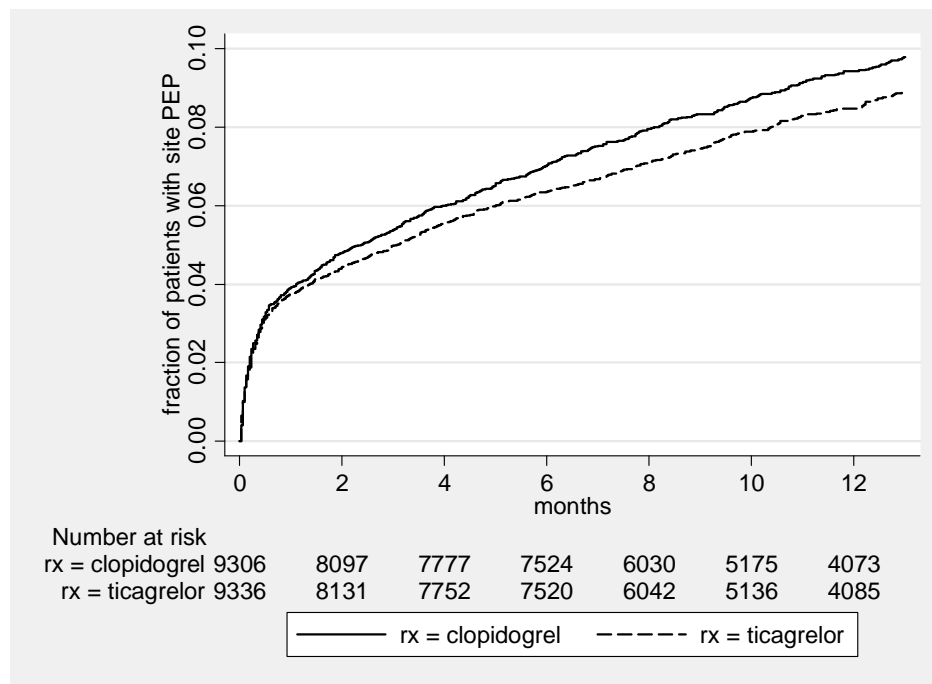


Both time-to-first event analyses are highly statistically significant by the log rank test. One relevant question is that, given the incompleteness of follow-up, are the results real?

### Site-Reported MACE

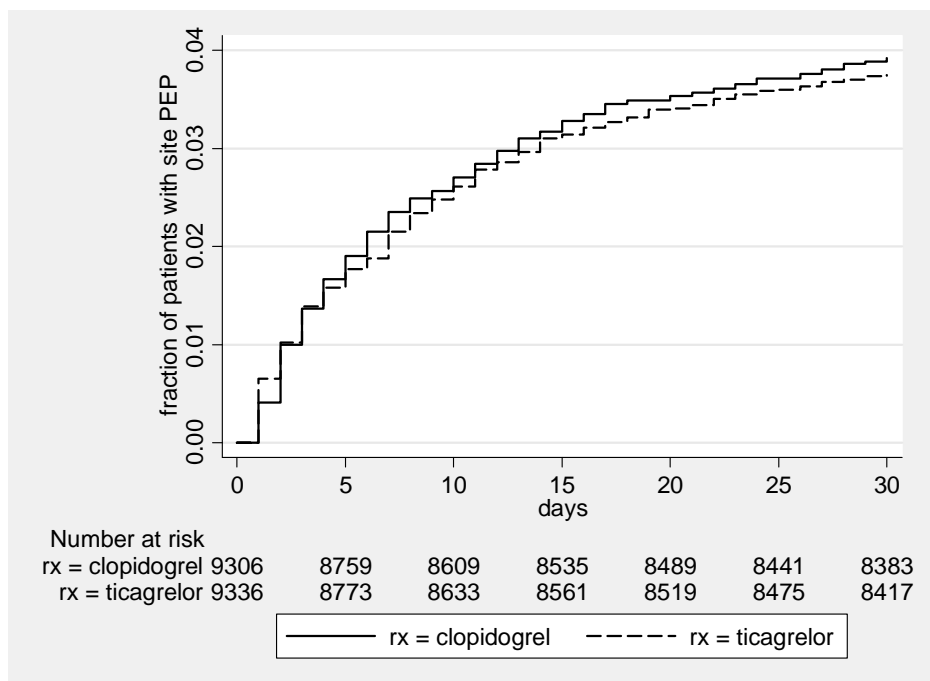
As a check I counted CV death, MI, and stroke events (MACE) as reported by the sites without the ICAC adjudication. For these site-reported statistics I also implemented two variations from the sponsor's classification of CV deaths: (1) The sponsor counted bleeding deaths as CV deaths. While that is 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 4.

**Figure 4: Time to Site-Reported First MACE**



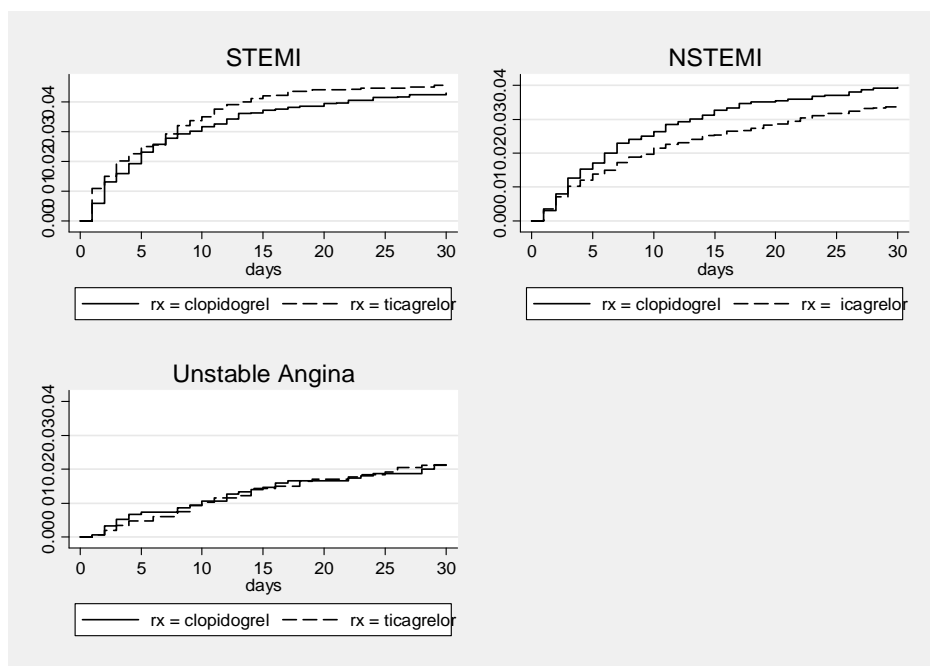
The possible benefit of ticagrelor is much less impressive for site-reported events and not statistically significant ( $p$  about 0.095 by log rank). For site-reported events there is only a slight benefit regarding MIs (relative risk (RR) about 0.94), a detriment regarding strokes (RR about 1.2), with 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.

**Figure 5: Time to Site-Reported First MACE – 30 Days**



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**

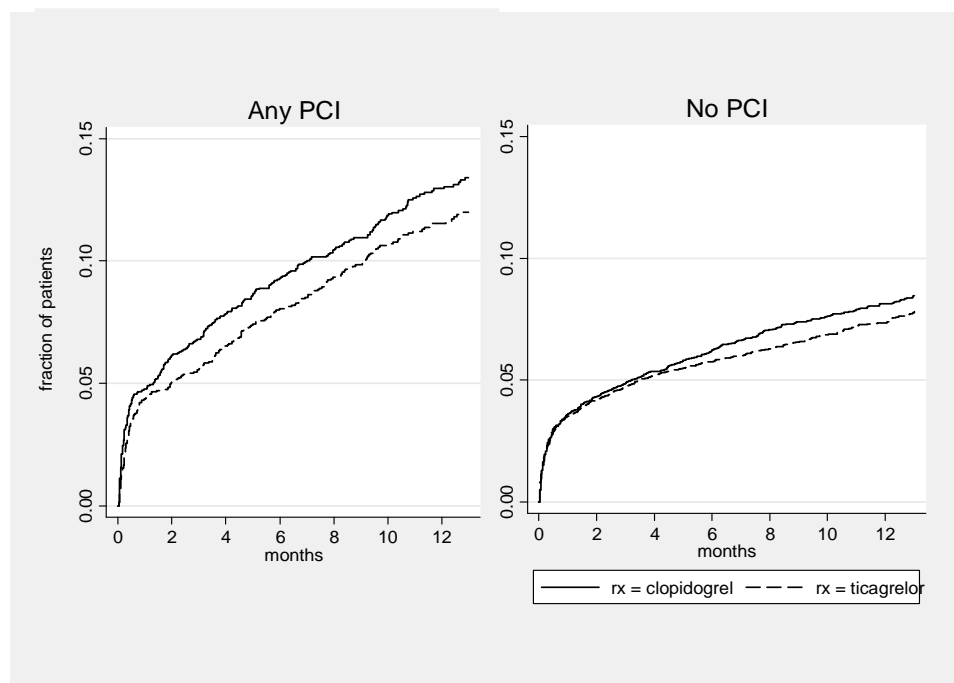


For all three types of index event ticagrelor appears to show beneficial effects longer term. The short term effects for ticagrelor are the opposite of what we've seen with prasugrel compared to clopidogrel: For prasugrel there was an immediate and dramatic benefit in STEMI patients in the TRITON trial 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.

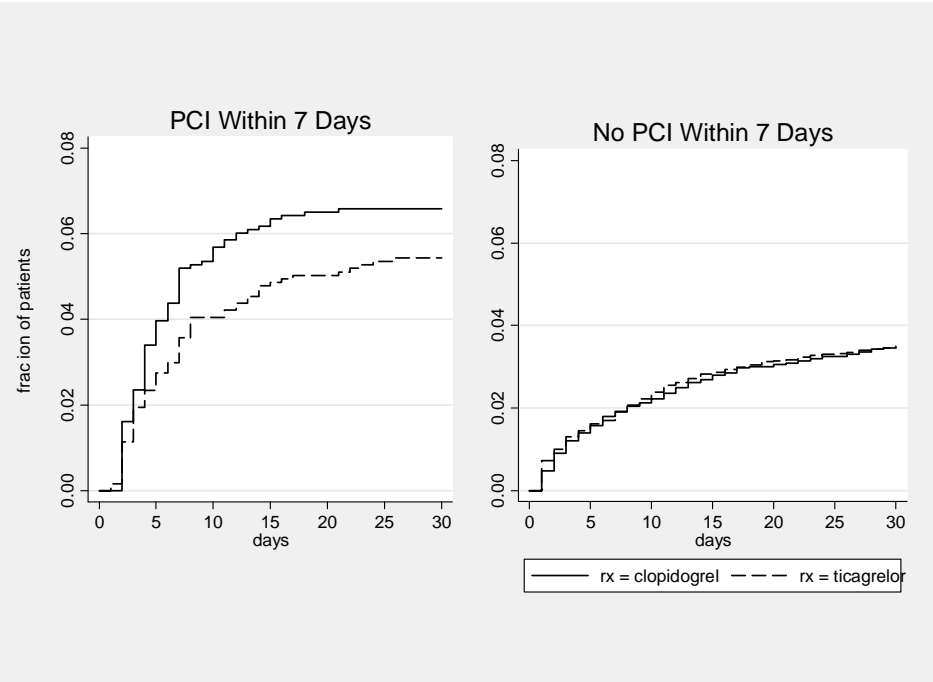
#### *Relationship to Subsequent Percutaneous Coronary Intervention (PCI)*

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 .

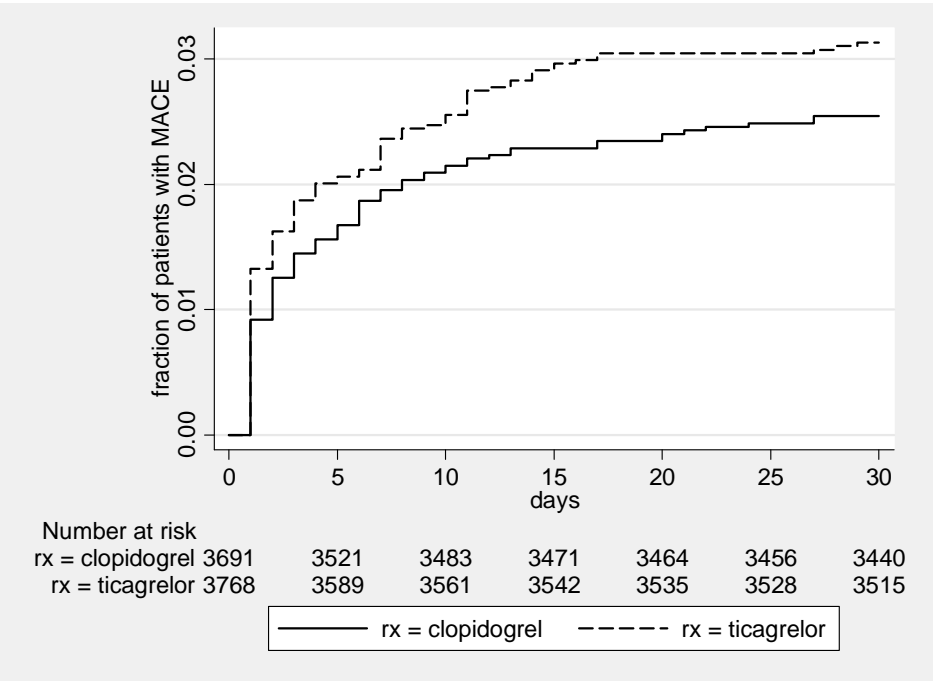
**Figure 7: Time to Site-Reported First MACE by PCI Anytime after Day 1**



**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

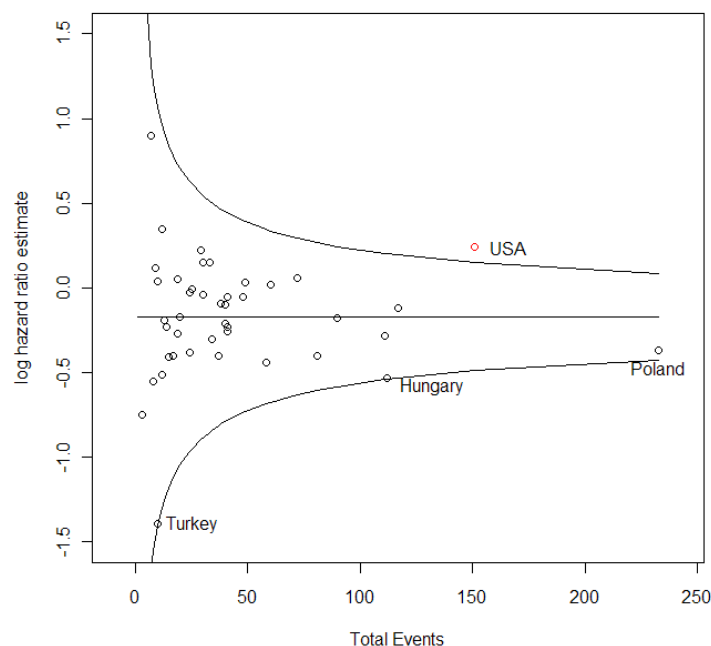
as that ticagrelor shows greater benefit in the sicker patients requiring PCI. Furthermore, the determination of the need for PCI is a post-randomization decision subject to biases—and PCI itself can be considered a CV endpoint. However, that ticagrelor may show a detrimental effect in patients with 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

could also have a beneficial impact upon ventricular arrhythmias. I examine ventricular arrhythmia rates in Safety below.

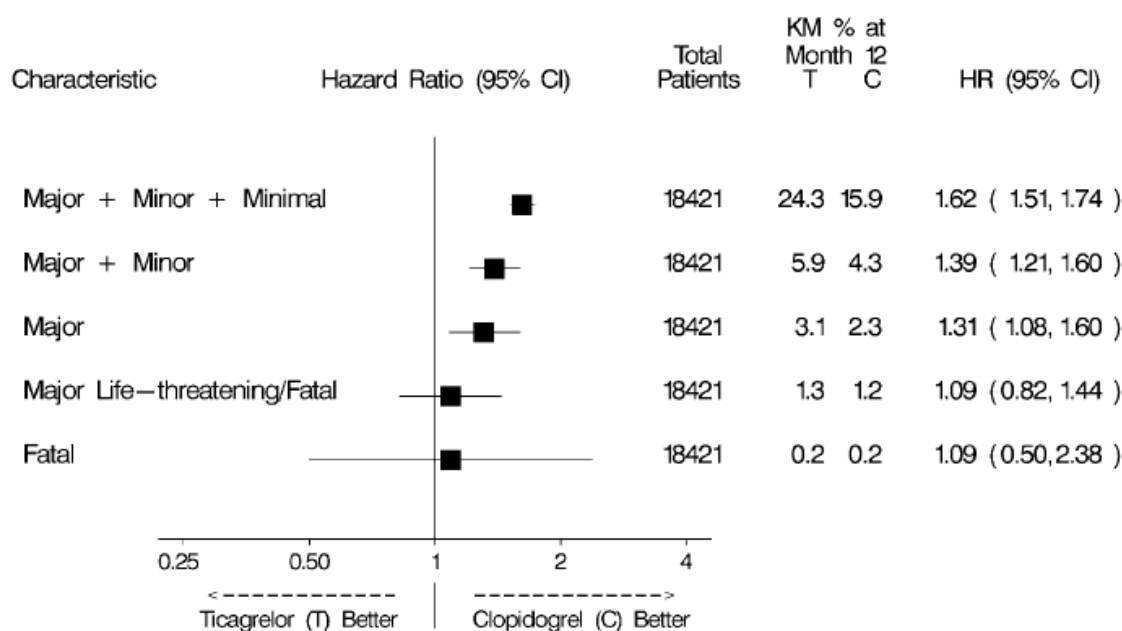
## Safety

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**



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.



### *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  $\geq 3$  seconds and  $\geq 5$  seconds compared to clopidogrel; this difference was statistically significant for ventricular pauses  $\geq 3$  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.)

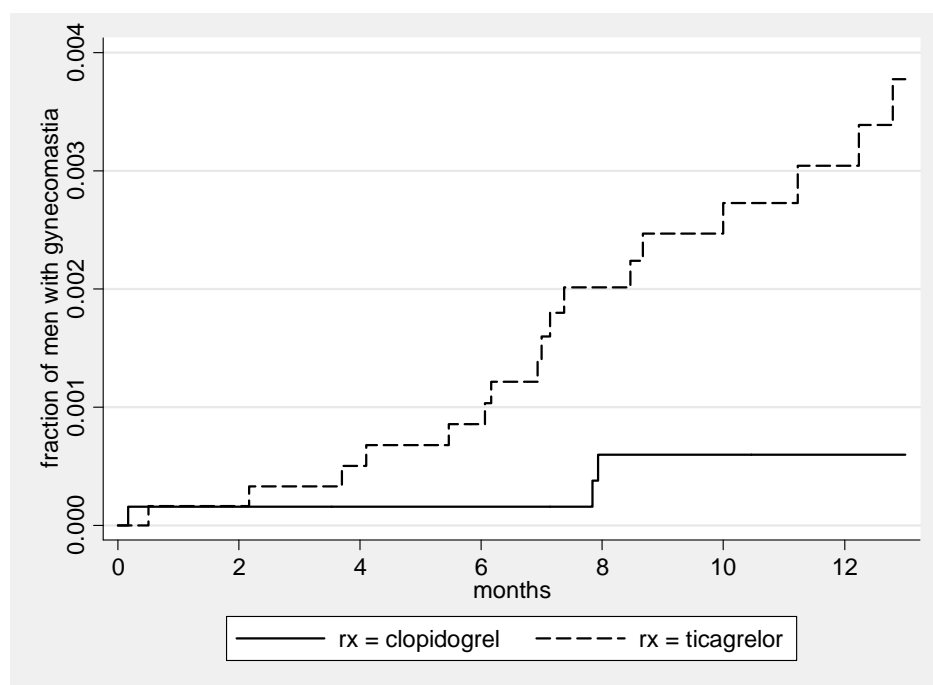
I also recoded ventricular tachycardia and ventricular fibrillation events. Both types of serious ventricular arrhythmias appear to be less frequent with ticagrelor, combined about 1.5% of ticagrelor patients and 1.8% of clopidogrel patients. Only about 13% of these arrhythmias were reported in patients 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  $\geq 10$  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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THOMAS A MARCINIAK  
06/29/2010

# CLINICAL PHARMACOLOGY REVIEW

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<b>NDA Number:</b>	022433
<b>Submission Type; Code:</b>	S
<b>Applicant Name:</b>	AstraZeneca
<b>Submission Dates:</b>	November 16 <sup>th</sup> , 2009
<b>Brand Name:</b>	Brilinta <sup>TM</sup> (proposed)
<b>Generic Name</b>	Ticagrelor
<b>Dosage Form:</b>	Immediate Release Tablets
<b>Dosage Strengths:</b>	90 mg
<b>Proposed Indication:</b>	Reduction of thrombotic events in acute coronary syndrome patients.
<b>OCP Division:</b>	DCP1
<b>Primary Reviewer:</b>	Islam R. Younis, Ph.D.
<b>Team Leader:</b>	Rajanikanth Madabushi, Ph.D.
<b>Pharmacometrics Reviewer</b>	Kevin M. Krudys, Ph.D.
<b>Pharmacometrics Team Leader</b>	Pravin R. Jadhav, Ph.D.
<b>Pharmacogenomics Reviewer</b>	Michael A. Pacanaowski, Pharm.D., M.P.H
<b>Pharmacogenomics Team Leader</b>	Issam Zineh, Pharm D., M.P.H

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## **1 EXECUTIVE SUMMARY**

Ticagrelor is a selective and reversible P2Y<sub>12</sub> ADP-receptor antagonist that is indicated to reduce the rate of thrombotic events (including stent thrombosis) for patients with acute coronary syndrome (ACS), unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction, who are to be managed medically or invasively. The proposed loading dose for ticagrelor is 180 mg and the proposed maintenance dose is 90 mg twice daily. Ticagrelor will be marketed as 90 mg immediate release tablets.

The application was first submitted to the FDA under IND 065,808 on April 28<sup>th</sup>, 2003. NDA 022433 was submitted on November 16<sup>th</sup>, 2009 and was granted a standard review status on January 15<sup>th</sup>, 2010.

A single Phase III study (PLATO) in patients with Non-ST or ST segment elevation ACS formed the basis for the submission. The primary efficacy endpoint was the time to first occurrence of any event from the composite of death from vascular causes, myocardial infarction (MI), and stroke. The primary objective of this study was to test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events.

The clinical pharmacology program of ticagrelor consisted of 43 studies that investigated the safety, tolerability, pharmacokinetics, pharmacodynamics, bioavailability, bioequivalence, food effect, drug-drug interactions, and pharmacokinetics in specific population. The population pharmacokinetics analysis was conducted in subset of patients from PLATO and the Phase II study (DISPERSEII). Pharmacogenomics analysis was performed using data from the pharmacodynamic study (RESPOND), phase II studies (DISPERSE and DISPERSE2), and PLATO.

### **1.1 Recommendations**

- The Office of Clinical Pharmacology has reviewed the submission and cannot resolve the differential effectiveness of ticagrelor in US and Non-US sites. Several factors, such as aspirin usage, statin usage, compliance, and differences in ticagrelor exposure between US and non-US sites were investigated. These factors did not satisfactorily explain the differential effectiveness. Given the overall results, the Office recommends approval of ticagrelor with a study post-approval aimed to reconcile the findings from US region.
- The Office finds the clinical pharmacology information acceptable pending on agreement of labeling changes (which will be conveyed in a separate document) and proposed post-marketing requirements and commitments.

### **1.2 Post Marketing Requirements**

- Pharmacokinetic study in subjects with moderate and severe hepatic impairment.

### 1.3 Post Marketing Commitment

- Clinical trial in patients with Non-ST or ST segment elevation ACS with at least 50% of the population from the US region. The proposed trial need not be a repetition of the PLATO study.

### 1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

#### Exposure-Response

- An exposure-response relationship could not be established for the composite efficacy endpoint of cardiovascular death, MI, and stroke in PLATO.
- A shallow relationship between ticagrelor exposure and major bleeding was established.
- A shallow relationship between ticagrelor exposure and dyspnea was established.
- An exposure-response relationship could not be established between ticagrelor exposure and occurrence of ventricular pauses  $\geq 3$  or  $\geq 5$  seconds in the Holter sub-study in PLATO.

#### Pharmacogenomics

- A series of exploratory genetic association studies assessing the influence of approximately 325 single nucleotide polymorphisms (SNPs) across 20 candidate genes (including *P2RY<sub>12</sub>* [target], *ABCB1*, and *CYP3A5*) on ticagrelor PD responses, exposure, and dyspnea revealed no compelling pharmacogenetic interactions. *CYP2C19* and *ABCB1* were genotyped in PLATO.
- 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.

#### Pharmacodynamics

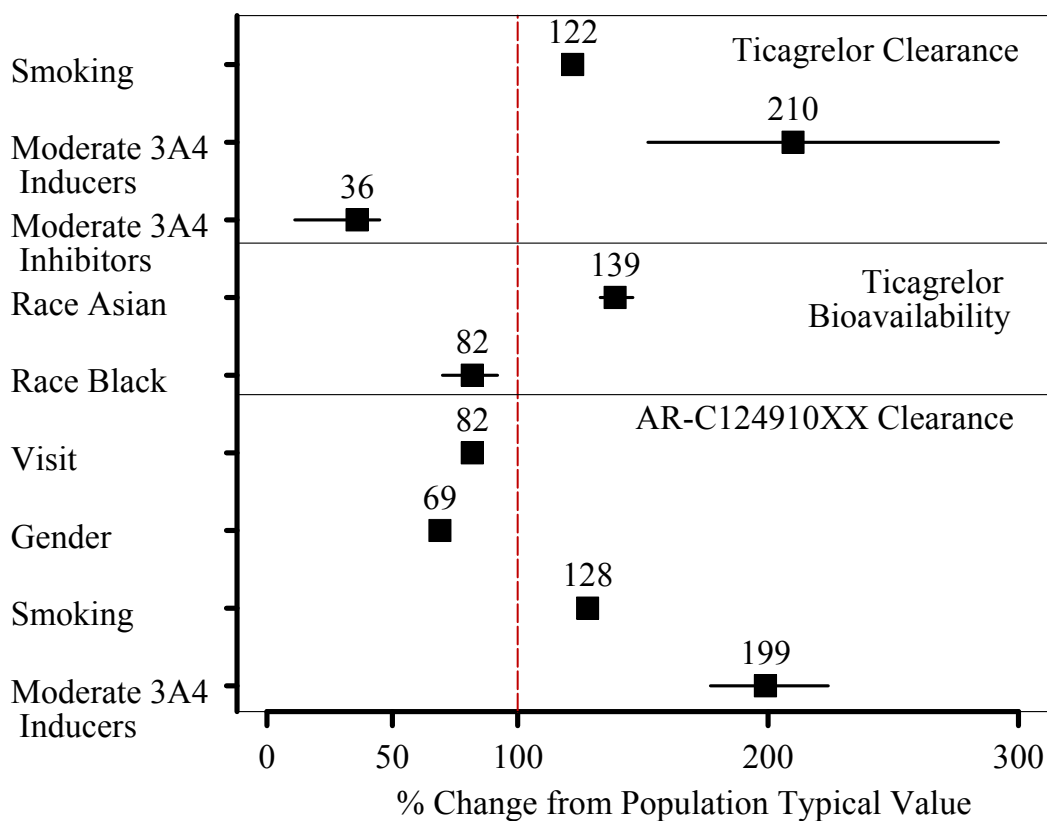
- The rate of onset of pharmacodynamic effect of ticagrelor measured by % inhibition of platelet aggregation (%IPA) is faster than that of clopidogrel in stable coronary artery disease (CAD) patients on aspirin.
- The rate of offset of pharmacodynamic effect (%IPA) of ticagrelor is faster than that in clopidogrel in CAD patients on aspirin. 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).
- 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 any changes in respiratory parameters in healthy elderly, patients with mild asthma, and patients with COPD.



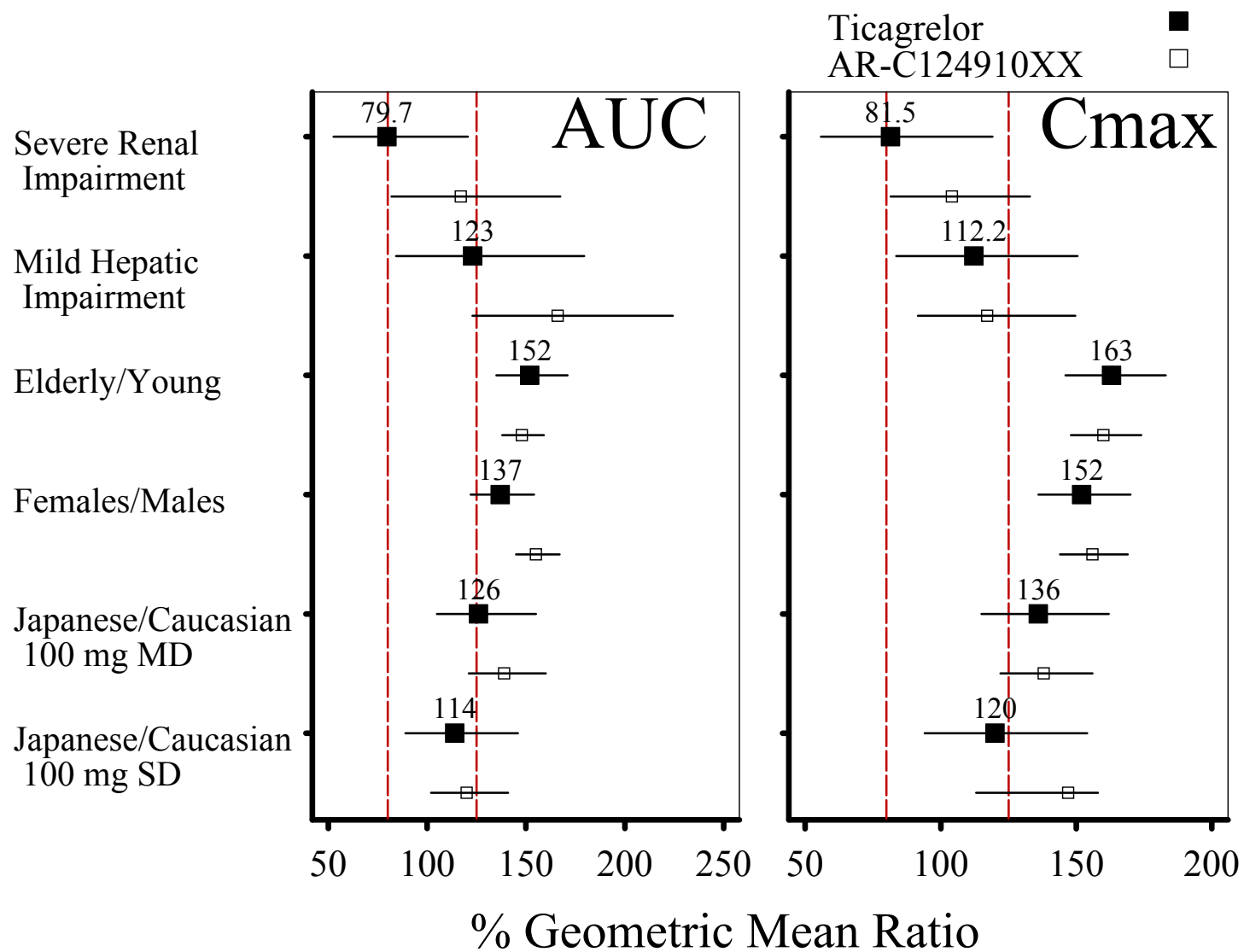
## Pharmacokinetics

- The plasma concentration of ticagrelor decline mono-exponentially
- Ticagrelor  $t_{1/2}$  is 8 h.
- Ticagrelor is rapidly absorbed with median  $T_{max}$  of 2.65 h.
- Ticagrelor is > 99% bound to plasma protein
- Ticagrelor is metabolized mainly by CYP3A4/5 to produce AR-C124910XX and AR-C133913XX.
- The major metabolite AR-C124910XX is rapidly formed with median  $T_{max}$  3.12 h. It is also equipotent as P2Y<sub>12</sub> 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 in patients with stable atherosclerotic disease.

## Population Pharmacokinetics

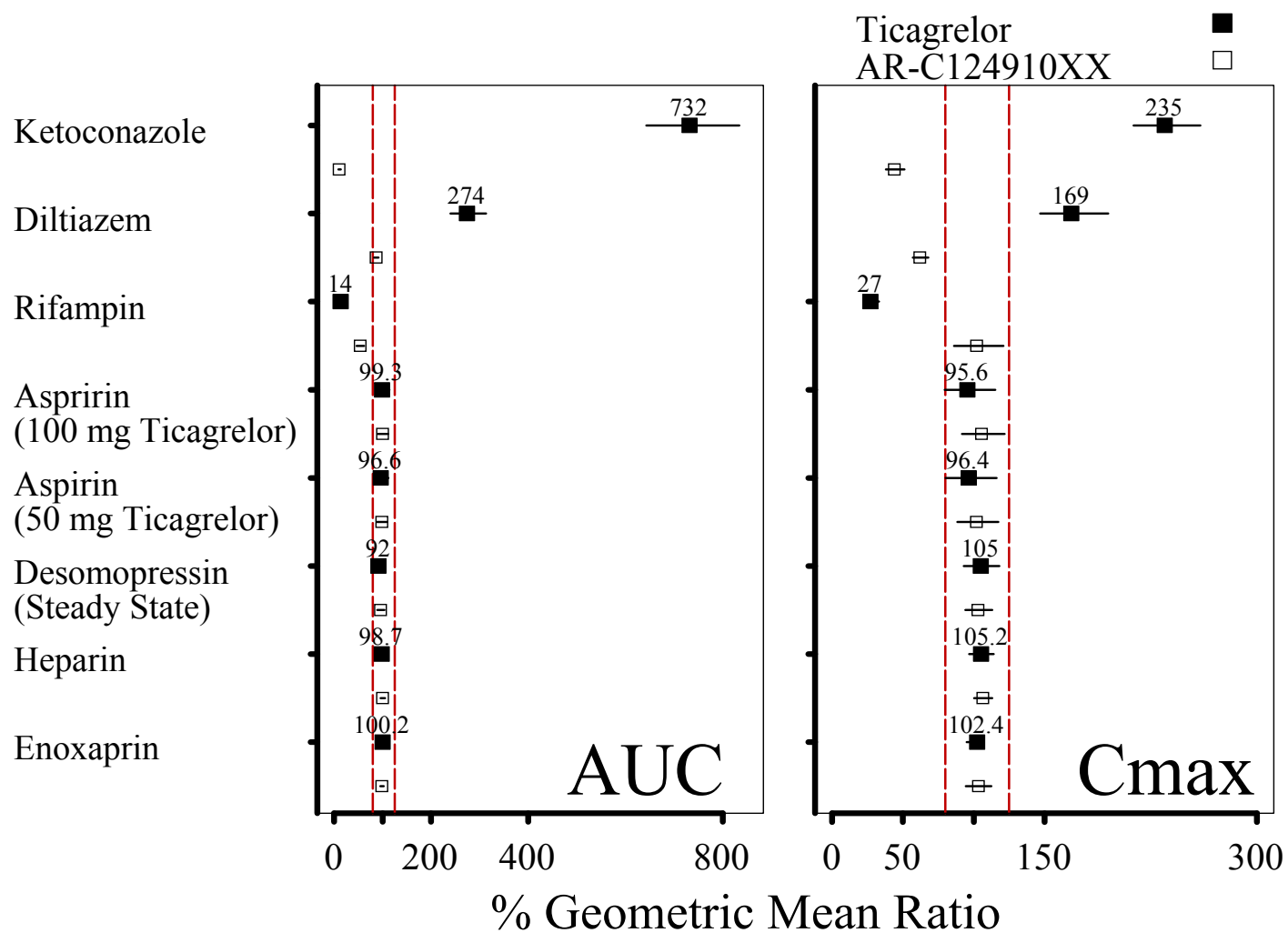


Specific population

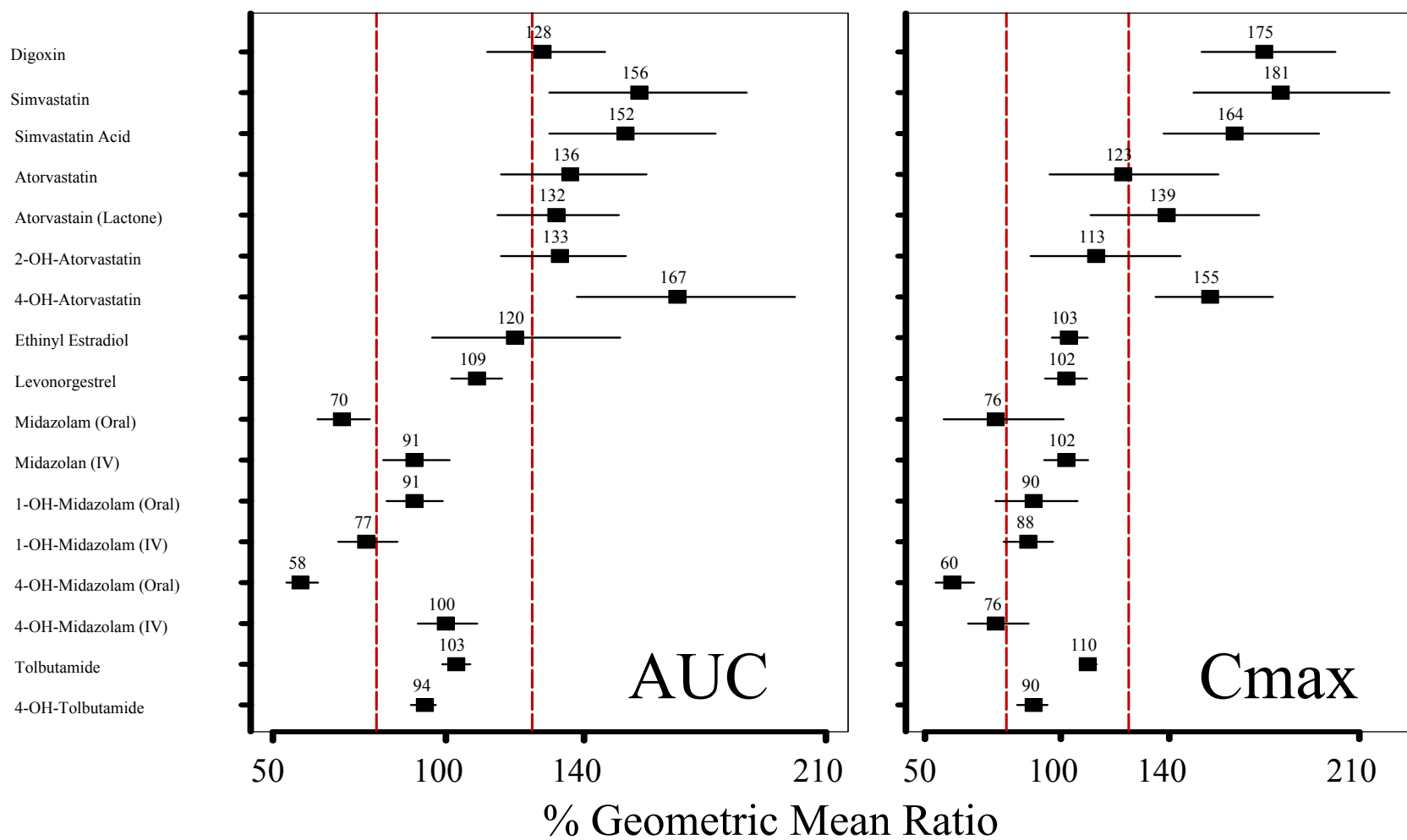


## Drug-Drug interactions

### 1. Effect of other medication on ticagrelor systemic exposure



## 2. Effect of ticagrelor on the systemic exposure of other medications



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06/17/2010

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06/17/2010

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Cc: NDA 22-332, HFD 110, HFD-860 (Younis, Mehta, Uppoor)

Clinical Pharmacology Briefing: 06/09/2010

Attendant: Lawrence Lesko, Norman Stockbridge, Stephen Grant, Shie Mei Huang, Mehul Mehta, Ramana Uppoor, Edward Bashaw, Atiqur Nam Rahman, , Chandrahas Sahajwalla, Elena Mishina, Padmaja Mummaneni , Ping Zhao, Nancy Hu, Divya Menon-Andersen, Darell Abernethy, Lin Zhou, Huixia Zhang, Sayed Al Habet, Jiang Liu, Xinning Yang, Bei Yu, Peter Hinderling, Ju-Ping Lai, Manoj Khurana, Michael Monteleone, Ritesh Jain, Immo Zdrojewski, Zhihong Li, Chinmay Shukla, Christian Grimstein, Suresh Naraharisetti, Arun Agrawal, Partha Roy, Liang Zhao, Sheetal Agarwal, Yoriko Harigaya, Frederico Goodsaid, Lokesh Jain, Sudharshan Hariharan, Rajnikanth Madabushi, Kevin Krudys, Michael Pacanowski, Robert Fiorentino, and Islam Younis.



**Drug Product:** Ticagrelor immediate release tablets are presented as round, biconvex, yellow film-coated containing 90 mg of ticagrelor. The tablets are marked with ‘90’ above ‘T’ on 1 side, and plain on the other. The proposed initial shelf life is 24 months without any special storage conditions. Table 2 displays the composition of ticagrelor tablets.

**Table 2.** Composition of ticagrelor tablets.

Component	Quantity	Function	Standard
<b>Tablet core:</b>			
Ticagrelor	90	Active	AstraZeneca
Mannitol	(b)	(b) (4)	USP
Dibasic calcium	(b)	(b) (4)	USP
Sodium starch	( )	(b) (6)	NF
Hydroxypropyl	( )	(b) (6)	NF
Magnesium stearate	( )	(b) (6) <sub>t</sub>	NF
Purified water	qs	(b) (6)	USP
Core tablet weight	(b) (6)		
<b>Tablet coating</b>			
Hypromellose	(b)	(b) (6)	USP
Titanium dioxide	(b)	(b) (6)	USP
Talc	(b)	(b) (6)	USP
Polyethylene glycol	(b)	(b) (6)	NF
Ferric oxide yellow	(b)	(b) (6)	NF
Purified water	(b) qs	(b) (6) <sub>t</sub>	USP

### 2.1.2 What are the proposed mechanism of action and therapeutic indications?

**Mechanism of Action:** reversible P2Y<sub>12</sub> ADP-receptor antagonist

**Proposed Indication:** Reduce the rate of thrombotic events (including stent thrombosis) for patients with acute coronary syndrome (ACS), unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction, who are to be:

1. Managed medically
2. Managed invasively with percutaneous coronary intervention (with or without stent) and/or coronary artery bypass graft (CABG).

### 2.1.3 What are the proposed dosages and routes of administration?

Ticagrelor drug product is immediate release tablet (90 mg ticagrelor) for oral administration. The proposed loading dose is 180 mg and the proposed maintenance dose is 90 mg BID.

## **2.2 General Clinical Pharmacology**

### **2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?**

Ticagrelor clinical pharmacology and clinical development program consisted of the following studies (number in parentheses represents the number of studies):

- I. Phase I (31) (Healthy Volunteers):
  1. Pharmacokinetics (5): Single Dose, Multiple Dose, and Mass Balance.
  2. Specific population (5): Renal Impairment, Mild Hepatic Impairment, Age/Gender, Race Chinese, and Race Japanese
  3. Biopharmaceutics (9): Bioavailability, Bioequivalence, and Food Effect.
  4. Drug-Drug Interactions (13): Desmopressin, Ketoconazole, Diltiazem, Rifampin, ASA, Heparin, Enoxaparin, Simvastatin, Digoxin, Atorvastatin, Oral Contraceptive, Tolbutamide, Midazolam
- II. Phase II (2)
  1. DISPERSE: Dose finding study in patients with documented atherosclerotic disease.
  2. DISPERSEII: Dose confirming study in patients with non-ST segment elevation ACS.
- III. Phase III (1): PLATO [A Study of PLATelet inhibition and Patient Outcomes]: A randomized, double-blind, parallel group, multi-center, efficacy and safety study to evaluate the superiority of ticagrelor (90 mg BID) to clopidogrel (75 mg QD) for prevention of vascular events in patients with Non-ST or ST elevation ACS. The duration of the study was 6, 9, or 12 month depending on the entry date. The primary efficacy endpoint was time from randomization to first occurrence of death from vascular causes (CV death), MI excluding silent MIs, and stroke. The primary safety endpoint was time from first dose of study drug to first occurrence of any total major bleeding event.
- IV. Pharmacodynamics (8):
  1. Study to compare the onset and offset of ticagrelor to that of clopidogrel in patients with stable coronary artery disease.
  2. RESPOND: Study in patients with stable coronary artery disease to compare platelet aggregation after switching from clopidogrel to ticagrelor and vice versa in clopidogrel responders and non-responders.
  3. Study in healthy volunteers to compare platelet aggregation following loading doses of ticagrelor and clopidogrel.
  4. Study in healthy male volunteers to evaluate the effect of ticagrelor on uric acid.
  5. Thorough QT
  6. Two studies to evaluate the effect of ticagrelor on respiratory parameters, one in elderly healthy subjects and the other in subjects with mild asthma or COPD.



7. Study in healthy volunteers to evaluate platelet aggregation of ticagrelor relative to clopidogrel.

Population pharmacokinetic analysis was performed using data from DISPERSEII and PLATO. Exposure-response (safety and efficacy) analysis was performed using data from PLATO.

Pharmacogenomics analysis was performed using data from DISPERSE, DISPERSE2, RESPOND, and PLATO.

## 2.2.2 What are the evidences of efficacy provided by the sponsor in support of the application?

The results of PLATO, the pivotal clinical trial, are presented in Table 3.

**Table 3.** PLATO primary efficacy analysis.

Event	Ticagrelor 90 mg BID N = 9333	Clopidogrel 75 mg QD N = 9291	Hazard Ratio (95% CI)	p-value
	Patients with Events	Patients with Events		
Primary Endpoint	864 (9.3%)	1014 (10.9%)	0.84 (0.77, 0.92)	0.0003
MI	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)	0.2249

### **2.2.3 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?**

The primary pharmacodynamic endpoint is ADP (20 µM) induced percent inhibition of platelet aggregation (%IPA) (Final Extent). %IPA is calculated as follows:

$$\% \text{ IPA} = \frac{\text{PA}_{\text{pre-dose}} - \text{PA}_{\text{post-dose}}}{\text{PA}_{\text{pre-dose}}}$$

Where PA is platelet aggregation measured by light transmittance aggregometry. Throughout the clinical pharmacology program PA was measured following induction using 5 µM ADP, 20 µM ADP, and 2 µg/mL collagen at final and maximum extent. PA induced by 20 µM ADP was used as the primary source for pharmacodynamic comparisons.

% IPA is widely used and accepted pharmacodynamic endpoint to evaluate platelet aggregation.

### **2.2.4 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

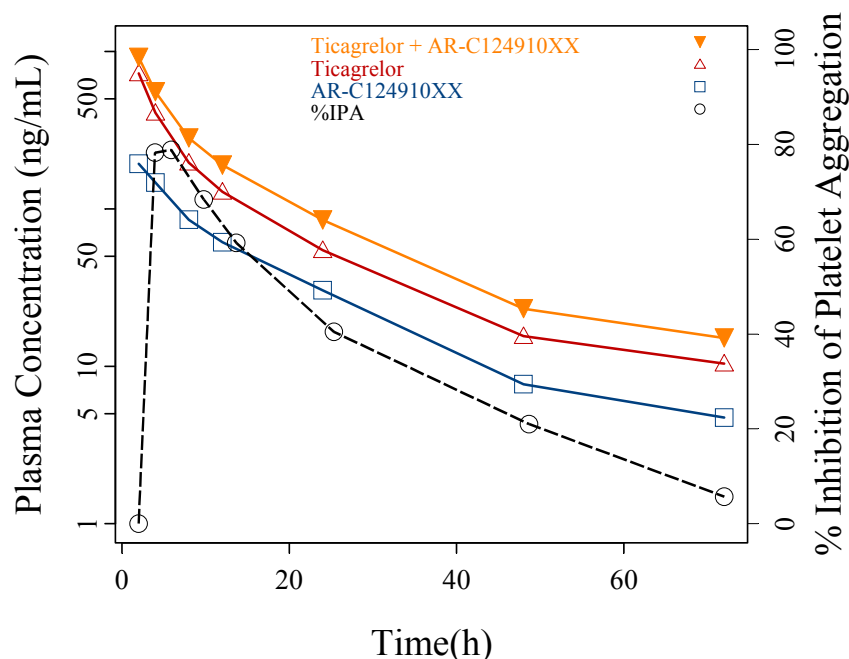
- Both ticagrelor and the active metabolite (AR-C124910XX) were appropriately identified using liquid chromatography and tandem mass spectrometry (LC-MS/MS).
- AR-C133913XX: (the other metabolite) which is 100 fold less active than ticagrelor) was quantified using an LC-MS/MS in one single dose PK study in healthy volunteers.

### **2.2.5 Exposure-Response**

#### **2.2.5.1 What are the characteristics of the exposure-response relationships for efficacy?**

An exposure-response relationship could not be established for the composite efficacy endpoint of cardiovascular death, MI, and stroke in PLATO. This is most likely due to the fact that only one dose (90 mg BID) was studied and the number of events was relatively small.

Following the administration of ticagrelor, maximum %IPA is observed 2 – 4 h post-dose and tapers off as ticagrelor and AR-124910XX plasma concentration declines, as shown in Figure 2. This observation depicts the reversibility of action of ticagrelor as P2Y<sub>12</sub> inhibitor.



**Figure 2.** Ticagrelor mean pharmacokinetics and pharmacodynamics time profile following the administration of a single 90 mg dose in healthy volunteers.

#### 2.2.5.2 Is there evidence of efficacy in the US population?

The evidence of efficacy in the US population is equivocal. It should be noted that PLATO study was not designed specifically to show evidence of efficacy compared to clopidogrel in the US only.

- The hazard ratio for the primary efficacy endpoint within the USA was 1.27 (95% CI 0.92, 1.75) compared to 0.81 (95% CI 0.74, 0.90) for the non-USA region, suggesting a benefit of clopidogrel over ticagrelor in the USA.
- Several potential explanatory factors were explored, including: compliance, statin exposure, low ticagrelor exposure, chance finding, and a fructose-hyperuricemia relationship. None of these factors satisfactorily explained the observed benefit of clopidogrel over ticagrelor in the USA.
- In the sponsor's multivariate analysis, aspirin dose explained the largest treatment-by region effect, although aspirin dose was highly unbalanced, with most high-dose aspirin use (>300 mg) occurring in the USA. Furthermore, there are no pharmacokinetic or pharmacodynamic interactions that would predict an undesired effect at high aspirin doses.

#### 2.2.5.3 What are the characteristics of the exposure-response relationships for safety?

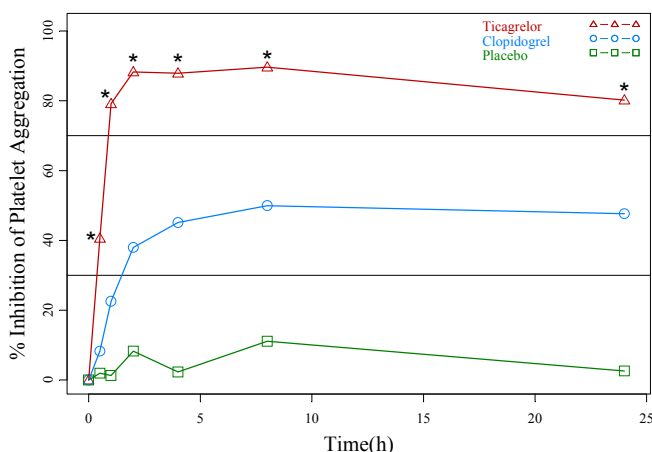
**Major Bleeding:** A shallow relationship between ticagrelor exposure and major bleeding was established. Given the 10-90<sup>th</sup> percentiles of total exposure in PLATO at Visit 1 in a patient 62 years of age, the probability of major bleeding was 2.8-3.2% (without coronary artery by-pass grafting (CABG) or percutaneous coronary intervention (PCI)), 58-63% (with CABG) and 0.6% (with PCI).

**Dyspnea:** A shallow relationship between ticagrelor exposure and dyspnea was established. The predicted probability of having a dyspnea event (mild, moderate or severe) given the 10-90<sup>th</sup> percentile of ticagrelor exposure at Visit 1 was 2.2-2.8% in a patient with no risk factors.

**Ventricular Pauses:** A positive exposure-response relationship could not be established between ticagrelor exposure and occurrence of ventricular pauses  $\geq 3$  or  $\geq 5$  seconds in the Holter sub-study in PLATO.

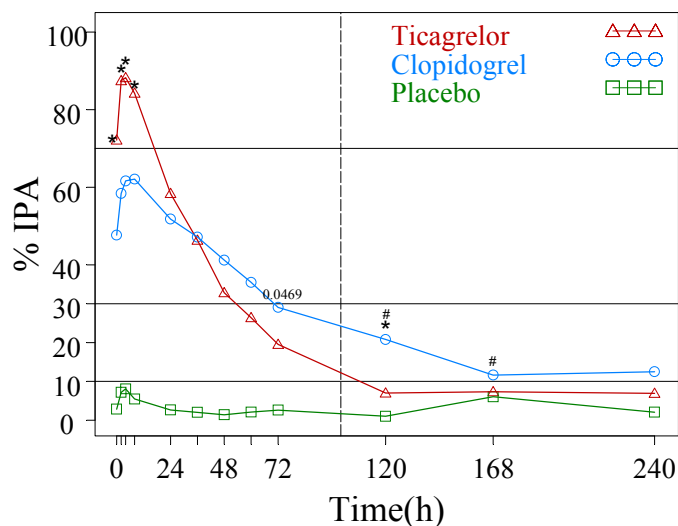
#### 2.2.5.4 What is the onset and offset of ticagrelor compared to clopidogrel?

**Onset:** In patients with stable coronary artery disease, onset of action (measured by 20  $\mu$ M ADP induced %IPA) is faster following the administration of 180 mg loading dose of ticagrelor compared to a 600 mg loading dose of clopidogrel (Figure 2)



**Figure 3.** %IPA (Final Extent) induced by 20  $\mu$ M ADP following the administration of ticagrelor, clopidogrel, and placebo on ASA background. Values represent mean. \* indicates significant difference ( $p < 0.0001$ ) using Wilcoxon sum rank test.

**Offset:** The rate of offset of effect (measured by 20  $\mu$ M ADP induced %IPA) in patients with stable coronary artery disease, after six weeks of ticagrelor twice daily administration of 90 mg is faster compared to the once daily administration of 75 mg clopidogrel (Figure 3).



**Figure 4.** %IPA induced by 20  $\mu$ M ADP following the administration of the last dose of ticagrelor, clopidogrel, and placebo on ASA background. Values represent mean. \* indicates significant difference ( $p < 0.05$ ) comparing ticagrelor to clopidogrel. Points in the ticagrelor and clopidogrel groups left to the dashed lines are significantly different from placebo ( $p < 0.05$ ). Points to the right of the dashed lines are not significantly different from placebo unless designated by #.

#### 2.2.5.5 What is the effect of switching between clopidogrel and ticagrelor?

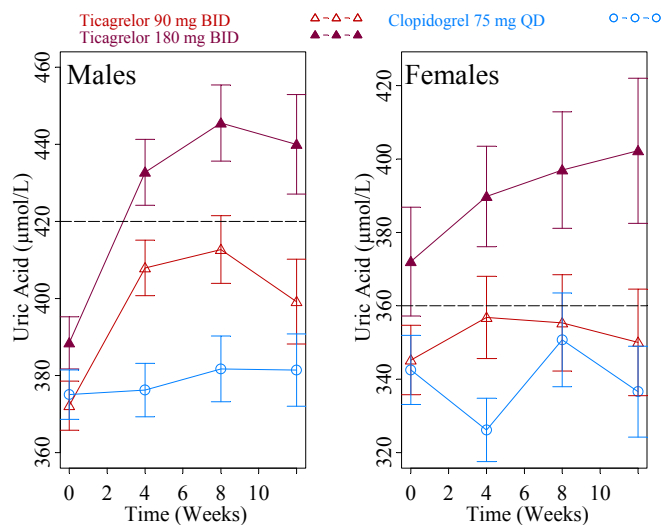
In patients with stable coronary artery disease with  $\leq 10\%$  absolute change in platelet aggregation in response to a single 300 mg oral dose of clopidogrel (arbitrarily defined non-responders by the sponsor), switching from clopidogrel 75 mg QD to ticagrelor 90 mg BID or vice versa resulted in 34.5 units absolute change in %IPA (4 h post-dose) at steady state.

In responders switching from clopidogrel to ticagrelor resulted in 16.8 units absolute increase in %IPA at steady state (4 h post-dose), while switching from ticagrelor to clopidogrel results in 29.4 units absolute decrease.

#### 2.2.5.6 What is the effect of ticagrelor on uric acid?

In a cross-over study in male healthy volunteers and following the administration of twice daily 90 mg ticagrelor for 5 days, ticagrelor produced a statically significant 10% increase serum uric acid concentrations relative to placebo

Similar mild increases were observed in patients with acute coronary artery disease (DISPERSEII and PLATO). Ticagrelor produced a dose dependant increase in serum uric acid (Figure 4).



**Figure 5.** Serum uric acid concentration following the administration of ticagrelor (180 mg and 90 mg BID) and clopidogrel (75 mg QD) in DISPERSEII. Values represent mean and error bars represent standard error of the mean. Dashed lines represents the threshold for hyperuricemia, 420 µmol/L for males and 360 µmol/L for females.

#### 2.2.5.7 What is the effect of ticagrelor on respiratory parameters?

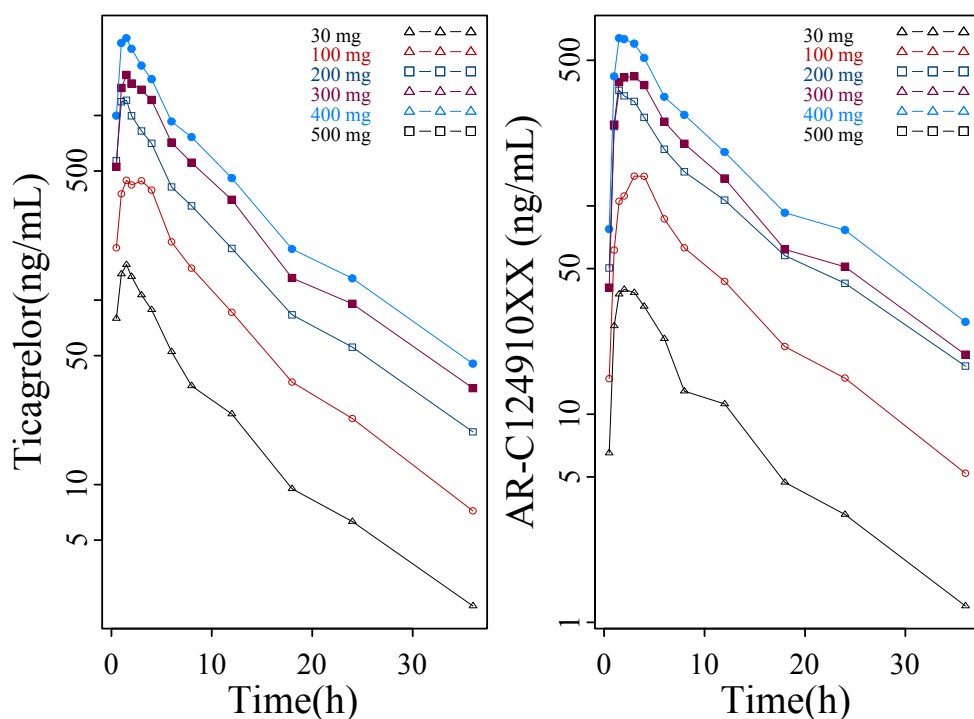
Dyspnea caused by ticagrelor is not attributed to changes in respiratory parameters. The administration of ticagrelor, 450 mg loading dose + 180 mg BID for 4 days, in healthy elderly, patients with mild asthma, and patients with mild COPD:

- did not affect respiratory rate, minute ventilation, or tidal volume.
- did not cause bronchospasm as assessed by spirometry.
- had no effect on exercise performance, caused no worsening in sensation of breathing or change in perception of breathlessness as measured by the Modified Borg Scale and Bidirectional Dyspnea Index, and had no effect on pulse oximetry.

#### 2.2.6 What are the PK characteristics of the drug?

##### 2.2.6.1 What are the single and multiple dose PK parameters?

**Single Dose (Healthy Volunteers):** Ticagrelor pharmacokinetics was evaluated in the dose range 3.0 to 1260 mg in 3 single ascending dose studies in healthy volunteers. The plasma concentrations of ticagrelor and AR-C124910XX decline mono-exponentially (Figure 5) with a half-life of ~ 8 and 9 h, respectively. Pharmacokinetic parameters following single dose (30 – 400 mg) are displayed in Table 4. The average between subject variability is ~ 34%.



**Figure 5.** Ticagrelor and AR-C124910XX mean plasma concentration vs. time profile following the administration of a single dose of ticagrelor in healthy volunteers.

**Table 4.** Ticagrelor PK and AR-C124910XX PK parameters following a 30 – 400 mg single oral dose

Ticagrelor Pharmacokinetic Parameters , Mean (%CV)						
Dose (mg)	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h) Median (range)	AUC (ng h/mL)	t <sub>1/2</sub> (h)	CL/F (mL/min/kg)
30	7	161 (20.5)	1.5 (1-2)	1005 (14.3)	7.77 (13.0)	6.72 (17.7)
100	9	586 ( 28.8)	1.5 (1-4.1)	3683 (20.4)	7.30 (18.9)	6.52 (22.4)
200	8	1295 (32.2)	1.49 (1-3)	8213 (25.7)	8.09 (14.1)	5.71 (24.0)
300	8	1746 (18.2)	1.5(1-3.05)	13170 (22.6)	7.57 (14.0)	5.31 (23.5)
400	7	2711 (21.0)	1.5 (1-2)	18547 (23.8)	7.88 (13.2)	5.03 (25.8)
AR-C124910XX Pharmacokinetic Parameters , Mean (%CV)						
Dose (mg)	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h) Median (range)	AUC (ng h/mL)	t <sub>1/2</sub> (h)	CL/F (mL/min/kg)
30	7	42.1 (31.7)	2.0 (1.03-3)	376 (26.1)	9.39 (22.5)	18.25 (15.5)
100	9	166 (27.2)	3.0(1.5-4.1)	1460 (27.9)	8.63 (19.9)	16.71 (21.8)
200	8	367 (34.9)	1.5(1.5-3)	3722 (44.8)	10.05 (17.7)	13.10 (23.9)
300	8	462 (32.2)	2.49 (1.5-4)	4611 (25.4)	8.54 (17.3)	14.99 (16.7)
400	7	713 (21.8)	1.97 (1.47-3)	6577 (32.3)	8.77 (15.1)	14.13 (18.2)

**Multiple Doses (Healthy Volunteers):** Ticagrelor steady state was achieved within 2-3 days following multiple once daily (QD) and twice daily (BID) doses. Table 5 displays ticagrelor and AR-C124910XX PK parameters following multiple doses. On average, the between subject variability was ~ 35%. **Table 5.** Ticagrelor and AR-C124910XX PK parameters following multiple doses.

	Treatment	N	AUC $\tau$		C $_{\max}$		T $_{\max}$		CL/F	
			(ng h/mL)		(ng/mL)		(h)		(L/h)	
			Mean	%CV	Mean	%CV	Median	Range	Mean	%CV
Ticagrelor										
QD	50mg	7	1961	30.7	233	34.9	3	2-4	43.59	34.8
	100mg	7	4585	36.3	609	43.3	2.71	1.5-4	41.9	46.0
	200mg	14	8648	43.3	1109	39.1	2.43	1.5-4	46.58	46.6
	300mg	7	11066	32.1	1384	22.6	1.71	1.5-2	49.02	29.5
	400mg	6	15342	23.4	1873	12.0	1.58	1-2	45.81	27.2
	600mg	6	25111	30.4	3072	27.3	2	1-3	43.42	34.2
BID	50mg	14	1771	33.2	264	34.5	2.82	1-4	54.03	35.1
	100mg	13	4455	44.9	687	48.7	2.69	1-6	44.14	43.3
	200mg	13	9781	25.3	1487	26.1	2.62	1.5-4	37.97	35.6
	300mg	7	15754	46.7	2263	56.9	3.14	2-4	41.97	47.9
AR-C124910XX										
QD	50mg	7	799	46.6	77	48.1	4	3-6		
	100mg	7	2026	44.5	189	54.8	3.43	2-4		
	200mg	14	3371	50.1	319	45.7	3.01	2-4.12		
	300mg	7	4061	27.6	377	31.5	1.93	1.5-3		
	400mg	6	5792	30.6	513	14.7	2.33	2-3		
	600mg	6	9376	32.7	819	27.9	2.42	1.5-3		
BID	50mg	NA	NA	NA	NA	NA	NA	NA		
	100mg	14	666	34.8	84	30.1	3.25	1.5-6		
	200mg	13	1894	59.5	247	61.7	3.12	1.5-6		
	300mg	13	4152	61.9	514	55.7	3.19	1.5-6		
$\tau$ = 24 h for QD and 12 h for BID, NA: not available										



#### **2.2.6.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?**

At a 100 mg BID dose (which is bioequivalent to the 90 mg IR tablet) AUC and  $C_{\max}$  are ~ 17% lower on average in patients with documented atherosclerotic disease compared to healthy volunteers. The between subject variability in patients with documented atherosclerotic disease was ~ 50%.

#### **2.2.6.3 What are the characteristics of drug absorption?**

Ticagrelor is rapidly absorbed with a median  $T_{\max}$  of 2.65 h. *In vitro*, ticagrelor and AR-C124910XX are substrates for P-glycoprotein and a moderate inhibitors of P-gp mediated digoxin transport.

#### **2.2.6.4 What are the characteristics of drug distribution?**

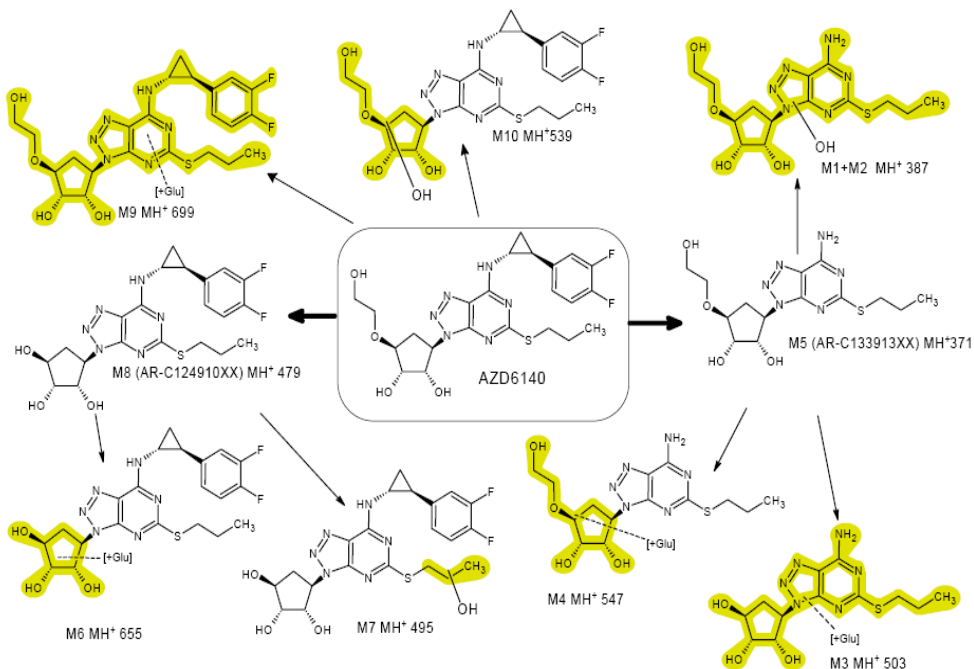
Ticagrelor and AR-C124910XX are more than 99% bound to plasma proteins.

#### **2.2.6.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

- Ticagrelor is extensively metabolized and less than 1% of the ticagrelor dose is excreted unchanged in the urine.
- AR-C124910XX appears to be the major metabolite of ticagrelor and together with the parent accounted for ~ 90% of the plasma radioactivity.

#### **2.2.6.6 What are the characteristics of drug metabolism?**

- Ticagrelor is rapidly and extensively metabolized by CYP3A4/5.
- The majority of ticagrelor metabolism is oxidative and the main metabolites are AR-C124910XX (loss of the hydroxy-ethyl side chain) and AR-C133913XX (loss of the difluorophenyl-cyclopropyl group).
- The major metabolite AR-C124910XX is rapidly formed with median  $T_{\max}$  3.12 h. It is also equipotent as  $P_2Y_{12}$  inhibitor as ticagrelor and metabolized by CYP3A4/5. AR-C124910XX to ticagrelor ratio is 36% – 52%.
- AR-C133913XX (inactive metabolite) to ticagrelor ratio is 12%.



**Figure 6.** Ticagrelor proposed metabolic route.

#### 2.2.6.7 What are the characteristics of drug elimination?

Ticagrelor is converted into two major metabolites that are in turn either undergoes glucuronidation or further oxidation prior to excretion. Glucuronides of ticagrelor were also identified.

#### 2.2.6.8 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

In the dose range 30 mg – 400 mg in healthy volunteers, ticagrelor and AR-C124910XX pharmacokinetics is slightly more than dose proportional (Table 6).

**Table 6.** Ticagrelor and AR-C124910XX pharmacokinetics dose proportionality.

	Parameter	Dose Proportionality(95% CI)
Ticagrelor	AUC (ng.h/mL)	1.11 (1.07, 1.15)
	C <sub>max</sub> (ng/mL)	1.07 (0.99, 1.14)
AR-C124910XX	AUC (ng.h/mL)	1.10 (1.06, 1.15)
	C <sub>max</sub> (ng/mL)	1.07 (1.0, 1.14)

In patients with atherosclerosis (DISPERSE) ticagrelor and AR-C124910XX  $C_{\max}$  and AUC increased dose proportionally at doses 50, 100, 200 mg BID and 400 mg QD following the first dose of ticagrelor. At steady state, both  $C_{\max}$  and AUC increased dose proportional between the 50 and 100 mg BID dose and approximately 50% more than dose proportional for the 200 BID and 400 mg QD.

## **2.3 Intrinsic Factors**

### **2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**

Race, age, gender, severe renal impairment, and mild hepatic impairment alter ticagrelor systemic exposure as described below.

### **2.3.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments are recommended for each group?**

#### **2.3.2.1 Elderly**

Ticagrelor AUC and  $C_{\max}$  were 52% and 63% significantly higher in elderly ( $\geq 65$  years old) males and females subjects compared to young subjects following a single 200 mg oral dose. However, this does not require ticagrelor dose adjustment.

#### **2.3.2.2 Pediatric Patients**

Ticagrelor was not evaluated in pediatric patients.

#### **2.3.2.3 Race**

##### **Japanese:**

- Ticagrelor systemic exposure is significantly 20% higher (by median  $\sim 20\%$ ) in healthy Japanese compared to healthy Caucasian following the administration of a single oral dose (50 - 600 mg).
- Ticagrelor systemic exposure is 20% higher in healthy Japanese males compared to healthy Caucasian males following multiple oral twice daily 100 mg doses for 7 day.

**Asian:** In population PK analysis of DIPSERSEII and PLATO, Asian patients had 39% (95% CI 33% - 46%) higher ticagrelor bioavailability compared to Caucasian.

**African American:** In population PK analysis of DIPSERSEII and PLATO, patients self identified as black in had a 19% lower (95% CI 6%-28%) bioavailability compared to Caucasians.

There is no need to adjust ticagrelor dose based on race.

#### **2.3.2.4 Renal Impairment**

- In subjects with sever renal impairment, relative to subjects with normal renal function, following a 180 mg single oral dose of ticagrelor:
  1. Ticagrelor AUC and  $C_{max}$  were significantly lower by 20% and 18.5%, respectively.
  2. AR-C124910XX AUC and  $C_{max}$  were significantly higher by 17.1% and 4.1%, respectively.
- There was no relationship between creatinine clearance and ticagrelor or AR-C124910XX systemic exposure.
- Ticagrelor unbound fraction was < 1% in subjects with normal renal function and subjects with severe renal impairment.
- There is no need to adjust ticagrelor dose in patients with severe renal impairment.

#### **2.3.2.5 Hepatic Impairment**

- In subjects with mild hepatic impairment, relative to subjects with normal liver function, following a 90 mg single oral dose:
  1. Ticagrelor AUC and  $C_{max}$  were significantly higher by 23% and 12%, respectively.
  2. AR-C124910XX AUC and  $C_{max}$  were significantly higher by 66% and 17%, respectively.
- Ticagrelor and AR-C124910XX unbound fraction to plasma protein is <1% in subjects with mild hepatic impairment and subjects with normal renal function.
- There is no need to adjust ticagrelor dose in patients with mild hepatic impairment.

#### **2.3.2.6 Gender**

Ticagrelor AUC and  $C_{max}$  were 37% and 52% significantly higher in female subjects compared to male subjects following a single 200 mg oral dose. However, this does not require ticagrelor dose adjustment.

#### **2.3.2.7 Genetics**

The applicant submitted a series of exploratory candidate gene association studies for 1) ticagrelor antiplatelet responses and pharmacokinetics, 2) dyspnea, and 3) clinical outcomes in

the PLATO trial. DNA was collected on a voluntary basis from subjects participating in DISPERSE (90%), DISPERSE2 (78%), RESPOND (72%), and PLATO (56%). Subjects were genotyped for approximately 325 single nucleotide polymorphisms (SNPs) across 20 candidate genes. SNPs were selected on the basis of putative functionality or haplotype-tagging properties. The main findings of the applicant's pharmacogenetic (PG) investigations are summarized below. Please see the appended Genomics Group review for additional details.

**PK/PD:**

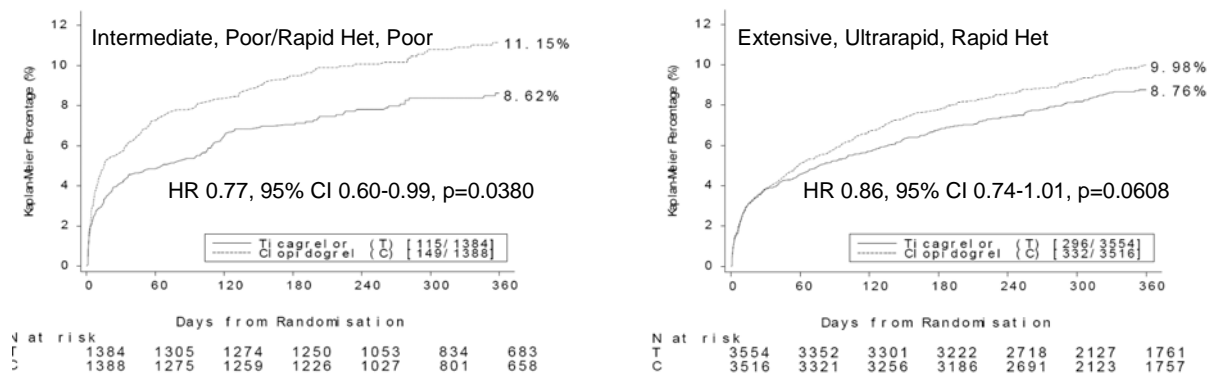
- SNPs in ticagrelor's target, *P2RY12*, or the principal mediators of ticagrelor disposition, *ABCB1* and *CYP3A5*, did not appear to significantly influence antiplatelet responses (maximal or final ADP-mediated platelet aggregation) or ticagrelor exposure after 4 weeks of treatment in DISPERSE and DISPERSE2.
- Other polymorphisms that broadly characterize the genetic diversity of *P2RY1*, *ITGA2*, *ITGB3*, which encode platelet receptors and glycoproteins, also did not influence antiplatelet responses.
- None of these polymorphisms have consistently been shown to modulate responses to other *P2RY12* antagonists such as clopidogrel.

**Dyspnea:**

- Case-control analysis of dyspnea (89 ticagrelor-treated cases, 544 controls) in DISPERSE and DISPERSE2 focused primarily on SNPs in adenosine receptors and transporters (97 SNPs in 11 genes), but did not reveal any robust PG associations with dyspnea status. These findings do not necessarily refute the adenosine hypothesis.
- SNPs in *PLA2G7* and *PON1*, mediators of lipid oxidation and inflammation, demonstrated nominal associations with dyspnea (odds ratios for variant homozygotes were 0.27 [P=0.004] and 3.23 [P=0.04], respectively). These findings are exploratory in nature and would need to be replicated or supported by additional experimental evidence.
- SNPs in the PK or PD candidate genes, *ABCB1*, *CYP3A5*, *P2RY12*, *P2RY1*, *ITGA2*, and *ITGB3*, were also not associated with dyspnea.

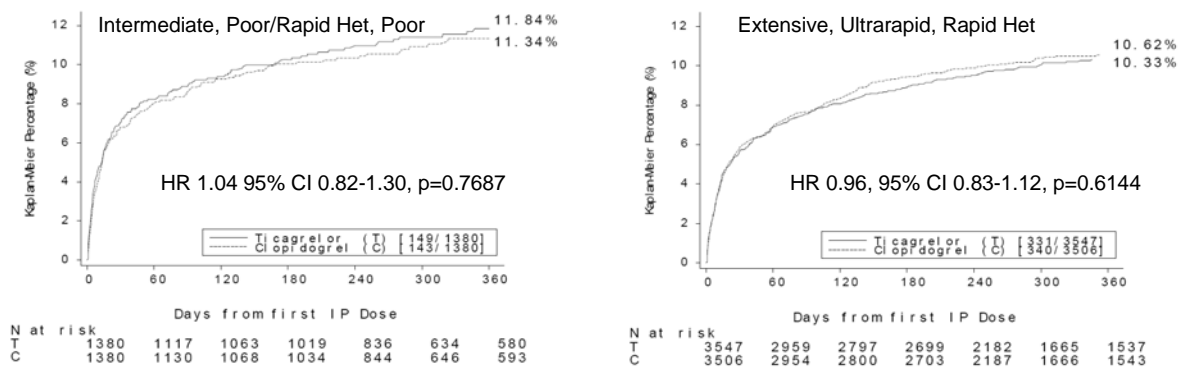
**Outcomes:**

- Numerically higher event rates were observed in clopidogrel-treated patients with one or more *CYP2C19* loss-of-function alleles, particularly for death and stent thrombosis. Treatment differences tended to be greater, in favor of ticagrelor, in this population.



**Figure 7.** Primary efficacy endpoint (death, myocardial infarction, stroke composite) by CYP2C19 genotype-predicted phenotype (full sub-study population; source: PLATO Genetics Sub-study Report, pages 25, 26)

- Bleeding rates were comparable between ticagrelor and clopidogrel, irrespective of *CYP2C19* genotype. No relative excess of bleeding was noted for ticagrelor in intermediate/poor metabolizers, or for clopidogrel in ultrarapid *CYP2C19* metabolizers.



**Figure 8.** PLATO 'total major' bleeding by CYP2C19 genotype-predicted phenotype (safety population; source: PLATO Genetics Substudy Report, page 35)

- Factors such as timing of sample collection, proton pump inhibitor use, and stent implantation did not alter the magnitude of *CYP2C19* genetic effects on clopidogrel.
- *CYP2C19* genotype distribution did not differ in the U.S. vs. non-U.S. regions and did not account for the geographic differences in outcomes, although the analysis was limited to a very small subset.
- *ABCB1* genotype was not robustly associated with outcomes in either treatment arm, considering previously published findings for *ABCB1* genetic effects on clopidogrel response and the lack of supportive evidence from PK/PD endpoints.

### 2.3.3 What pregnancy and lactation use information is there in the label?

Not Available.

## **2.4 Extrinsic Factors**

### **2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**

CYP3A4/5 inducers and inhibitors will alter the systemic exposure of ticagrelor.

### **2.4.2 What are the drug-drug interactions?**

#### **2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?**

Ticagrelor is a substrate for CYP450 and has the potential to induce and inhibit some of CYP450 enzymes.

#### **2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?**

In human liver microsomes, ticagrelor metabolism was inhibited approximately 98% by 1  $\mu$ M ketoconazole (CYP3A inhibitor) and 30-40% by 50  $\mu$ M omeprazole (CYP2C9 inhibitor) and 10-18% by 10  $\mu$ M furafylline (CYP 1A2 inhibitor).

Ticagrelor metabolism is not expected to be influenced by genetic variations.

#### **2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?**

- In human liver microsomes, ticagrelor was found to be a moderate inhibitor for CYP 2C9 ( $IC_{50}$  2.1  $\mu$ M), 2D6 ( $IC_{50}$  5.3  $\mu$ M), a weak inhibitor of CYP3A4, and strong inhibitor of CYP 3A5 ( $IC_{50}$  1.8  $\mu$ M).
- Ticagrelor and AR-C124910XX appeared to induce CYP 2C9.

#### **2.4.2.4 Is the drug an inhibitor and/or an inducer of P-gp transport processes?**

Ticagrelor and AR-C124910XX are substrates and inhibitor of P-gp. *In vitro*, both compounds inhibited digoxin transport in dose dependant manner with  $IC_{50}$  of  $7.8 \pm 2.6$   $\mu$ M and  $9.9 \pm 5.1$   $\mu$ M for ticagrelor and AR-C124910XX, respectively.

#### **2.4.2.5 Are there other metabolic/transporter pathways that may be important?**

Information is not available

#### **2.4.2.6 Does the label specify co-administration of another drug?**

Ticagrelor label states that it should be administered with low dose (75 – 100 mg) of aspirin.

#### **2.4.2.7 What other co-medications are likely to be administered to the target population?**

Aspirin, anti-platelet,  $\beta$ -blockers, glycoprotein IIb/IIIa inhibitor for patients undergoing PCI, heparin, nitroglycerin, and ACE inhibitors.

#### **2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

##### **Effect of other Medications on Ticagrelor exposure:**

##### **Ketoconazole:**

The co-administration of ketoconazole (200 mg BID for 10 days) with a single oral 90 mg dose of ticagrelor on Day 4:

- Significantly increases ticagrelor AUC by 7.32 fold and  $C_{max}$  by 2.35.
- Significantly decreases AR-C124910XX AUC by 56% and  $C_{max}$  by 89%.
- Ticagrelor should be contraindicated with ketoconazole and strong CYP3A inhibitors

##### **Diltiazem:**

The co-administration of diltiazem (240 mg QD for 14 days) with a single oral 90 mg dose of ticagrelor on Day 8:

- Significantly increases ticagrelor AUC by 2.74 fold and  $C_{max}$  by 1.69.
- Decreases AR-C124910XX AUC by 13% and significantly decreases its  $C_{max}$  by 38%.
- Simulation of the plasma concentration-time course suggest a QD regimen of ticagrelor with moderate CYP3A inhibitors such as diltiazem which will result in steady-state trough and  $AUC_{0-24}$  similar to that obtained with ticagrelor 90 mg BID in the absence of diltiazem.

##### **Rifampin:**

The co-administration of rifampin (600 mg QD for 14 days) with a single oral 180 mg dose of ticagrelor on Day 12:

- Significantly decreases ticagrelor AUC by 86% and  $C_{max}$  by 73%
- Significantly reduces AR-C124910XX AUC by 46% and does not affect  $C_{max}$ .
- Strong CYP3A inducers should not be used with ticagrelor as this may result in lower concentrations and may lead to potential loss of efficacy.



**Aspirin:**

The co-administration of aspirin (300 mg QD for 10 days) with multiple oral doses of ticagrelor 50 mg BID for 5 days followed by 200 mg BID for another 5 days did not alter the systemic exposure of ticagrelor.

**Desmopressin:**

The co-administration of desmopressin (0.3 µg/Kg IV infusion for 2 h) following 5 days of the administration of ticagrelor loading dose (270 mg) and maintenance (90 mg BID) did not alter the systemic exposure of ticagrelor.

**Heparin:**

The co-administration of unfractionated heparin (100 IU/Kg IV bolus) with a single oral 180 mg dose of ticagrelor did not alter the systemic exposure of ticagrelor.

**Enoxaprin:**

The co-administration of enoxaprin (1 mg/kg SC injection) with a single oral 180 mg dose of ticagrelor did not alter the systemic exposure of ticagrelor.

**Effect of ticagrelor on the systemic exposure of other medications:****Digoxin:**

The co-administration of ticagrelor (400 mg QD for 16 days) with digoxin (0.25 mg QD for 9 days) significantly increases digoxin acid AUC<sub>0-72</sub>, C<sub>ss,max</sub>, and C<sub>ss,min</sub> by 28%, 75%, and 31%, respectively. Hence, digoxin concentrations should be monitored if co-administered with ticagrelor.

**Simvastatin:**

The co-administration of ticagrelor (Loading dose 270 mg, maintenance dose 180 mg for 7 days) with simvastatin 80 mg QD on Day 5:

- Significantly increases simvastatin AUC by 56% and C<sub>max</sub> by 81%.
- Significantly increases simvastatin acid AUC by 52% and C<sub>max</sub> by 64%.
- Does not require dose adjustment as the increases are not deemed to be clinically significant.

**Atorvastatin:**

The co-administration of ticagrelor (Loading dose 270 mg, maintenance dose 180 mg for 7 days) with atorvastatin 80 mg QD on Day 5:

- Significantly increases atorvastatin acid AUC by 36% and  $C_{max}$  by 23%.
- Significantly increases atorvastatin lactone AUC by 32% and  $C_{max}$  by 39%.
- Significantly increases 2-OH atorvastatin AUC by 33% and  $C_{max}$  by 13%.
- Significantly increases 4-OH atorvastatin AUC by 67% and  $C_{max}$  by 55%.
- Does not require dose adjustment as the increases are not deemed to be clinically significant.

### **Oral Contraceptive:**

The co-administration of ticagrelor (90 mg for QD 21 days) with oral contraceptive containing ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg QD for 21 days:

- Significantly increases ethinyl estradiol AUC,  $C_{max}$ , and  $C_{min}$  by 20%, 30.6%, and 20.2%, respectively.
- Does not alter the systemic exposure of levonorgestrel.

### **Midazolam:**

The co-administration of ticagrelor (Loading dose 270 mg, maintenance dose 180 mg for 7 days) with oral (7.5 mg) and IV (2.5 mg) midazolam on Day 1 and Day 7:

- Significantly reduces oral midazolam AUC by 10%, and 4'-OH-midazolam by 42%, but does not alter 1'-OH- midazolam AUC.
- does not alter the systemic exposure of IV midazolam and 1'-OH-midazolam, and significantly reduces 4'-OH- midazolam systemic exposure by ~ 23%.

### **Tolbutamide:**

The co-administration of ticagrelor (180 mg BID for 9 days) with tolbutamide (500 mg QD on Day 5) does not alter the systemic exposure of tolbutamide or 4-OH-tolbutamide.

## **2.5 General Biopharmaceutics**

### **2.5.1 What is the absolute bioavailability of the proposed to-be-marketed formulation?**

The absolute bioavailability of ticagrelor immediate release tablets is 36% (95% CI 30% – 42%)

### **2.5.2 What is the effect of food on the bioavailability of the drug from the dosage form?**

When administered with food:

1. Ticagrelor AUC significantly increased by 23% and 21% for the micronized and non-micronized formulations, respectively.
2. Ticagrelor  $C_{max}$  significantly decreased by 7% and 8% for the micronized and non-micronized formulations, respectively.

AR-C124910XX AUC was not affected; however,  $C_{\max}$  was significantly reduced by 27% and 22% for the micronized and non-micronized formulations, respectively.

3. Ticagrelor can be taken with or without food.

## **2.6 Analytical Section**

### **2.6.1 How are the active moieties identified and measured in the plasma?**

Table 7 displays a list of the analytical methods type, calibration curve, matrix and analyte quantified, that were used in ticagrelor clinical pharmacology development program. Both the bioanalytical methods i.e., validation and performance during study sample's analysis are acceptable and consistent with the recommendations of the FDA Guidance on Bioanalytical Method Validation.

### **2.6.2 Which metabolites have been selected for analysis and why?**

AR-C124910XX concentrations were quantified in all clinical pharmacology studies since it is the major metabolite and is equipotent to ticagrelor. The inactive metabolite AR-C133913XX concentrations were quantified in two clinical pharmacology studies.

### **2.6.3 For all moieties measured, is free, bound, or total measured?**

Total concentration was measured except when protein binding was evaluated.

**Table 7.** Analytical methods used throughout ticagrelor clinical pharmacology clinical development program. CIA: Chemiluminescent Immunometric Assay

Analyte	Method	Calibration Range	Matrix
Ticagrelor	LC-MS/MS	1.0 – 500 ng/mL 5- 5000 ng/mL	Plasma
AR-C124910XX	LC-MS/MS	2.5 – 500 ng/mL 2.5 – 2500 ng/mL	Plasma
AR-C133913XX	LC-MS/MS	2 – 1000 ng/mL	Plasma
Unbound Ticagrelor Unbound AR-C124910XX	LC-MS/MS	0.25-100 ng/mL	Dialysate
Ticagrelor AR-C124910XX	LC-MS/MS	2.5-2500 ng/mL	Urine
Acid Metabolite of Clopidogrel	LC-MS/MS	5 – 5000 ng/mL	Plasma
Ketoconazole	LC-MS/MS	10 – 5000 ng/mL	Plasma
Diltiazem	LC-MS/MS	1 – 250 ng/mL	Plasma
Rifampin	LC-MS/MS	2.5-2500 ng/mL	Plasma
Simvastatin/ Simvastatin Acid	LC-MS/MS	0.25 - 250 ng/mL	Plasma
Atorvastatin/Atorvastatin Lactone 2-OH Atorvastatin/4-OH Atorvastatin	LC-MS/MS	0.25 - 250 ng/mL	Plasma
Digoxin	LC-MS/MS	2.5 – 500 ng/mL	Plasma
Ethinyl Estradiol	LC-MS/MS	2 – 1000 pg/mL	Plasma
Levonorgestrel	LC-MS/MS	0.1- 50 ng/mL	Plasma
17-β-Estradiol	LC-MS/MS	2 – 2000 ng/mL	Plasma
Follicle Stimulating Hormone	cELISA	0.05 – 40 mIU/mL	Plasma
Luteinizing Hormone	cELISA	0.1- 50 mIU/mL	Plasma
Progesterone	LC-MS/MS	20 – 2000 pg/mL	Plasma
Sex Hormone Binding Globulin	CIA	4.0 & 77.0 nM	Plasma
Midazolam 1'-Hydroxymidazolam Midazolam 4'-Hydroxymidazolam	LC-MS/MS	0.1 – 100 ng/mL	Plasma
Tolbutamide/ 4-OH-tolbutamide	LC-MS/MS	10 – 5000 ng/mL	Plasma

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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Concur with the reviewer's findings and conclusions

## 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

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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  $\geq 180$  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  $\geq 80$  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  $\geq 250$  mg/kg/day; rats  $\geq 180$  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 sternbrae were seen in rabbits. Supernumerary liver lobes and incomplete ossification of the parietal bone, sternbrae, misshapen/misaligned sternbrae, 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  $\geq 10$  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 P2Y<sub>12</sub> 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 P2Y<sub>12</sub> 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 C<sub>max</sub> of both ticagrelor and its active metabolite show approximately proportional increases with increasing oral doses, indicating linear PK. Mean terminal elimination half-life (t<sub>1/2</sub>) for ticagrelor was 6.9 hours (range 4.5 to 12.8 hours). Ingestion of a high-fat meal had no effect on ticagrelor C<sub>max</sub>, 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 P2Y<sub>12</sub> 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 t<sub>1/2</sub> of 6.9 hours and the t<sub>1/2</sub> 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

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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.

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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. Hemorrhagic 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 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 were 18 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
<b>Ticagrelor 180 mg bd</b>	360	51.9	51.2
<b>Ticagrelor 90 mg bd</b>	513	44.4	62.4
<b>Ticagrelor 50 mg bd</b>	41	27.9	31.3
<b>Ticagrelor 400 mg od</b>	46	27.5	3.5
<b>Clopidogrel 75 mg od</b>	498	45.2	61.7
<b>Placebo</b>	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)

<b>Deaths</b>	<b>Ticagrelor 90 mg bd N=9333</b>	<b>Clopidogrel 75 mg od N=9291</b>	<b>Total N=18624</b>	<b>RR</b>
Total known deaths	443 (4.75)	540 (5.81)	983	<b>0.82</b>
Discovered after withdrawal of consent, not adjudicated	25 (0.27)	20 (0.22)	45	<b>1.24</b>
All adjudicated deaths	418 (4.48)	520 (5.6)	938	<b>0.8</b>
Adjudicated deaths within efficacy period (randomisation to last scheduled visit date)	399 (4.28)	506 (5.45)	905	<b>0.78</b>
Adjudicated deaths 1 to 30 days after efficacy period (PSOP)	15 (0.16)	12 (0.13)	27	<b>1.24</b>
Adjudicated deaths after PSOP	4 (0.04)	2 (0.02)	6	<b>1.99</b>
Adjudicated deaths counted in safety analyses	408 (4.37)	505 (5.44)	913	<b>0.8</b>
Deaths in safety on-treatment analysis (randomization to 7 days after the last dose of study drug)	283 (3.03)	339 (3.65)	622	<b>0.83</b>
Within efficacy period	281 (3.01)	339 (3.65)	620	<b>0.83</b>
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	<b>0.75</b>
Adjudicated deaths not counted in safety analyses – patient never took study drug	10 (0.11)	15 (0.16)	25	<b>0.66</b>

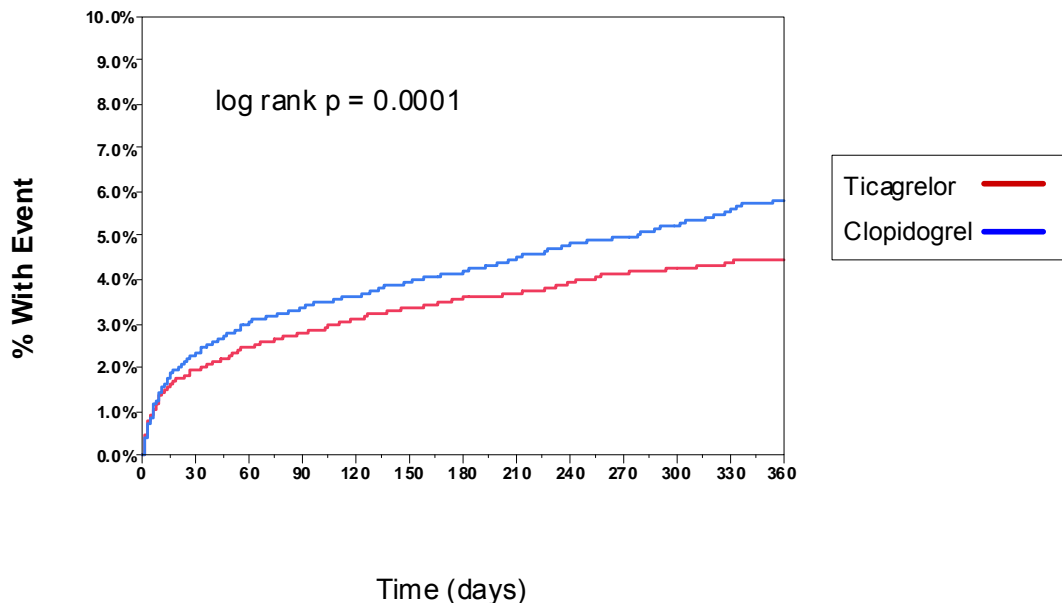
**Source:** Source: Adapted from PLATO study report, p. 250

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



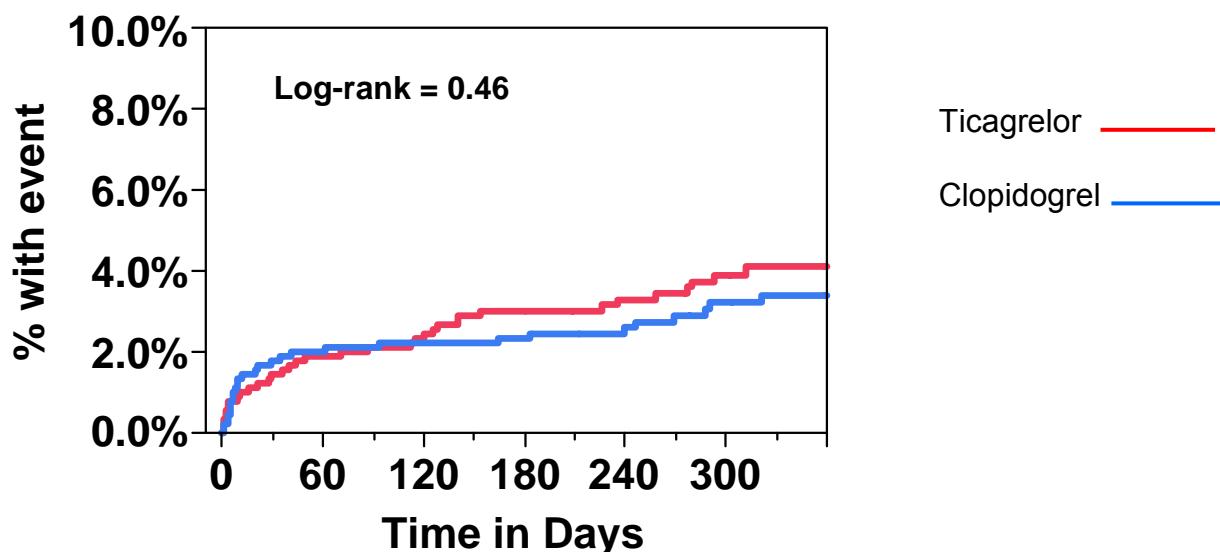
Group	Number failed	Number censored	Percent failed
Ticagrelor 90 mg bd	389	8846	4.21%
Clopidogrel 75 mg od	491	8695	5.65%
Combined	880	17541	5.02%

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

<b>Category</b>	<b>Ticagrelor 90 mg bd N=9235</b>	<b>Clopidogrel 75 mg od N=9186</b>
All deaths <sup>a</sup>	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%)

<sup>a</sup> 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)

Characteristic	Randomised Treatment	
	Ticagrelor 90 mg bd N = 9333	Clopidogrel 75 mg od 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  $\geq 0.2\%$  in the ticagrelor treatment group where there was  $\geq 0.2\%$  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 ( $\geq 0.2\%$  where the difference between groups was  $\geq 0.2\%$  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  $\geq 0.2\%$  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 tabular presentation of my SAE analysis using renamed AE terms. This analysis is similar to the sponsor'

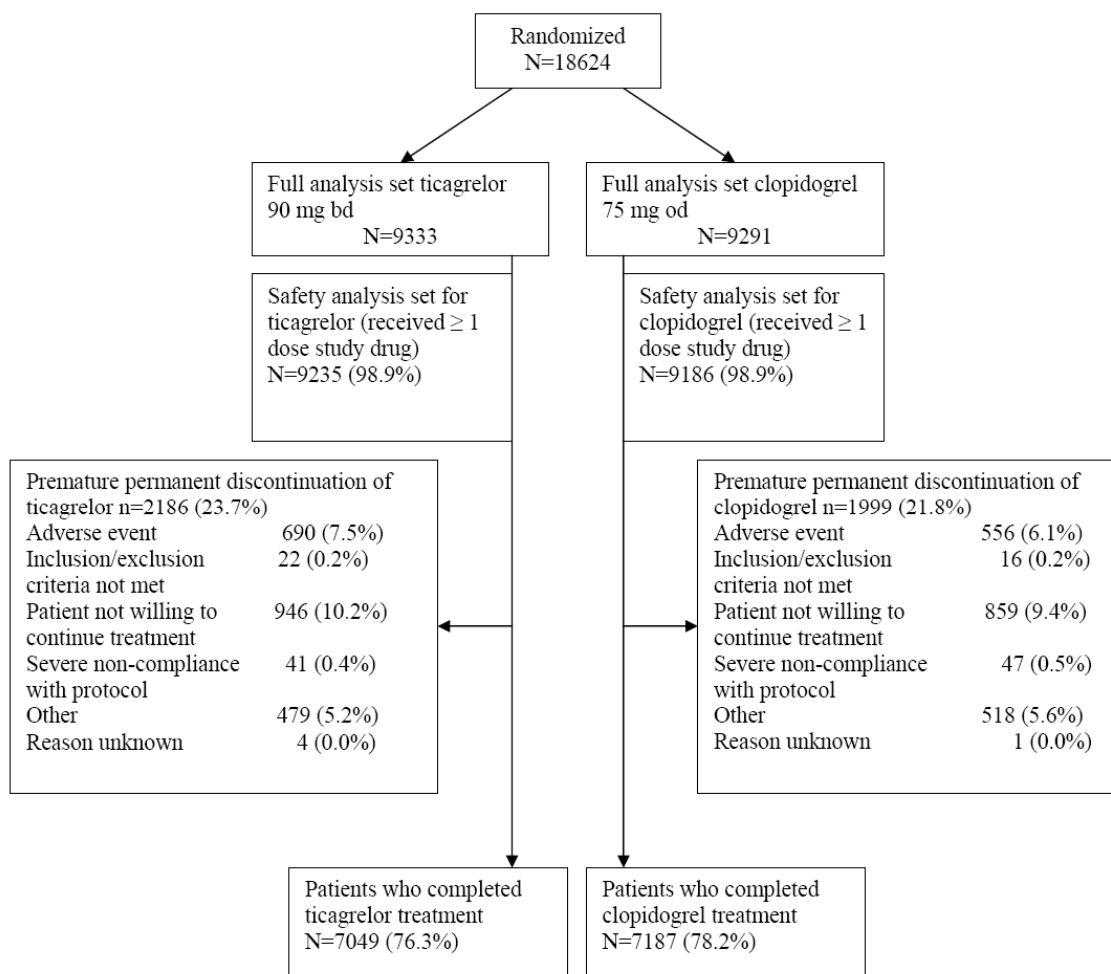
Table 7: Serious AE Table (analysis done using renamed terms)

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)
Retroperitoneal 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)
Thromboembolic 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
<b>Patients with at least one event</b>	<b>687 (7.4%)</b>	<b>500 (5.4%)</b>
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
<b>PLATO-defined Major Fatal/Life threatening</b> 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	<b>TIMI-defined Major</b> 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%)
	<b>TIMI-Life threatening</b> 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
<b>PLATO-defined Major Other</b> 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.	<b>TIMI-defined Minor</b> 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
<b>PLATO-defined Minor</b> Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).	<b>TIMI-defined Minimal</b> 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%)
<b>PLATO-defined Minimal</b> All others not requiring intervention or treatment	

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

	Ticagrelor 90 mg bd N = 9235		Clopidogrel 75 mg od N = 9186		
<u>Characteristic</u>	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)
<u>Primary safety</u>					
Total Major	1031	961 (10.4%), 11.6%	997	929 (10.1%), 11.2%	1.04 (0.95, 1.13)
<u>Secondary safety endpoints -</u>					
<u>Total Major bleeding by</u>					
<u>severity -</u>					
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  $\geq 30$ cc/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

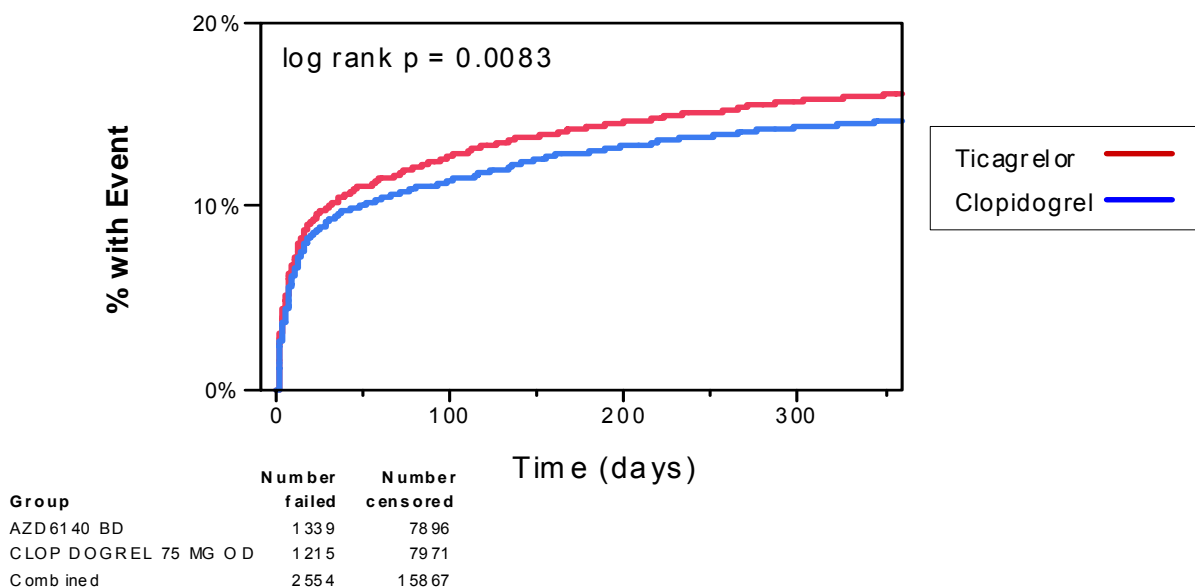


<b>Major Bleeds</b>	<b>Ticagrelor 90 mg bd N=9235</b>	<b>Clopidogrel 75 mg od N= 9186</b>
<b>CABG-related</b>	623 (6.7%)	659 (7.2%)
<b>non-CABG procedure related</b>	30 (0.3%)	46 (0.5%)
<b>Spontaneous</b>	251 (4.5%)	190 (0.21%)
<b>Total</b>	<b>1031 (11.2%)</b>	<b>997 (10.9%)</b>

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)



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.

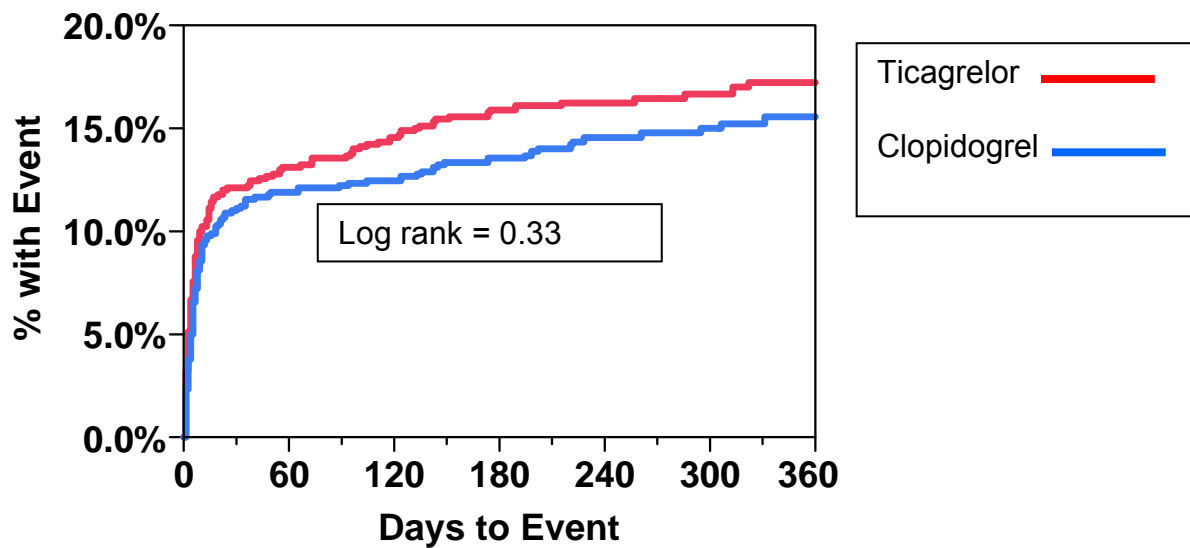
Table 13: Fatal Bleeding Events and Corresponding Characteristics

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
<b>Total Fatal</b>	21	24	20 ( 0.2%)	23 ( 0.3%)
<b>Not related to CABG surgery</b>	15	17	15 ( 0.2%)	16 ( 0.2%)
<b>Not procedure-related</b>	13	13	13 ( 0.1%)	12 ( 0.1%)
<b>Non-CABG procedural</b>	2	4	2 (0.0%)	4 (0.0%)
<b>Procedure-related</b>	8	10	8 ( 0.1%)	10 (0.1%)
<b>Non-coronary</b>	1	2	1 (0.0%)	2 (0.0%)
<b>Coronary</b>	7	8	7 ( 0.1%)	8 (0.1%)
<b>CABG-related</b>	6	6	6 ( 0.1%)	6 (0.1%)
<b>PCI-related</b>	1	2	1 (0.0%)	2 (0.0%)
<b>Coronary angiography related</b>	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

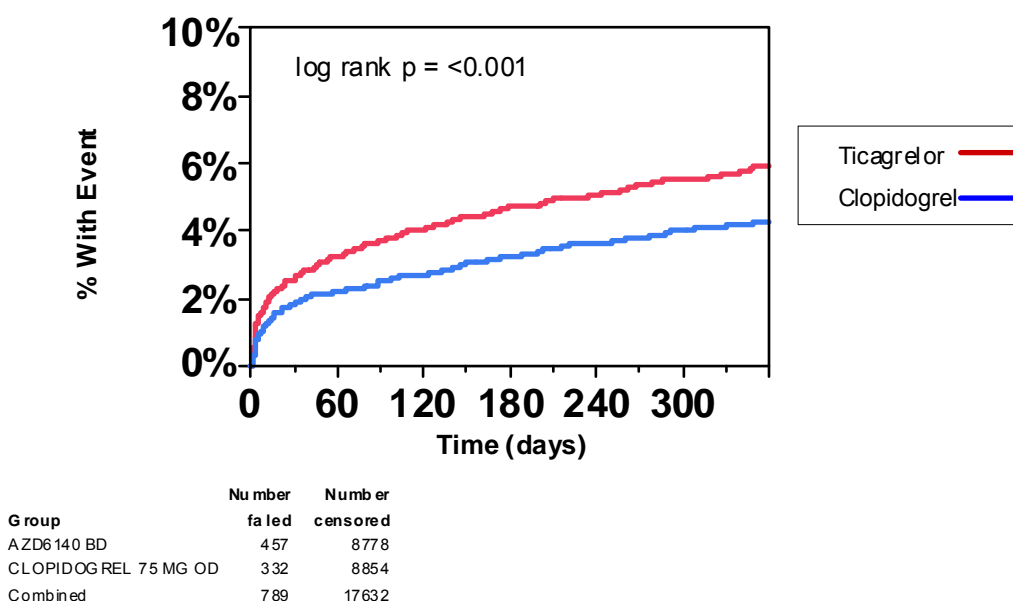
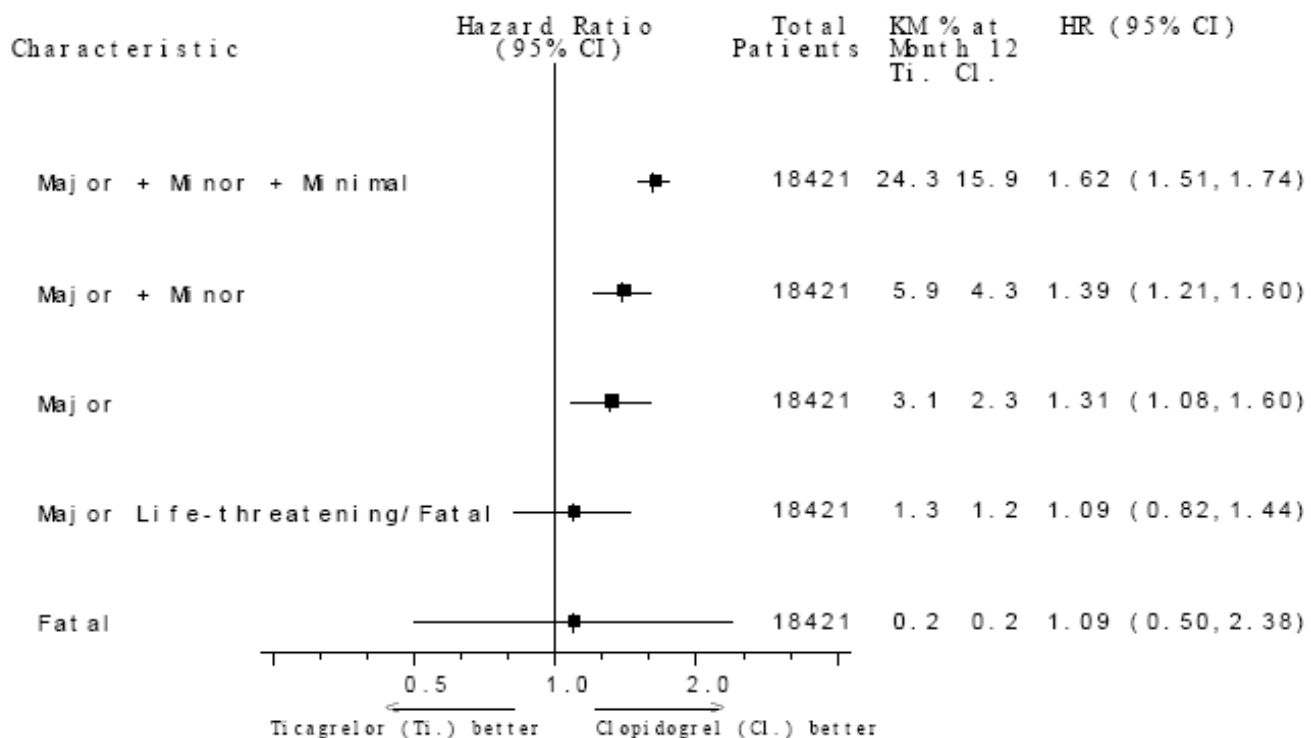


Figure 7: Hazard Ratio (95%CI) for non-procedural bleeds by severity



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 tabular 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
<b>Patients with CABG procedures</b>	770 ( 100%)	814 ( 100%)
<b>No bleeding event</b>	33 (4.3%)	31 (3.8%)
<b>Any bleeding event</b>	737 (95.7%)	783 (96.2%)
<b>Major</b>	619 (80.4%)	654 (80.3%)
<b>Major Fatal/Life-threatening</b>	329 (42.7%)	341 (41.9%)
<b>Fatal</b>	6 ( 0.8%)	6 ( 0.7%)
<b>Major Other</b>	290 (37.7%)	313 (38.5%)
<b>Minor</b>	47 (6.1%)	58 (7.1%)
<b>Minimal</b>	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

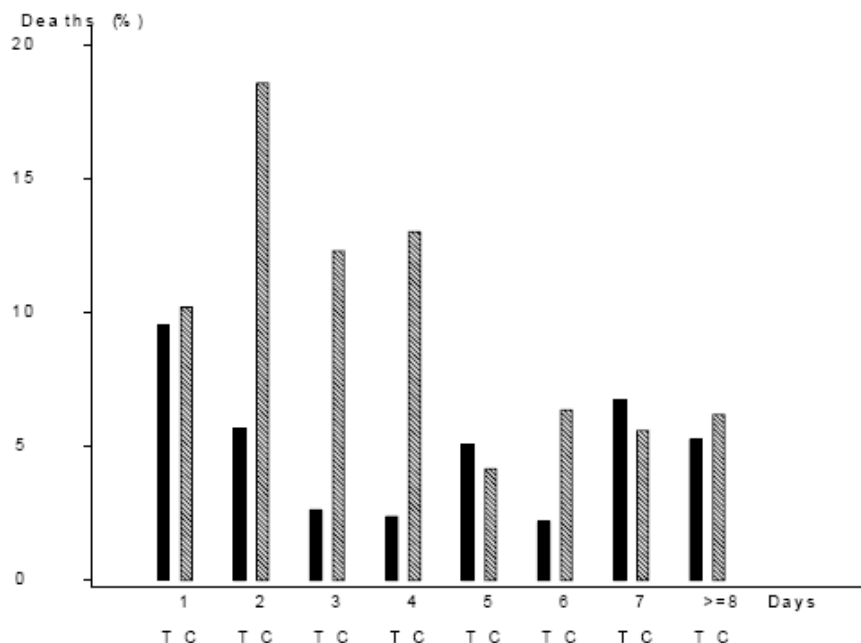
Table 16: Sponsor Analysis: ICAC-adjudicated PLATO-defined 'Major, Life-threatening/Fatal, Fatal' CABG-related bleeding by time from last dose of study drug to procedure – safety analysis set

	Patients with CABG		Major		Life-threatening/Fatal		Fatal	
Hours from last dose to CABG	Ticagrelor 90 mg bd	Clopidogrel 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
<b>Total</b>	<b>741</b>	<b>776</b>	<b>599 (80.8%)</b>	<b>627 (80.8%)</b>	<b>319 (43.0%)</b>	<b>333 (42.9%)</b>	<b>6 (0.8%)</b>	<b>6 (0.8%)</b>

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 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, 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  $\geq 75$  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

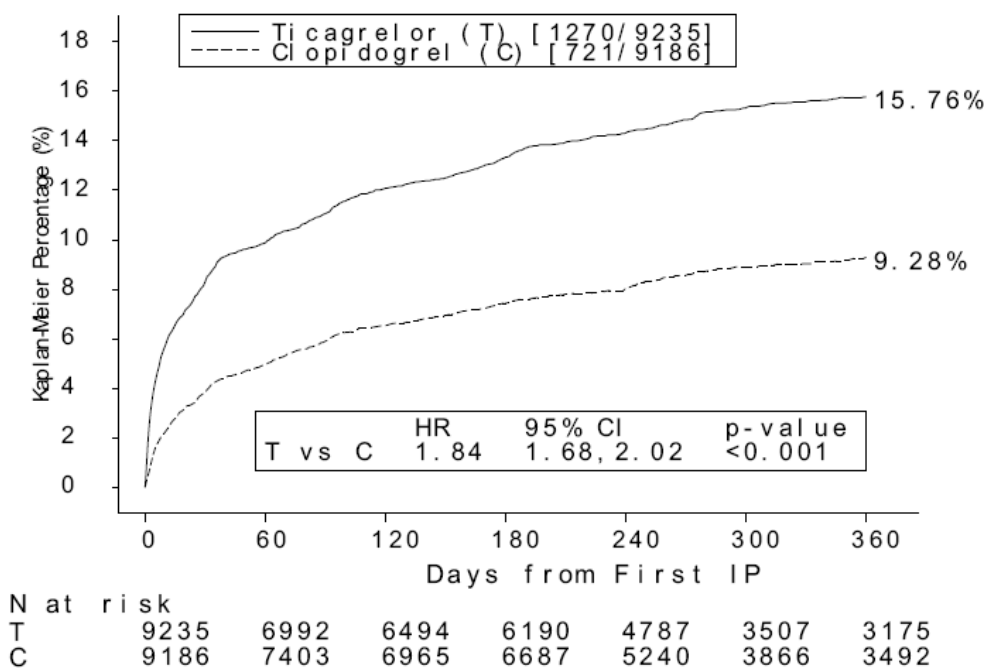
had a higher incidence of dyspnea events. One would imagine that heavier patients with recent ACS would have a greater tendency to be dyspneic compared to thinner patients. Perhaps ticagrelor may just push heavier people over the threshold and make them more likely to report dyspnea to the investigator. 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  $\geq 20$  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  $\geq 20$  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

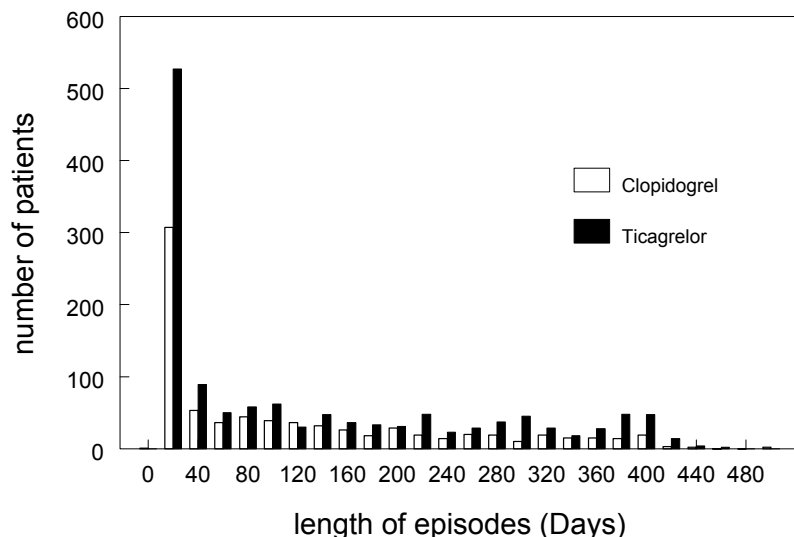
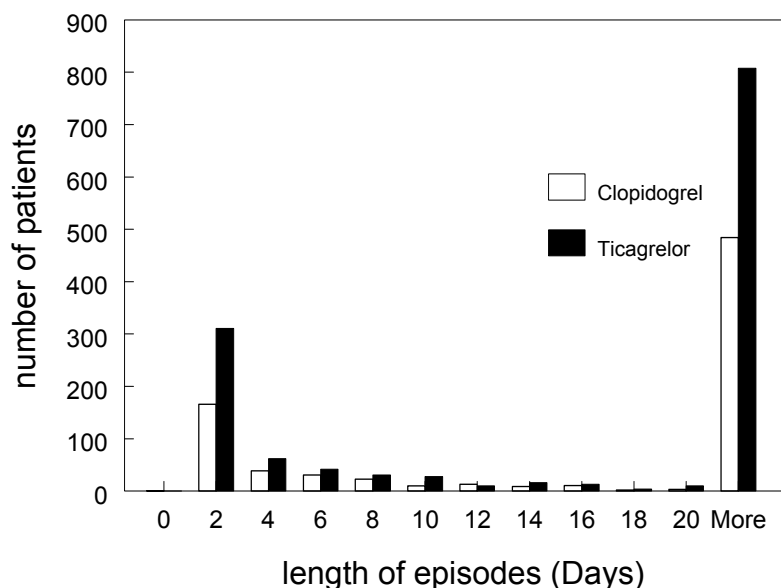




Figure 11: Frequency of Different Lengths of Dyspnea Episodes II



#### 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

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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

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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 (IC<sub>50</sub>) value of 1.72  $\mu$ M. 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<sub>12</sub> 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
<b>Arrhythmia</b>	1349 (14.61%)	1330 (14.48%)	1.01	(0.94, 1.08)
<b>Atrial fibrillation</b>	447 (4.84%)	455 (4.95%)	0.98	(0.86, 1.11)
<b>Atrial Flutter</b>	48 (0.52%)	46 (0.5%)	1.04	(0.69, 1.55)
<b>Atrio-ventricular block</b>	104 (1.13%)	104 (1.13%)	0.99	(0.76, 1.3)
<b>Bradycardia</b>	398 (4.31%)	369 (4.02%)	1.07	(0.93, 1.23)
<b>Bundle Branch Blocks and QRS prolongation</b>	20 (0.22%)	25 (0.27%)	0.8	(0.44, 1.43)
<b>Conduction disturbance</b>	145 (1.57%)	142 (1.55%)	1.02	(0.81, 1.28)
<b>Nodal, Junctional or Idioventricular rhythm</b>	13 (0.14%)	13 (0.14%)	0.99	(0.46, 2.14)
<b>Nonsustained ventricular tachycardia, SVT, unspecified Ventricular tachycardia</b>	193 (2.09%)	191 (2.08%)	1.01	(0.82, 1.23)
<b>Premature atrial contraction</b>	41 (0.44%)	35 (0.38%)	1.17	(0.74, 1.83)
<b>Premature ventricular contraction</b>	107 (1.16%)	130 (1.42%)	0.82	(0.63, 1.06)
<b>Serious Atrioventricular Block (type 2b, 3)</b>	64 (0.69%)	61 (0.66%)	1.04	(0.74, 1.48)
<b>Sick sinus syndrome</b>	28 (0.3%)	23 (0.25%)	1.21	(0.7, 2.1)
<b>Sinus Arrest, Pause, Block, Dysfunction</b>	20 (0.22%)	17 (0.19%)	1.17	(0.61, 2.23)
<b>Sudden Death/ arrest, Electromechanical dissociation, cardiogenic shock</b>	160 (1.73%)	199 (2.17%)	0.8	(0.65, 0.98)
<b>Supraventricular arrhythmia</b>	688 (7.45%)	659 (7.17%)	1.04	(0.94, 1.15)
<b>Sustained Ventricular Tachycardia</b>	5 (0.05%)	6 (0.07%)	0.83	(0.25, 2.72)
<b>Syncope, Presyncope</b>	182 (1.97%)	146 (1.59%)	1.24	(1, 1.54)
<b>Tachycardia</b>	357 (3.87%)	358 (3.9%)	0.99	(0.86, 1.15)
<b>Ventricular Arrhythmia</b>	375 (4.06%)	415 (4.52%)	0.9	(0.78, 1.03)
<b>Ventricular Fibrillation</b>	73 (0.79%)	95 (1.03%)	0.76	(0.56, 1.04)
<b>Vertigo, Dizziness, Giddiness</b>	603 (6.53%)	536 (5.83%)	1.12	(1, 1.25)

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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  $\geq 3$  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  $\geq 3$  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

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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

		Ticagrelor		Clopidogrel	
Visit schedulea		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  $<30\text{cc/min/1.73m}^2$  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  $<30\text{cc/min/1.73m}^2$  developed renal failure while only 0.1% of ticagrelor-treated patients with eGFRs  $> 90\text{ cc/min/ } 1.73\text{ m}^2$  were reported to have renal failure. Also when comparing treatment groups, in the subgroup of patients with baseline eGFRs less than  $30\text{ cc/min/1.73m}^2$ , 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.

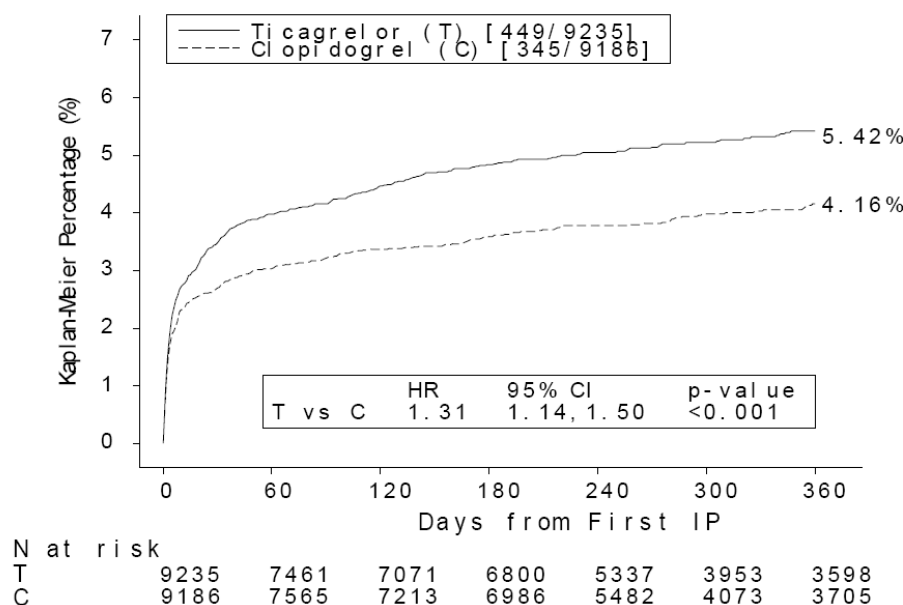
Overall, more ticagrelor-treated patients developed renal AEs [449 (4.9%) in the ticagrelor treatment group compared to 345 (3.8%) in the clopidogrel-treatment group]. The most frequent preferred terms (occurring in order of descending frequency) for renal-related AEs while on treatment were hematuria, 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
<b>ACEI USE: YES</b>	<b>Total at risk for &gt;50% creatinine increase</b>	2721 (100%)	2763 (100%)	<b>ACEI USE: NO</b>	752 (100%)	744 (100%)
	<b>Creatinine increase &gt;50%</b>	228 (8.4%)	187 (6.8%)		51 (6.8%)	37 (5.0%)
	<b>Total at risk for a renal-related AE</b>	6056 (100.0%)	6059 (100.0%)		1874 (100.0%)	1883 (100.0%)
	<b>Renal related AE</b>	249 (4.1%)	206 (3.4%)		95 (5.1%)	58 (3.1%)
	<b>Total at risk for renal function AE</b>	6056 (100%)	6059 (100%)		1874 (100%)	1883 (100%)
	<b>Renal function AE</b>	119 (2.0%)	82 (1.4%)		56 (3.0%)	39 (2.1%)
<b>ARB USE: NO</b>	<b>Total at risk for &gt;50% creatinine increase</b>	511 (100%)	508 (100%)	<b>ARB USE: NO</b>	3300 (100%)	3322 (100%)
	<b>Creatinine increase &gt;50%</b>	57 (11.2%)	36 (7.1%)		251 (7.6%)	212 (6.4%)
	<b>Total at risk for a renal-related AE</b>	1127 (100.0%)	1126 (100.0%)		7634 (100.0%)	7585 (100.0%)
	<b>Renal related AE</b>	73 (6.5%)	48 (4.3%)		333 (4.4%)	265 (3.5%)
	<b>Total at risk for renal function AE</b>	1127 (100%)	1126 (100%)		7634 (100%)	7585 (100%)
	<b>Renal function AE</b>	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 determined 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

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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).

#### Mechanism of Elevation of Uric Acid

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 14<sup>th</sup> day of treatment, a causal relationship in this particular case is not possible.

Table 22: AEs that might be hormonally related

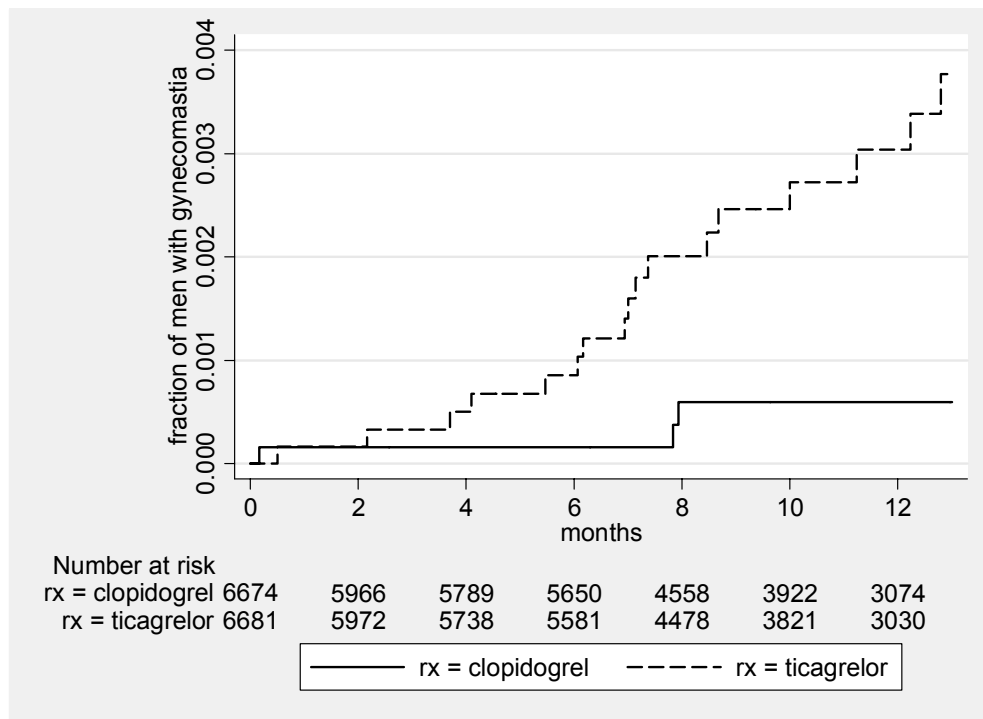
Category of possibly hormonally related AE	Ticagrelor 90 mg bd N= 9235	Clopidogrel 75 mg QD N= 9186	RR
	<u>n(percent)</u>	<u>n(percent)</u>	
Vaginal bleeding	22 (0.24)	17 (0.19)	1.3
Breast tenderness/ pain	8 (0.09)	6 (0.04)	2.3
Gynecomastia	15 (0.16)	3 (0.03)	5.3
Breast Cancer	4 (0.03)	10 (0.03)	1
Prostate 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

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 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.

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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 as 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
Dementia	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)
Thromboembolic event	63 (0.68%)	53 (0.58%)	1.18	(0.82, 1.7)
Transient Ischemic Attack	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

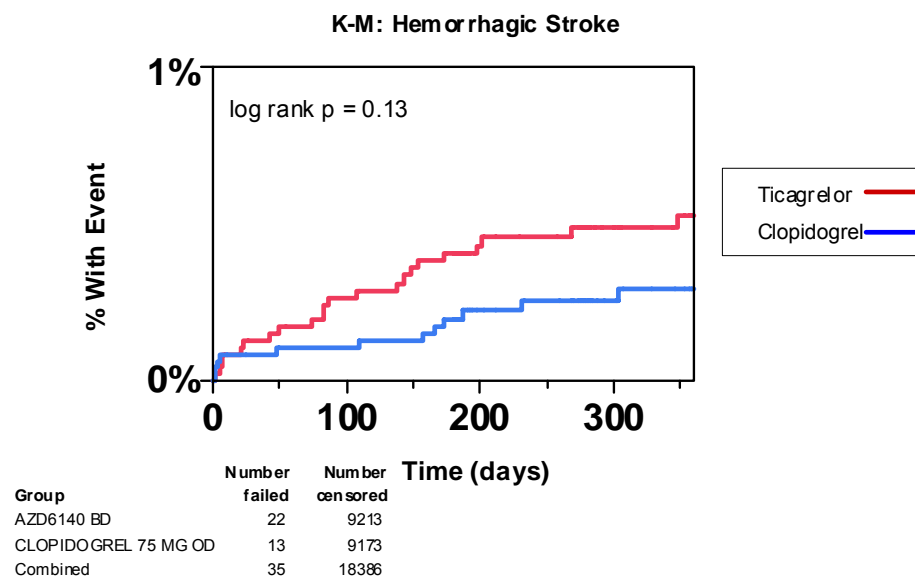


Figure 15: K-M: Stroke

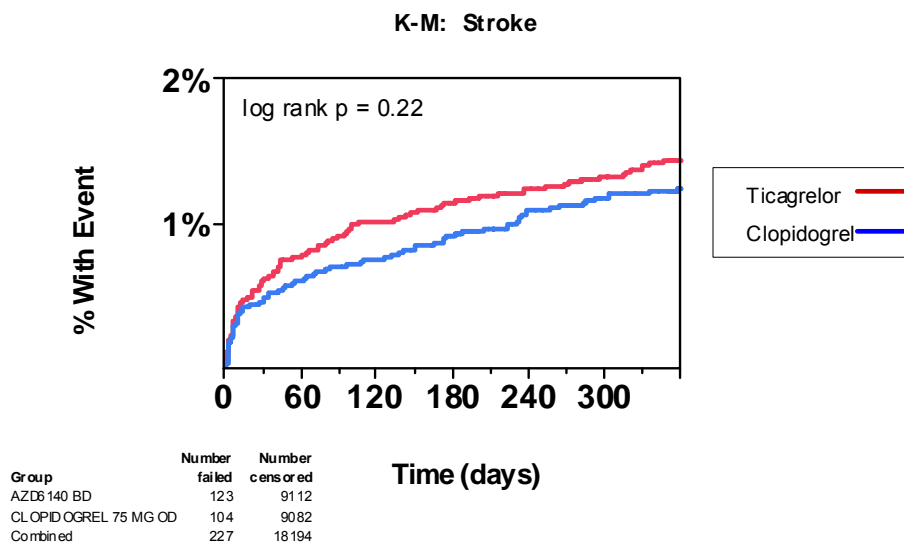


Table 24 shows the higher frequency of major/life-threatening intracranial hemorrhagic bleeds and fatal hemorrhagic bleeds in the ticagrelor group. Most notable is that the ticagrelor treatment group had 11 fatal intracranial bleeds compared to the 1 fatal intracranial bleed in the clopidogrel treatment group.

Table 24: Intracranial Bleeds

Characteristic	Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N =9186	RR
<b>Number (percent) of Major Fatal/ Life-threatening Intracranial Bleeds</b>	27 (26 patients) (0.3)	14 (0.15)	2
<b>Fatal Events</b>	11 (0.12)	1 (0.0)	
<b>Out of the Hospital Events</b>	17 (0.19)	10 (0.11)	1.73
<b>Average days to bleed</b>	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  $\geq 2\%$  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  $\geq 2\%$  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

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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  $\geq 2\%$  of the time

Category	ticagrelor 90 mg b 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, Surgical, Post-surgical bleed/hematoma	911 (9.86%)	904 (9.84%)	1	(0.92, 1.09)	99
Lower Gastrointestinal disorders	821 (8.89%)	843 (9.18%)	0.97	(0.88, 1.06)	120
Coronary Artery Bypass Graft Bleed	806 (8.73%)	786 (8.56%)	1.02	(0.93, 1.12)	90
Supraventricular arrhythmia	748 (8.1%)	748 (8.14%)	0.99	(0.9, 1.1)	101
Headache, migraine	688 (7.45%)	659 (7.17%)	1.04	(0.94, 1.15)	75
Nausea, Vomiting	640 (6.93%)	578 (6.29%)	1.1	(0.99, 1.23)	60
Vertigo, Dizziness, Giddiness	622 (6.74%)	539 (5.87%)	1.15	(1.03, 1.28)	48
Epistaxis	603 (6.53%)	536 (5.83%)	1.12	(1, 1.25)	53
Acute and Chronic Heart failure, Cardiac asthma, Cardio-pulmonary heart failure, Diastolic	574 (6.22%)	325 (3.54%)	1.76	(1.54, 2.01)	5
Malaise, Fatigue, Weakness, Somnolence	555 (6.01%)	576 (6.27%)	0.96	(0.86, 1.07)	122
Bacterial infection	552 (5.98%)	570 (6.21%)	0.96	(0.86, 1.08)	122
Hypertension Increase, Crisis, Unstable Blood Pressure	506 (5.48%)	492 (5.36%)	1.02	(0.91, 1.15)	90
Viral Infection	490 (5.31%)	522 (5.68%)	0.93	(0.83, 1.05)	133
	466 (5.05%)	415 (4.52%)	1.12	(0.98, 1.27)	53

Category	ticagrelor 90 mg b N=9235	clopidogrel 75 mg od N=9186	RR	95% CI	RANK
<b>Atrial fibrillation</b>	447 (4.84%)	455 (4.95%)	0.98	(0.86, 1.11)	<b>116</b>
<b>Renal dysfunction, Polyuria, Anuria/oliguria, Incontinence</b>	444 (4.81%)	362 (3.94%)	1.22	(1.07, 1.4)	<b>35</b>
<b>Bradycardia</b>	398 (4.31%)	369 (4.02%)	1.07	(0.93, 1.23)	<b>70</b>
<b>Diarrhea</b>	382 (4.14%)	339 (3.69%)	1.12	(0.97, 1.29)	<b>53</b>
<b>Ventricular Arrhythmia</b>	375 (4.06%)	415 (4.52%)	0.9	(0.78, 1.03)	<b>140</b>
<b>Tachycardia</b>	357 (3.87%)	358 (3.9%)	0.99	(0.86, 1.15)	<b>101</b>
<b>Hypotension, Hypovolemic shock, Hypovolemia</b>	353 (3.82%)	350 (3.81%)	1	(0.87, 1.16)	<b>99</b>
<b>Anxiety and Agitation, Abnormal dreams, Stress, Agression</b>	342 (3.7%)	279 (3.04%)	1.22	(1.04, 1.42)	<b>35</b>
<b>Fever</b>	331 (3.58%)	318 (3.46%)	1.04	(0.89, 1.2)	<b>75</b>
<b>Gastrointestinal/ Anal bleed</b>	327 (3.54%)	255 (2.78%)	1.28	(1.09, 1.5)	<b>31</b>
<b>Anemia</b>	315 (3.41%)	291 (3.17%)	1.08	(0.92, 1.26)	<b>67</b>
<b>Edema (non-central, non-facial, non generalized)</b>	306 (3.31%)	320 (3.48%)	0.95	(0.82, 1.11)	<b>128</b>
<b>Accident, non-surgical/ procedural Trauma, Fracture</b>	302 (3.27%)	255 (2.78%)	1.18	(1, 1.39)	<b>42</b>
<b>Rash, Erythema</b>	302 (3.27%)	296 (3.22%)	1.01	(0.87, 1.19)	<b>94</b>
<b>Increased cholesterol, Decreased HDL, Increased lipids</b>	282 (3.05%)	254 (2.77%)	1.1	(0.93, 1.31)	<b>60</b>
<b>Hematuria</b>	242 (2.62%)	195 (2.12%)	1.23	(1.02, 1.49)	<b>34</b>
<b>Bronchopneumonia and Pneumonia, Pneumonitis</b>	233 (2.52%)	245 (2.67%)	0.95	(0.79, 1.13)	<b>128</b>
<b>Neuropathy, Paresthesia, Hypoaesthesia, Numbness, Neuralgia</b>	227 (2.46%)	230 (2.5%)	0.98	(0.82, 1.18)	<b>116</b>
<b>Sleep disorder</b>	226 (2.45%)	230 (2.5%)	0.98	(0.82, 1.17)	<b>116</b>
<b>Dyspnea on Exertion</b>	224 (2.43%)	160 (1.74%)	1.39	(1.14, 1.7)	<b>19</b>
<b>Constipation</b>	220 (2.38%)	250 (2.72%)	0.88	(0.73, 1.05)	<b>146</b>
<b>Electrolyte disorder</b>	207 (2.24%)	220 (2.39%)	0.94	(0.78, 1.13)	<b>131</b>
<b>Nonsustained ventricular tachycardia, SVT, unspecified Ventricular tachycardia</b>	193 (2.09%)	191 (2.08%)	1.01	(0.82, 1.23)	<b>94</b>

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  $\geq 2\%$  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)
Retroperitoneal 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.



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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, Helicobacter 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

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Weight quintile (1 is lowest weight, 5 is highest weight)	1	2	3	4	5	slope (ticagrelor)	slope (clopidogrel)
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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  $3 \times 10^9$  /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

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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 2 episodes 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) ticagrelor 180 mg bd; or 3)

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clopidogrel 75 mg od. In DISPERSE2 there was a dose-related association of ticagrelor treatment with an increased occurrence of ventricular pauses  $\geq 2.5$  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  $\geq 3$  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  $\geq 10$  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.

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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  $\geq 3$  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  $\leq 45$  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 ( $\geq 220$  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 1 and 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



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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  $\geq 3$  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  $\geq 5$  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  $\geq 3$  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  $\geq 3$  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 $\geq 3$ secs		58 ( 6.0%)	34 ( 3.5%)	21 ( 2.2%)	16 ( 1.6%)
AV node pause $\geq 3$ secs		15 ( 1.6%)	11 ( 1.1%)	6 ( 0.6%)	7 ( 0.7%)
SA node pause $\geq 3$ secs		43 ( 4.5%)	22 ( 2.2%)	17 ( 1.8%)	11 ( 1.1%)
Other pause $\geq 3$ secs		4 ( 0.4%)	4 ( 0.4%)	0	0
Ventricular pauses $\geq 5$ secs		20 ( 2.1%)	10 ( 1.0%)	8 ( 0.8%)	5 ( 0.5%)
AV node pause $\geq 5$ secs		6 ( 0.6%)	5 ( 0.5%)	2 ( 0.2%)	1 ( 0.1%)
SA node pause $\geq 5$ secs		15 ( 1.6%)	4 ( 0.4%)	7 ( 0.7%)	4 ( 0.4%)
Other pause $\geq 5$ 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.

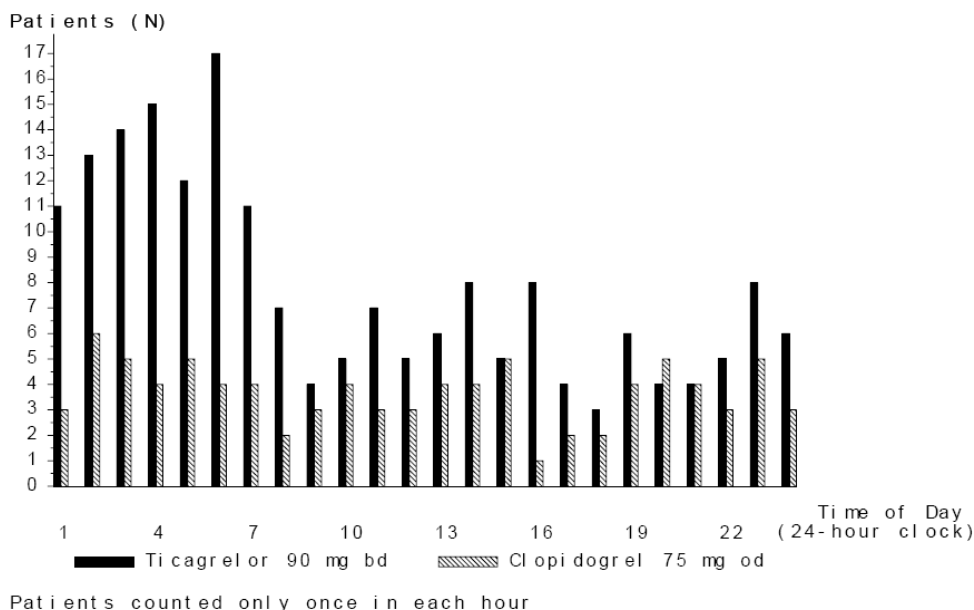
Patients with ventricular pauses  $\geq 3$  seconds had a higher mean weight, especially in the ticagrelor group, compared to patients without pauses; the mean weight was 86.1 kg for patients with pauses compared to 81.1 kg for patients without pauses in the ticagrelor-treated group. This pattern was 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  $\geq 3$  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  $\geq 3$  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  $\geq 5$  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  $\geq 3$  seconds during Holter monitoring periods. Only 23 and 10 patients fell 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  $\geq 3$  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 and Lerman 1991). The sponsor added that other mechanisms may also be involved in addition to an adenosine-mediated effect, e.g., increased vagal tone.

### Tachyarrhythmias

Tachyarrhythmias 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)  $\geq 4$  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 $\geq 1$ 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 <sub>a</sub>	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  $\geq 3$  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  $\geq 3$  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  $\geq 5$  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

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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.

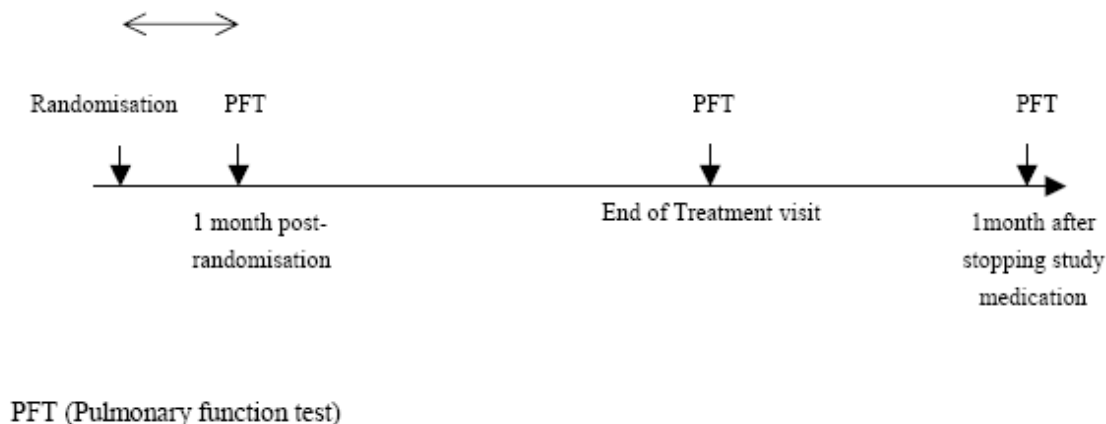
#### **Primary Objective**

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<sub>1</sub>) 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



The following measurements were done in order of measurement:

1. Blood oxygen saturation (SpO<sub>2</sub>) 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<sub>SB</sub>).
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<sub>1</sub>); forced vital capacity (FVC); mean forced expiratory flow between 25% and 75% of the FVC (FEF<sub>25-75</sub>) before and 20 minutes after a short-acting  $\beta_2$  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 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
<b>Anaphylaxis, Anaphylactoid reaction</b>	8 (0.09%)	9 (0.1%)	0.88	(0.34, 2.29)
<b>Allergy, Hypersensitivity</b>	148 (1.6%)	158 (1.72%)	0.93	(0.75, 1.16)
<b>Angioedema</b>	14 (0.15%)	8 (0.09%)	1.74	(0.73, 4.15)
<b>Laryngeal Edema</b>	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
<b>Anaphylaxis, Anaphylactoid reaction</b>	3 (0.03%)	4 (0.04%)	0.75	(0.17, 3.33)
<b>Allergy, Hypersensitivity</b>	7 (0.08%)	18 (0.2%)	0.39	(0.16, 0.93)
<b>Angioedema</b>	3 (0.03%)	4 (0.04%)	0.75	(0.17, 3.33)
<b>Laryngeal Edema</b>	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 C<sub>max</sub> 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,

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respectively, had mild hepatic impairment. From a phase 1 study (D5130C000016), C<sub>max</sub> 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, 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.

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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 chlordiazepoxide 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: 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 (b) (6) with new-onset cardiac ischemic symptoms, including dyspnea and angina, and with persistent ST elevation  $\geq 1$  mm)  $\geq 20$  min on ECG, h/o carotid stenosis ( $\geq 50\%$ ), 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 (b) (6) (b) (6) 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 (b) (6) Cause of death: myocardial infarction. Patient was **non-compliant with medication following discharge.**

Medications during hospitalization:

Nitroglycerin, Maalox, Lidocaine, Donnato, Lopressor, Morphine, Aspirin, Benadryl, Darvocet, Lipitor, Enalapril, Dilaudid, Protonix, Lisinopril, Heparin  
Aggrastat

**E1602058:** 71 y/o Caucasian woman with prior h/o MI, presented on (b) (6) with cardiac ischemic symptoms at rest  $\geq 10$  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 (b) (6). Ejection fraction was 30 - 39%. EF was measured as 50% 9 days later. Treatment with ticagrelor was interrupted on (b) (6) for a non-bleeding adverse event (COPD exacerbation which required hospitalization). Date restarted was (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 (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: rabeprazole, temazepam, advair, tylenol with codeine #3, atrovent, ventolin, lipitor, synthroid, Spireva, alendronate, altace, nitroglycerin, metoprolol, 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 (b) (6) (b) (6) with ischemic symptoms and elevated cardiac enzymes. Diagnosis: NSTEMI.

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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  $\geq 1$  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

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MELANIE J BLANK  
06/28/2010

## 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] who are to be managed medically or managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG.

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<sub>12</sub> 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 2<sup>nd</sup> 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 ( $\leq 1.5\%$ ) 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  $\leq 100$ mg 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  $\geq 12$  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 than 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-measurable (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<sub>12</sub> 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
<b>Aspirin</b>	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-A <sub>2</sub> in platelets via the irreversible inactivation of the cyclooxygenase (COX) enzyme, producing an inhibitory effect on platelet aggregation
<b>Clopidogrel (Plavix)</b>	Clopidogrel bisulfate is indicated for the reduction of atherothrombotic events as follows: <b>Recent MI, Recent Stroke or Established Peripheral Arterial Disease</b> 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. <b>Acute Coronary Syndrome</b> 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 <sub>12</sub> class of ADP receptors on platelets.
<b>Prasugrel (Effient)</b>	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 <sub>12</sub> class of ADP receptors on platelets.

**Source: R. Fiorentino, Clinical Reviewer**

Ticlopidine (Ticlid) is another irreversible ADP P2Y<sub>12</sub> 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 stroke 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 CYP3A4/5 to produce AR-C124910XX and AR-C133913XX.
- The major metabolite AR-C124910XX is rapidly formed with median  $T_{max}$  2.5 h. It is also equipotent as P2Y<sub>12</sub> 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
<b>ID: D5130C00008</b> “ <b>DISPERSE</b> ”: 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
<b>ID: D5130C00002</b> “ <b>DISPERSE2</b> ”: 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
<b>ID: D5130C05262</b> “ <b>PLATO</b> ”: 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  $\geq 3$  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.

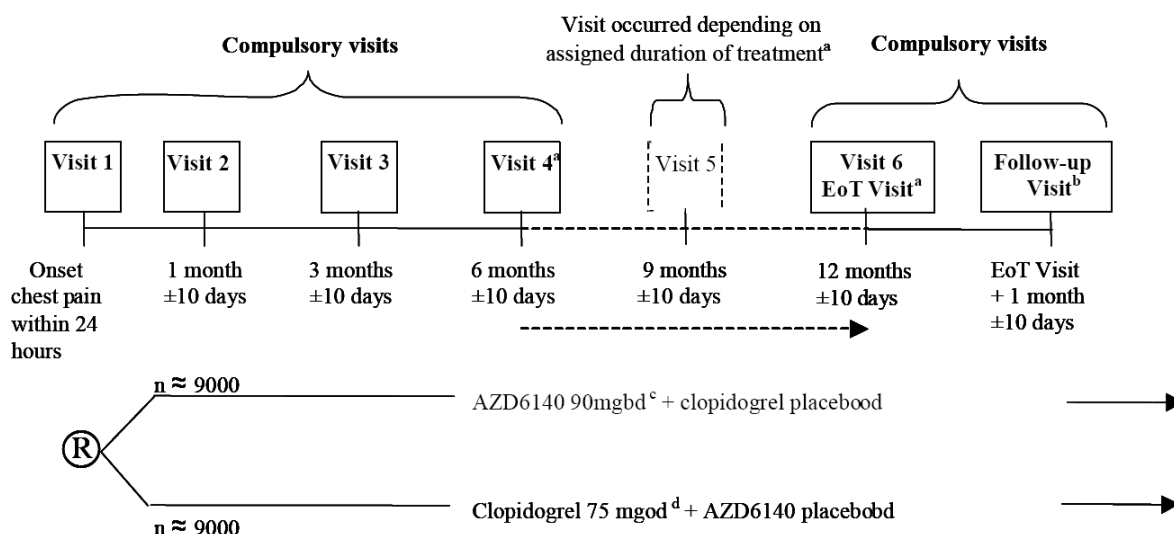
#### **5.3.1.4 Study Design**

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**



<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> 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.

<sup>d</sup> 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<sup>1</sup> of  $\geq 10$  minutes duration at rest<sup>2</sup> and:

- a. Persistent ST segment elevation<sup>3</sup>  $\geq 1$ mm (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<sup>1</sup> of  $\geq 10$  minutes duration at rest<sup>2</sup> (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<sup>4</sup>  $\geq 1$ mm (0.1mV) in 2 or more contiguous leads  
**or**  
Transient ST segment elevation<sup>5</sup>  $\geq 1$  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 limit<sup>6</sup> 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)

---

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, atazanavir, 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  $100 \times 10^9/L$  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**

<b>Study drug</b>	<b>Loading dose at randomisation</b>	<b>Maintenance dose</b>	<b>Loading dose for PCI &lt;24 hours post randomisation</b>	<b>Loading dose for PCI &gt;24 hours post randomisation</b>
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  $\geq 3$  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			Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 End of Treatment (EoT) Visit	Follow-up Visit
	Enrolment	Randomisation	Discharge	1 month $\pm 10$ d	3 m $\pm 10$ d	6 m $\pm 10$ d	9 m $\pm 10$ d	12 months $\pm 10$ d	EoT Visit + 1 month $\pm 10$ d
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 <sup>a</sup> (Local lab)	✓ <sup>a</sup>								
12-lead ECG <sup>b</sup>	✓		✓ <sup>c</sup>	✓				✓	
Holter ECG monitoring & diary <sup>d</sup>		✓		✓					
Clinical chemistry & haematology		✓		✓ <sup>e</sup>	✓ <sup>e</sup>	✓ <sup>e</sup>		✓ <sup>e</sup>	✓ <sup>e</sup>
Blood core substudy <sup>f</sup>		✓	✓ <sup>c</sup>	✓		✓			
Urine and/or blood pregnancy test	✓					✓ <sup>g</sup>		✓ <sup>g</sup>	
Myocardial necrosis biomarkers (Central lab)		✓ <sup>h</sup>							
PK blood sample <sup>i</sup>			✓ <sup>c</sup>	✓					
Dispense investigational product		✓	✓	✓	✓	✓	✓		
Return investigational product				✓	✓	✓	✓	✓	
Compliance/ drug accountability			✓	✓	✓	✓	✓	✓	
Medications	✓ <sup>j</sup>	✓ <sup>j</sup>	✓ <sup>j</sup>	✓ <sup>j</sup>	✓ <sup>j</sup>	✓ <sup>j</sup>	✓ <sup>j</sup>	✓ <sup>j</sup>	✓ <sup>j</sup>
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 P2Y<sub>12</sub> 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
<b>Age (years)</b>	Mean	62.1	62.3
	Median	62.0	62.0
<b>Age Group</b>	≥ 65 Years	4022 (43.1%)	3957 (42.6%)
	≥ 75 Years	1396 (15.0%)	1482 (16.0%)
<b>Sex</b>	Male	6678 (71.6%)	6658 (71.7%)
	Female	2655 (28.4%)	2633 (28.3%)
<b>Race (self-reported)</b>	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%)
<b>Weight (kg)</b>	Mean	80.6	80.3
	Median	80.0	80.0
<b>Weight Group</b>	≥ 60 kg	8653 (92.7%)	8603 (92.6%)
	≥ 80 kg	4788 (51.3%)	4725 (50.9%)
<b>Gender-specific median weight group</b>	Male ≥ 82kg; Female ≥ 71kg	4806 (51.5%)	4761 (51.2%)
<b>Waist Circumference(cm)</b>	Mean	98.5	98.6
	Median	98.0	98.0
<b>BMI (kg/m<sup>2</sup>)</b>	Mean	27.9	27.8
	Median	27.4	27.3
	≥ 30 kg/m <sup>2</sup>	2650 (28.4%)	2528 (27.2%)
<b>Troponin I</b>	Positive	7525 (80.6%)	7564 (81.4%)
	Negative	1525 (16.3%)	1443 (15.5%)
	Unknown	283 (3.0%)	284 (3.1%)
<b>Smoking Status</b>	Non-smoker	3592 (38.5%)	3664 (39.5%)
	Ex-smoker	2373 (25.4%)	2303 (24.8%)
	Habitual smoker	3360 (36.0%)	3318 (35.7%)
<b>Proton Pump Inhibitor at Rand.</b>	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**

	<b>Ticagrelor 90 mg bid N = 9333</b>	<b>Clopidogrel 75 mg qD N = 9291</b>
<b>Patients with at least one medication</b>	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 be 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 was 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**

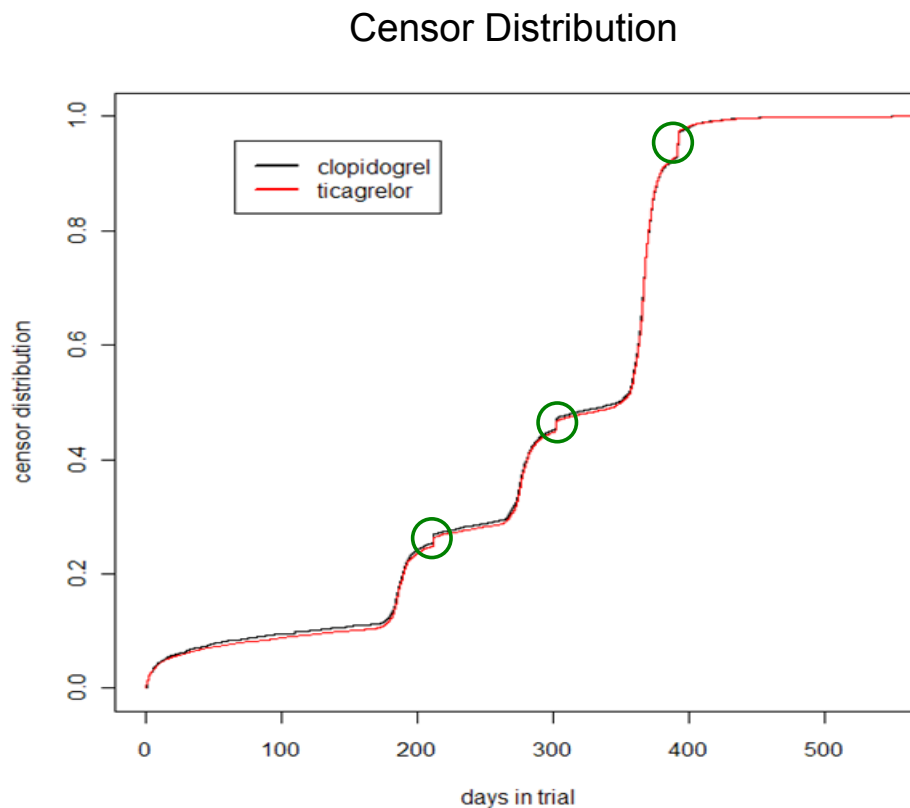
Subject Category	Ticagrelor	Clopidogrel	Total
Completers	6863	6731	13594
Projected by randomisation date	722	713	1435
Projected by last dispense date	1078	1118	2196 <sup>a</sup>
Withdrawal of consent	273	231	504
Death	397	498	895

<sup>a</sup> 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**



**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)**

<b>ALL COUNTRIES</b>	<b>N (%)</b>
Subjects Enrolled (Informed consent received)	18,758
Subjects Randomized	18,624 (99.3%)
Subjects Not Randomized	<b>134 (0.7%)</b>
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.)**

<b>United States</b>	<b>N (%)</b>
Subjects Enrolled (Informed consent received)	1,461
Subjects Randomized	1,413 (96.7%)
Subjects Not Randomized	<b>48 (3.3%)</b>
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**

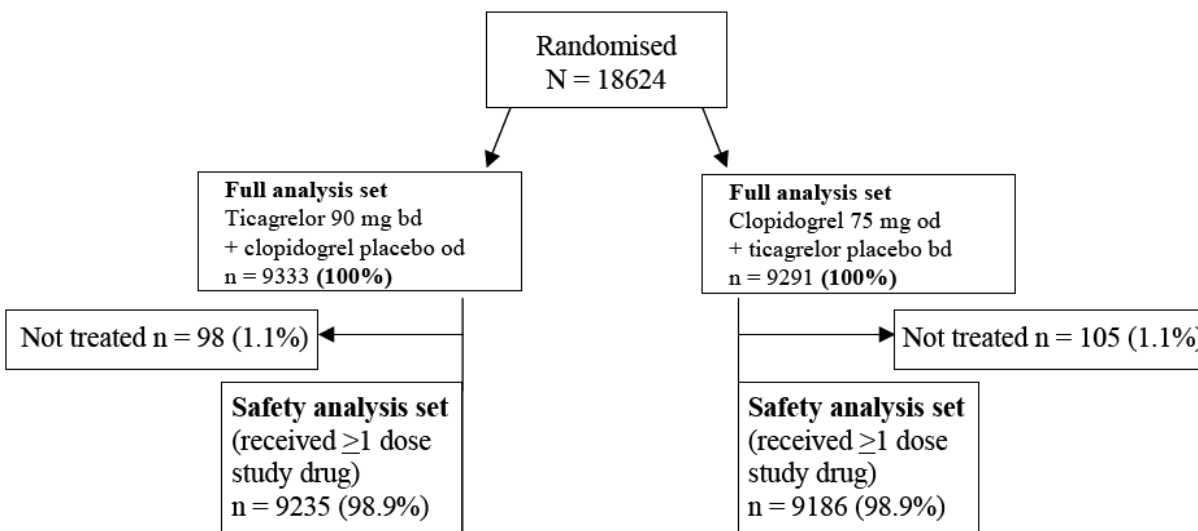
In the PLATO study, most of the patients not randomized to the study were excluded during the screening process (pre-consent) as evidenced by the low rate of enrolled but not randomized patients (134 patients out of 18,624).

## 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  $\geq 1$  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  $\pm$  10 days) and an additional 64 patients (36 ticagrelor and 28 clopidogrel) terminated participation by Visit 3 (3 months  $\pm$  10 days). The remainder terminated participation at other Visits.

**Table 12. Time to Permanent Premature Withdrawal from Study**

	<b>Ticagrelor 90mg bid</b>	<b>Clopidogrel 75 mg qD</b>	<b>Total</b>
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 $\pm$ 10 days)	62 (20.2%)	37 (14.5%)	99 (17.6%)
Visit 3 (3 months $\pm$ 10 days)	36 (11.7%)	28 (11.0%)	64 (11.4%)
Visit 4 (6 months $\pm$ 10 days)	12 (3.9%)	18 (7.1%)	30 (5.3%)
Visit 5 (9 months $\pm$ 10 days)	8 (2.6%)	7 (2.7%)	15 (2.7%)
Visit 6 (12 months $\pm$ 10 days)	3 (1.0%)	5 (2.0%)	8 (1.4%)
Follow-up (+1 month $\pm$ 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**

	<b>Ticagrelor</b>	<b>Clopidogrel</b>
<b>Consented and randomized (n)</b>	9333	9291
Premature withdrawal from the study	307 (3.3%)	255 (2.7%)
Incorrectly randomized	7 (0.1%) <sup>a</sup>	2 (0.0%) <sup>a</sup>
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%) <sup>b</sup>	0 (0.0%) <sup>b</sup>

<sup>a</sup> 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.

<sup>b</sup> 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**

	<b>Ticagrelor</b>	<b>Clopidogrel</b>
<b>Received <math>\geq 1</math> dose study drug (n)</b>	9235	9186
Premature permanent discontinuation of study drug <sup>a</sup>	2186 (23.7%)	1999 (21.8%)
Adverse event	690 (7.5%)	556 (6.1%)
Inclusion/exclusion criteria not met <sup>b</sup>	22 (0.2%)	16 (0.2%)
Patient not willing to continue treatment <sup>c</sup>	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%)

<sup>a</sup> 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

<sup>b</sup> Patients stayed on study treatment if the investigator decided there was a need for dual antiplatelet therapy

<sup>c</sup> 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**

	<b>Ticagrelor 90mg bid N=9333</b>	<b>Clopidogrel 75mg qD N = 9291</b>
Total completed Study	N= 9026	N=9036
<b>Final visit</b>	<b>7645 (81.9%)</b>	<b>7542 (81.2%)</b>
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.

**Table 16. Subjects with "Important" Protocol Deviations – Full analysis dataset**

<b>Category</b>	<b>Ticagrelor 90 mg bid N=9,333</b>	<b>Clopidogrel 75 mg qd N=9,291</b>	<b>Total N=18,624</b>
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**

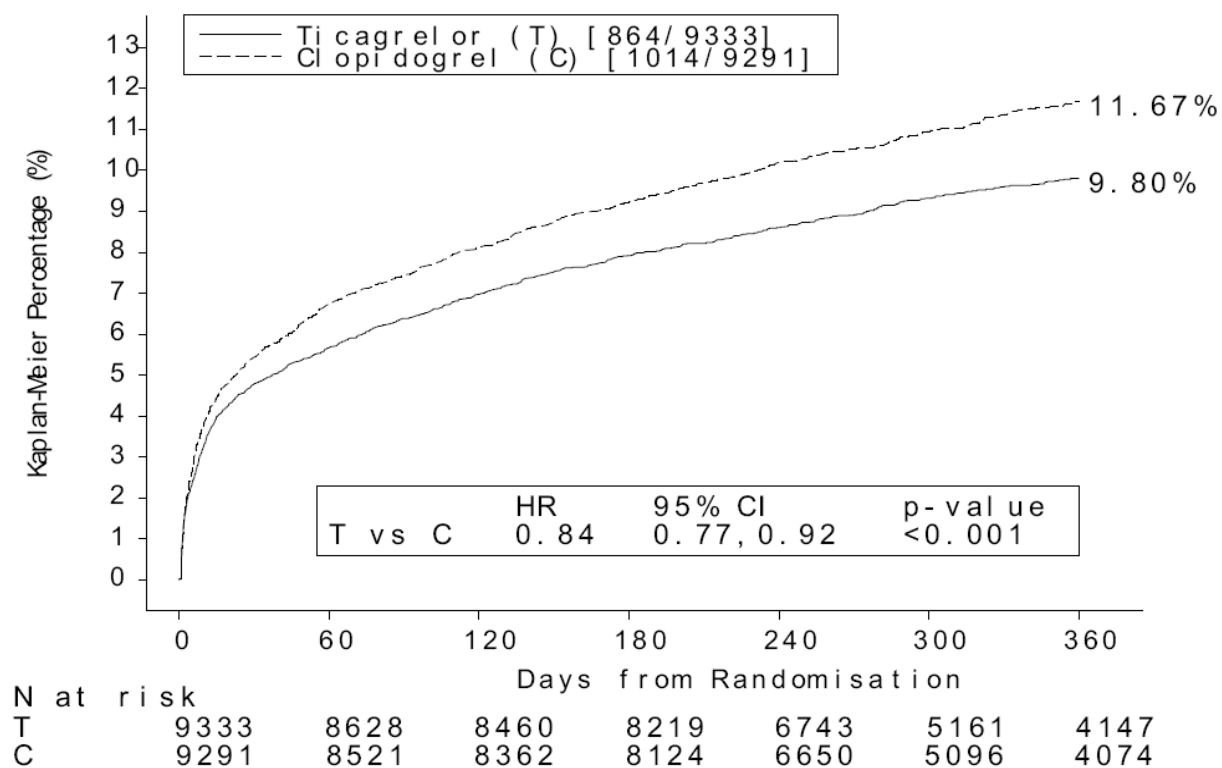
ENDPOINT	Ticagrelor 90 mg bd N = 9333		Clopidogrel 75 mg qd N = 9291			
	Patients with Events	KM %	Patients with Events	KM %	Hazard Ratio (95% CI)	p-value
<b>PRIMARY: Composite of CV Death/MI (excl. silent MI) /Stroke</b>	864 (9.3%)	<b>9.8%</b>	1014 (10.9%)	<b>11.7%</b>	0.84 (0.77, 0.92)	0.0003
<b>MI (excl. silent MI)</b>	504 (5.4%)	5.8%	593 (6.4%)	6.9%	0.84 (0.75, 0.95)	0.0045
<b>CV Death</b>	353 (3.8%)	4.0%	442 (4.8%)	5.1%	0.79 (0.69, 0.91)	0.0013
<b>Stroke</b>	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**

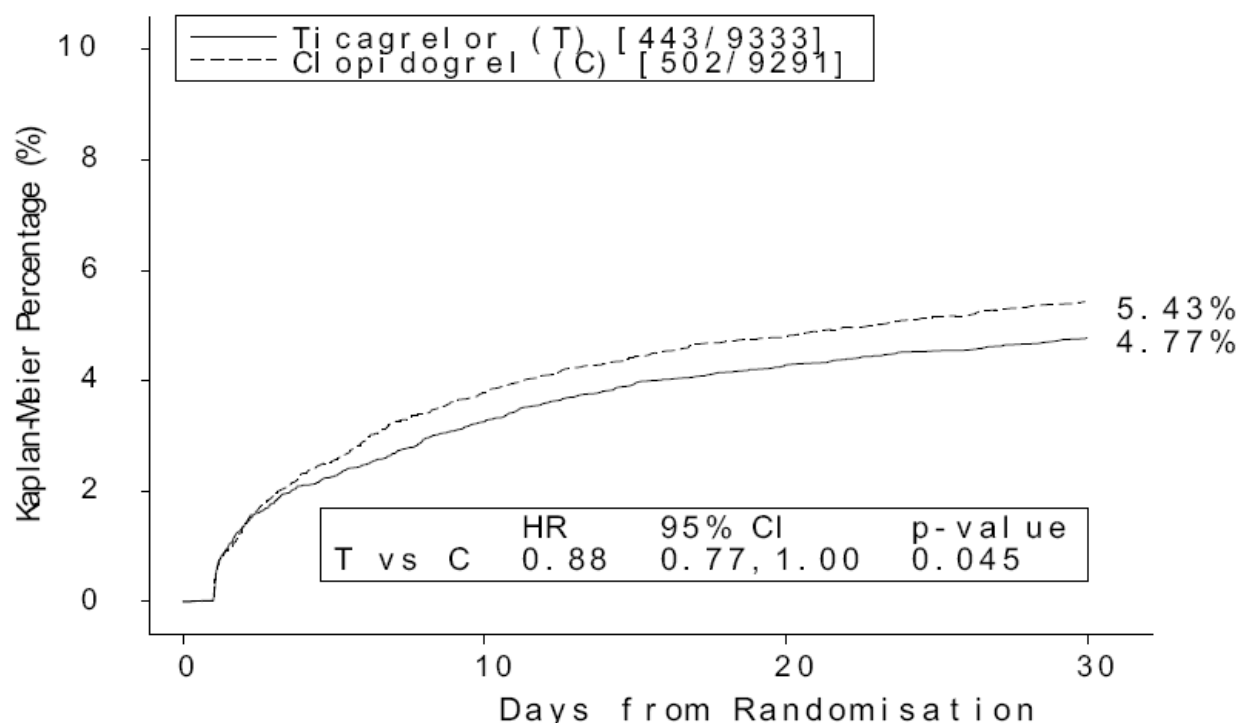
		Ticagrelor 90 mg bd N=9333			Clopidogrel 75 mg od N=9291				
Primary Endpoint	Time Interval	n	Patients with Events	KM %	n	Patients with Events	KM %	Hazard Ratio (95% CI)	p-value
Composite of CV Death, MI (excl. silent MI), Stroke	1- 30 days	9333	443 (4.7%)	4.8%	9291	502 (5.4%)	5.4%	0.88 (0.77,1.00)	0.0446
	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**

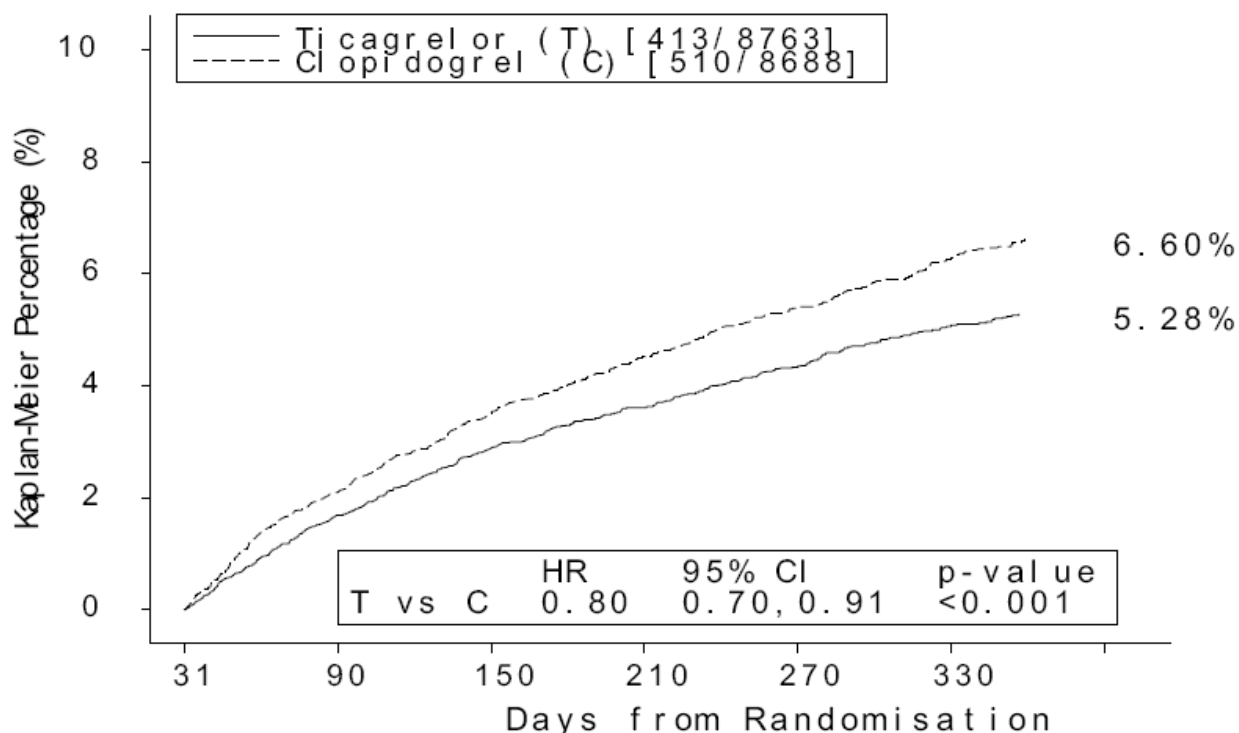


Source: Sponsor, CSR, p. 3421, Fig. 11.2.16

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**

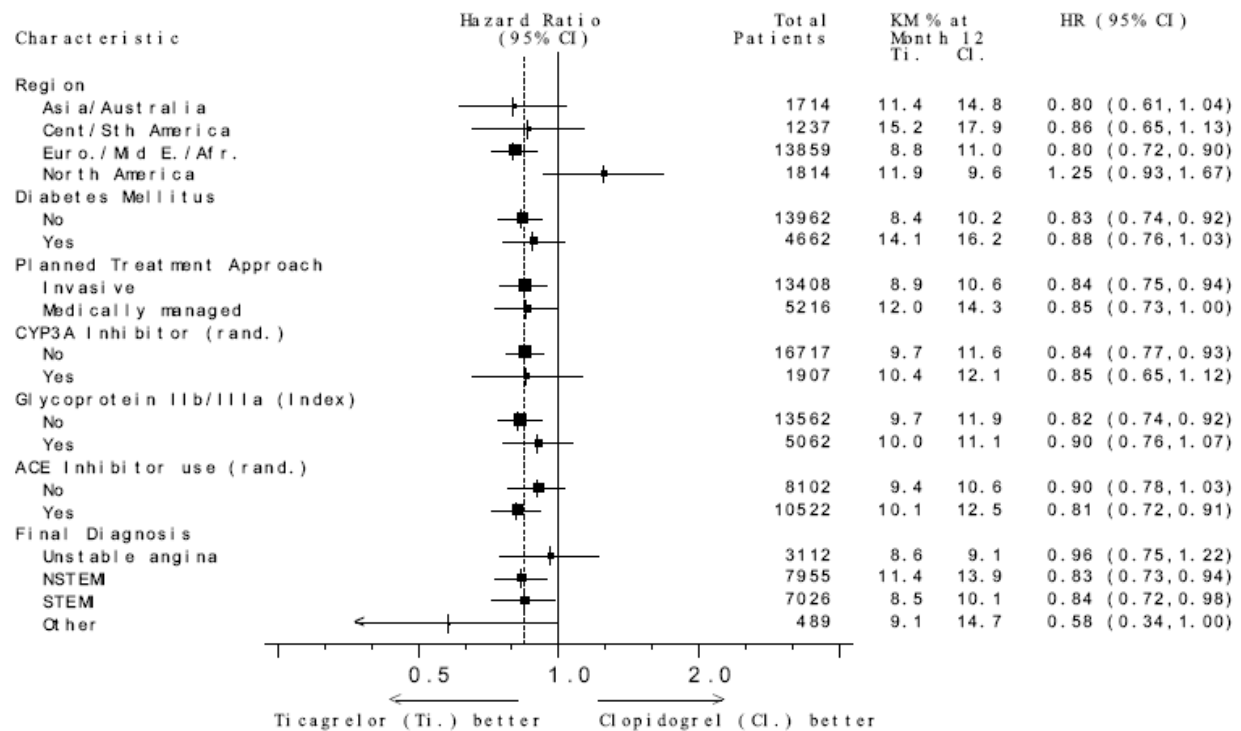
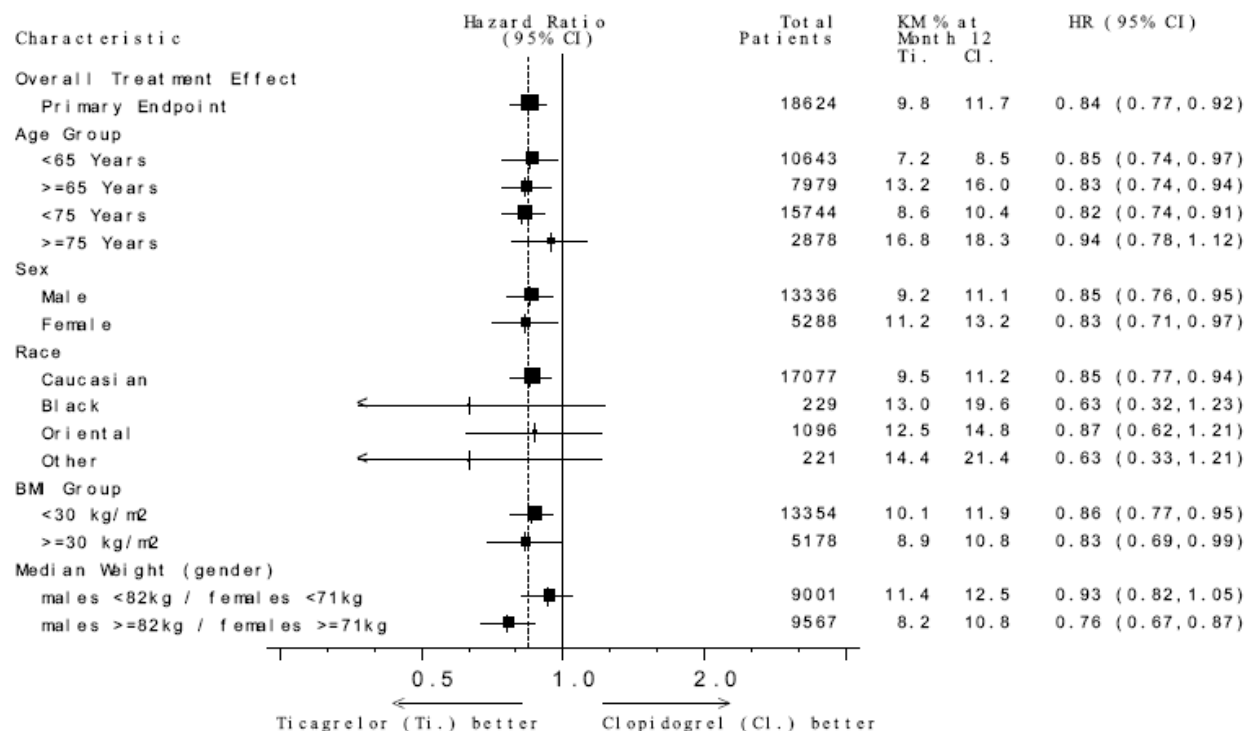


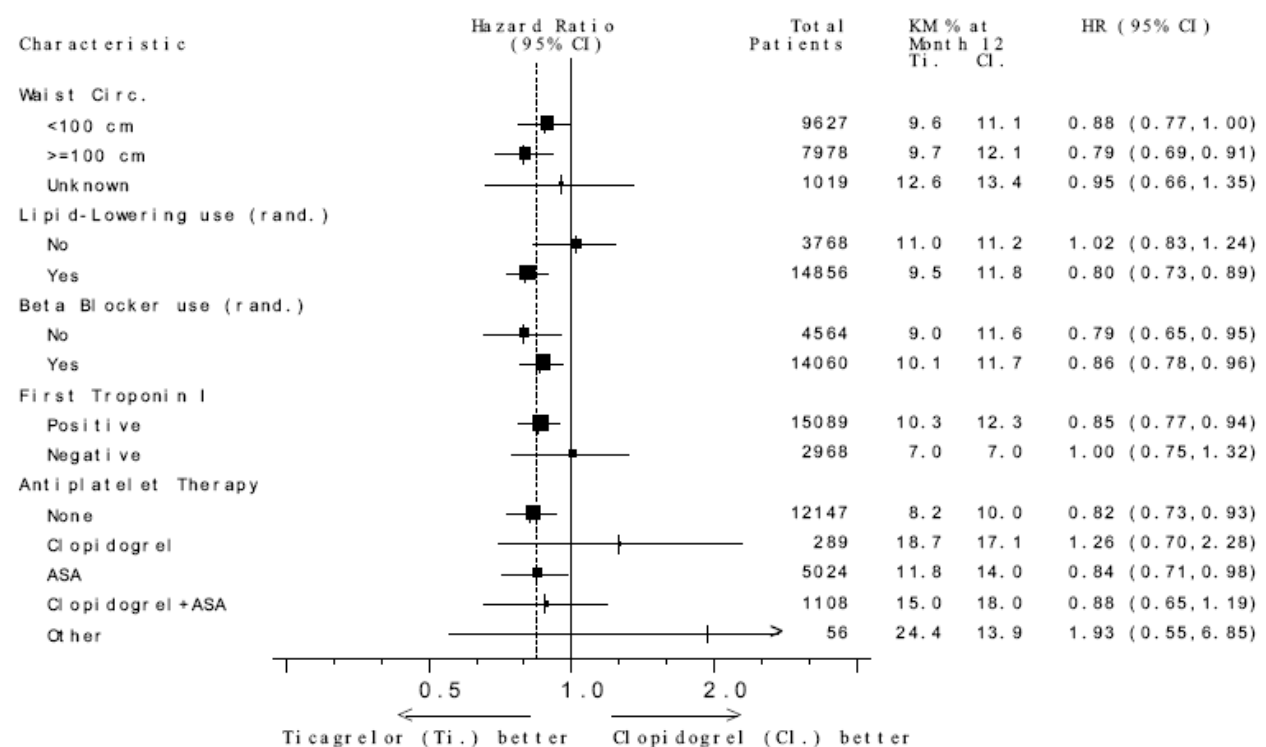
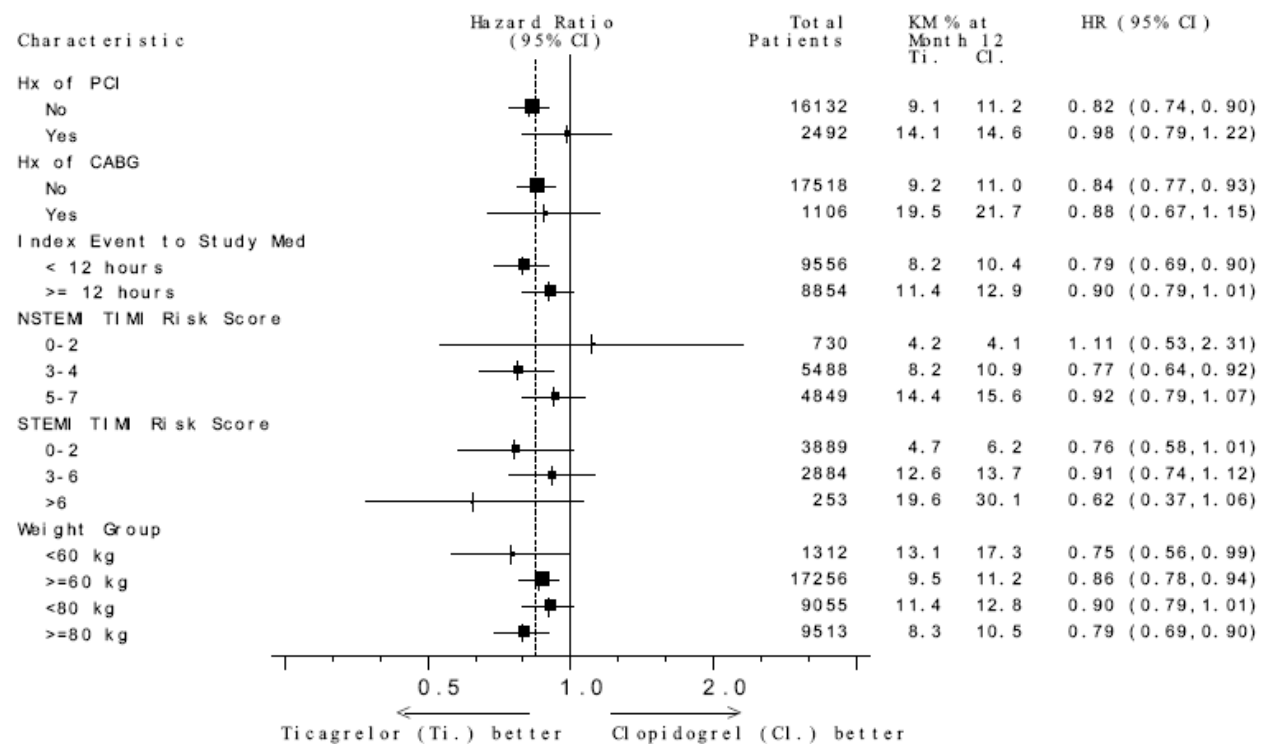
Source: Sponsor, CSR p. 3421, Fig. 11.2.16

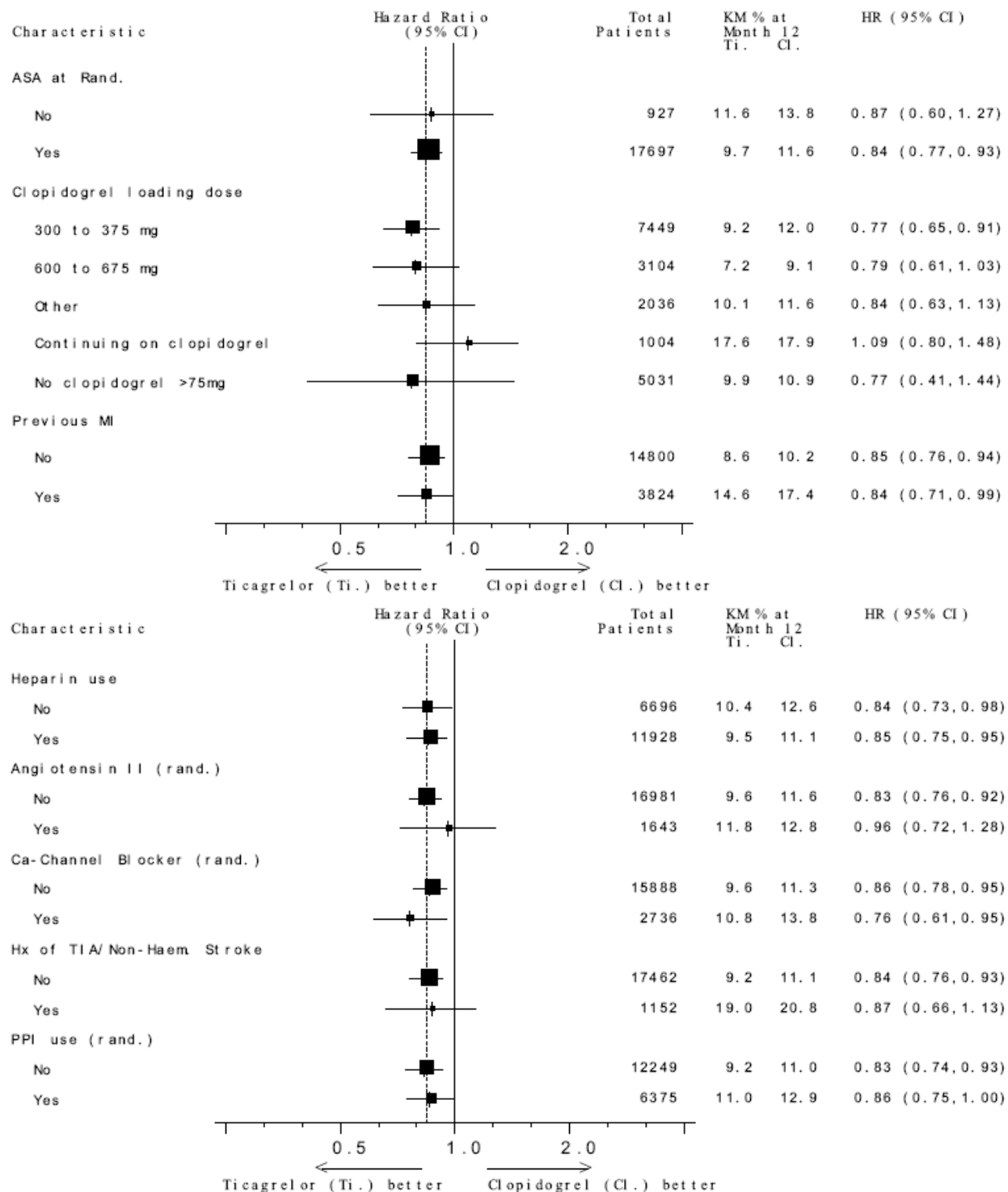
#### 6.1.4.2 Forest Plots: Primary Endpoint

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 Ratio and Rates of Primary Endpoint by Subgroup (forest plot)**







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)
<b>STEMI</b>	7,026	337/3530 (10.1%)	281/3496 (8.49%)	0.84 (0.72, 0.98)
<b>NSTEMI</b>	7,955	510/3950 (13.9%)	432/4005 (11.5%)	0.83 (0.73, 0.94)
<b>UA</b>	3,112	132/1563 (9.07%)	124/1549 (8.62%)	0.96 (0.75, 1.22)
<b>Other*</b>	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**

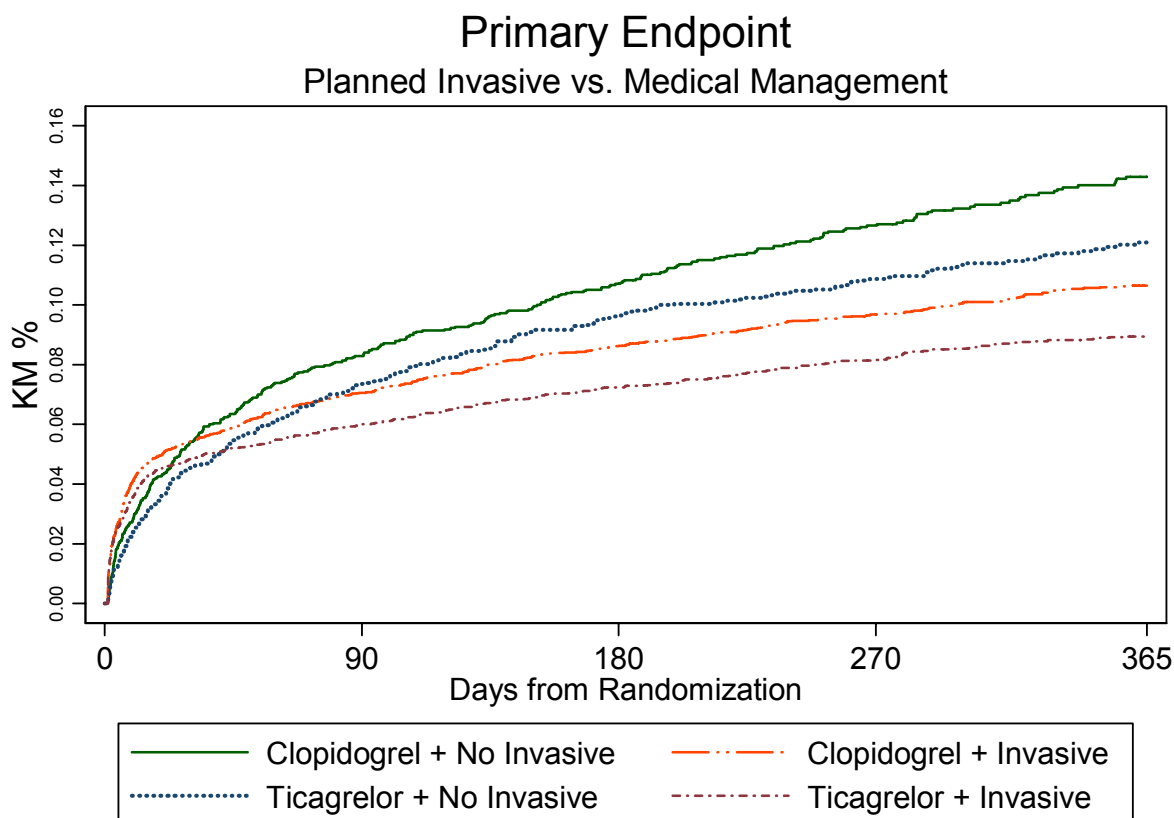
Planned Strategy	# subjects	Clopidogrel # events/n (KM% 365d)	Ticagrelor # events/n (KM% 365d)	HR (95% CI)
<b>Invasive Mgmt</b>	13,408	668/6676 (10.7%)	569/6732 (9.02%)	0.84 (0.75, 0.94)
<b>Medical Mgmt</b>	5,216	346/2615 (14.3%)	295/2601 (12.1%)	0.85 (0.73, 1.00)

**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**



**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)
<b>Early PCI*</b>				
<b>Yes</b>	9,254	407/4625	349/4629	0.85 (0.74, 0.99)
<b>No</b>	9,364	607/4666	515/4698	0.84 (0.75, 0.94)
<b>Any PCI (w/o prior event)</b>				
<b>Yes</b>	11,855	545/5931	484/5924	0.89 (0.78, 1.00)
<b>No</b>	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
<b>Medical Mgmt</b>	0.73 (0.46, 1.16) 75/451	0.85 (0.70, 1.02) 416/2910	0.97 (0.69, 1.37) 132/1726
<b>Invasive Mgmt</b>	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

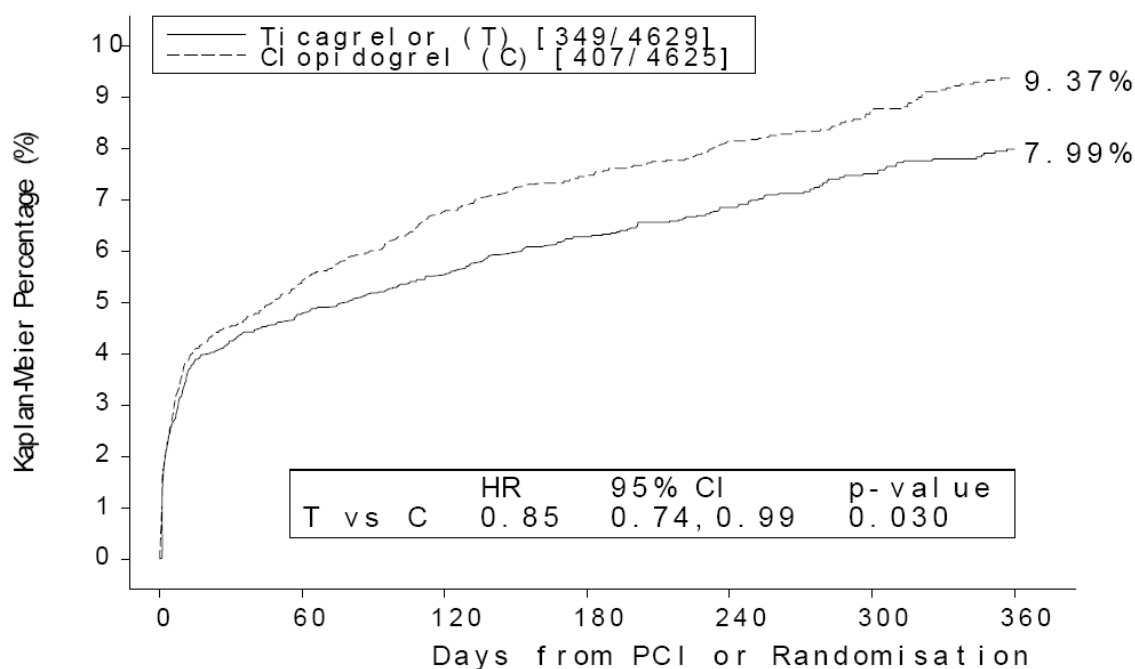
An exploratory analysis examined the primary endpoint following PCI in a subset of patients with planned invasive management who actually received PCI within ( $\pm$ ) 24 hours of randomization (early PCI).

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**

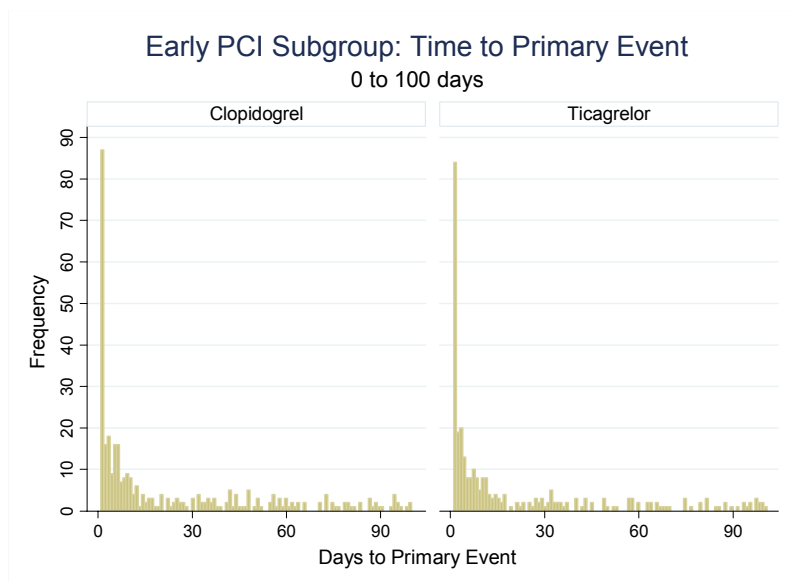


Source: Sponsor, CSR, p. 151, Fig. 15

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.

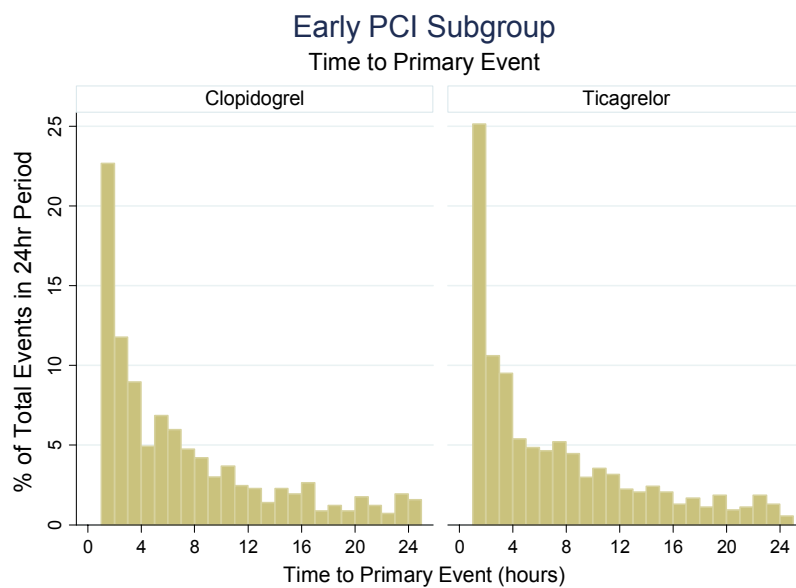


**Figure 10. Early PCI: Time to Primary Event**



**Source: R. Fiorentino, Clinical Reviewer**

**Figure 11. Early PCI: Time to Primary Event (first 24hrs)**



**Source: R. Fiorentino, Clinical Reviewer**

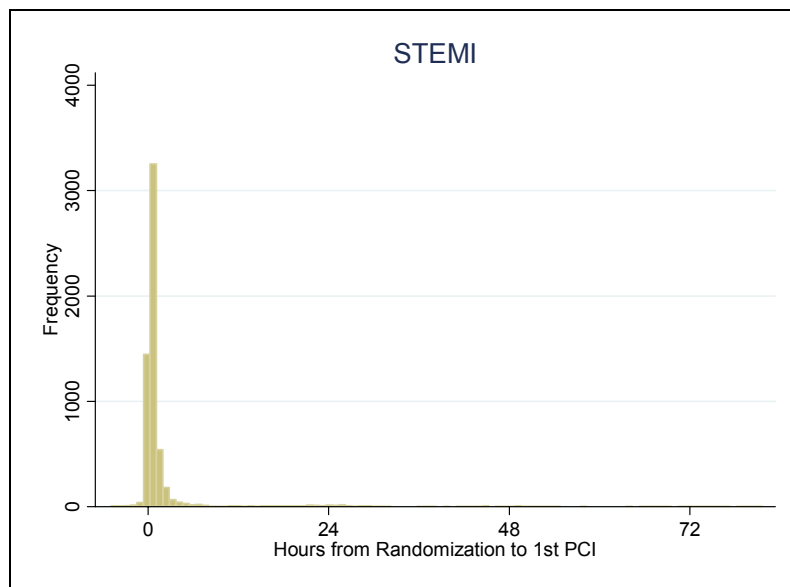
Time to 1<sup>st</sup> PCI

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 1<sup>st</sup> PCI were created on subjects who had either STEMI, NSTEMI or UA as the index event (Figure 12, Figure 13, Figure 14).

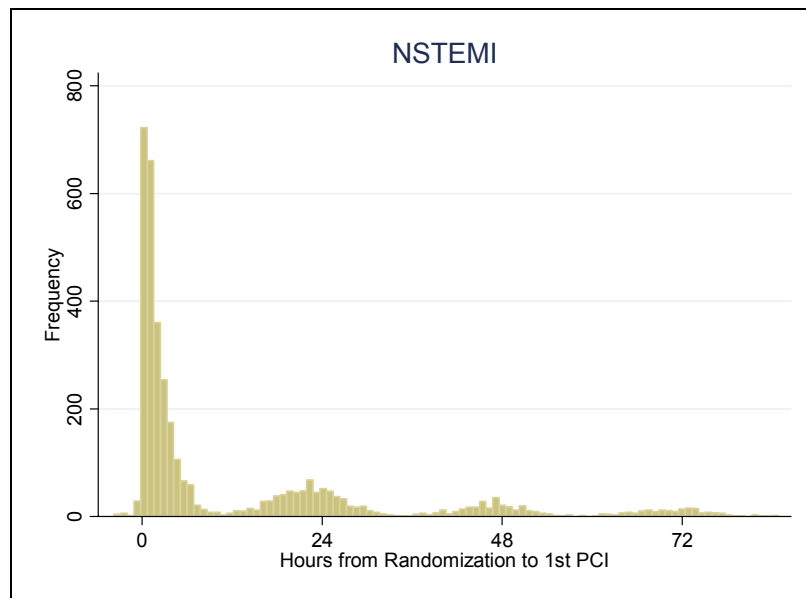
From these figures, it can be seen that STEMI subjects tended to undergo PCI early and frequently, as would be expected for a population with an indication for primary PCI. Both NSTEMI and UA also had an early spike of PCI but also showed delays in PCI procedures. The multimodal time course of PCIs in 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**



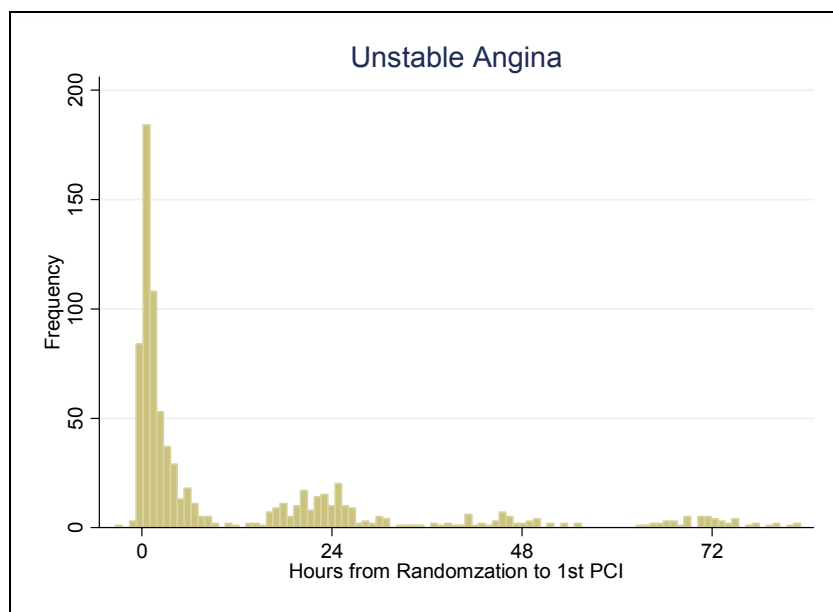
Source: R. Fiorentino, Clinical Reviewer

**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**

	Ticagrelor 90 mg bd N = 9333		Clopidogrel 75 mg od N = 9291				
Endpoint	Patients with Events	KM%	Patients with Event	KM%	HR (95%CI)	p-value	Significant?
<b>PRIMARY ENDPOINT</b>							
<b>Composite of CV Death/MI (excl. silent MI) /Stroke</b>	864 (9.3%)	9.8%	1014 (10.9%)	11.7%	0.84 (0.77, 0.92)	0.0003	Yes
<b>SECONDARY ENDPOINTS</b>							
<b>Composite of CV Death/MI (excl. silent MI) /Stroke - Intent to Invasively Manage*</b>	569 (8.5%)	8.9%	668 (10.0%)	10.6%	0.84 (0.75, 0.94)	0.0025	Yes
<b>Composite of All Cause Mortality/MI (excl. silent MI)/Stroke</b>	901 (9.7%)	10.2%	1065 (11.5%)	12.3%	0.84 (0.77, 0.92)	0.0001	Yes
<b>Composite of CV Death/Total MI/Stroke/ Severe Recurrent Cardiac Ischemia/ Recurrent Cardiac Ischemia/Transient Ischemic Attack/Other Arterial Thrombotic Events</b>	1290 (3.8%)	14.6%	1456 (15.7%)	16.7%	0.88 (0.81, 0.95)	0.0006	Yes
<b>MI (excl. silent MI)</b>	504 (5.4%)	5.8%	593 (6.4%)	6.9%	0.84 (0.75, 0.95)	0.0045	Yes
<b>CV Death</b>	353 (3.8%)	4.0%	442 (4.8%)	5.1%	0.79 (0.69, 0.91)	0.0013	Yes
<b>Stroke</b>	125 (1.3%)	1.5%	106 (1.1%)	1.3%	1.17 (0.91, 1.52)	0.2249	No
<b>All Cause Mortality</b>	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. <b>Source: Sponsor, CSR, p.3361, Table 11.2.1</b>							

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
<b>All MI (excl. silent MI)</b>	566	667	504 (5.4%)	593 (6.4%)
<b>MI detected by Investigator</b>	452	546	395 (4.2%)	482 (5.2%)
<b>MI detected from cardiac enzyme biomarkers</b>	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)
<b>STEMI</b>	7,026	136/3496 (4.2%)	184/3530 (5.7%)	0.74 (0.59, 0.93)
<b>NSTEMI</b>	7,955	288/4005 (7.9%)	324/3950 (8.9%)	0.87 (0.74, 1.02)
<b>UA</b>	3,112	76/1549 (5.2%)	75/1563 (5.1%)	1.02 (0.75, 1.42)
<b>OVERALL*</b>	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)
<b>Medical Mgmt</b>	5,216	176/2601 (7.3%)	187/2615 (7.8%)	0.94 (0.77, 1.15)
<b>Invasive Mgmt</b>	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
<b>Medical Mgmt</b>	0.99 (0.53, 1.85) 39/451	0.87 (0.68, 1.11) 248/2910	1.25 (0.78, 2.01) 70/1726
<b>Invasive Mgmt</b>	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 STEMI 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**

	<b>Ticagrelor 90 mg bd N = 9333</b>	<b>Clopidogrel 75 mg od N = 9291</b>
<b>Total number of MIs</b>	603	682
<b>Type 5 (CABG MI): Any peri-CABG MI</b>	45 (7.5%)	38 (5.6%)
<b>Type 4b: Any MI that is adjudicated as associated with stent thrombosis</b>	80 (13.3%)	113 (16.6%)
<b>Type 4a: Any peri-PCI MI</b>	100 (16.6%)	124 (18.2%)
<b>Type 3: Any MI not covered in types 4-5, accompanied by death</b>	18 (3.0%)	15 (2.2%)
<b>Types 1 and 2: Any MI not covered by definitions 3-5</b>	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**

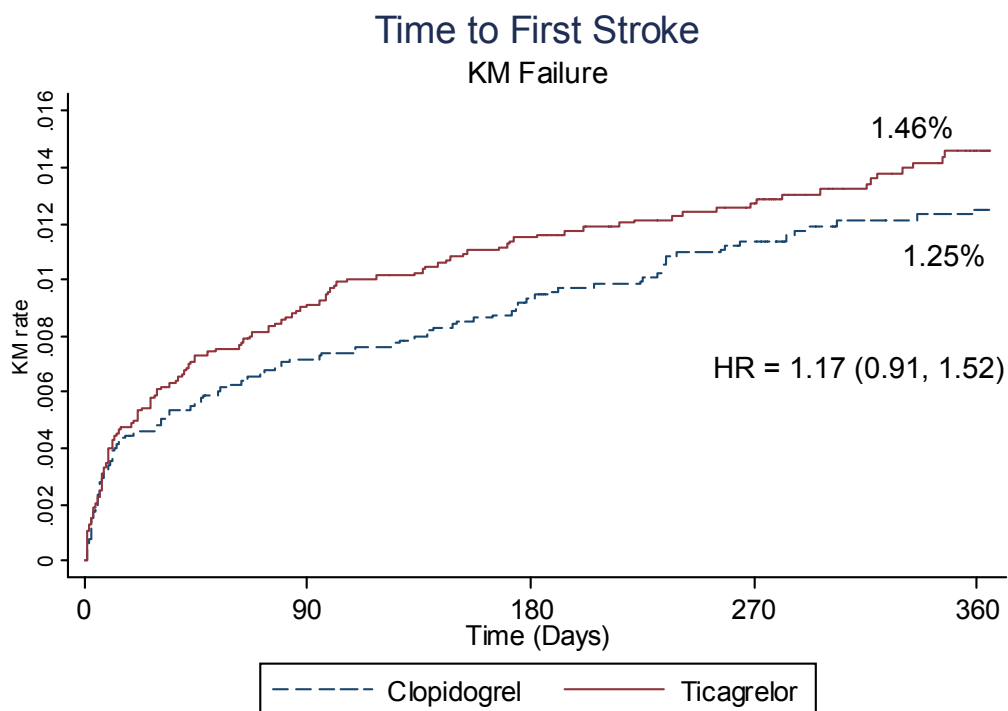
	<b>Ticagrelor N=9333 Events, (%)</b>	<b>Clopidogrel N=9291 Events, (%)</b>	<b>HR (95%CI)</b>
<b>Silent MI</b>	5 (0.1%)	6 (0.1%)	0.83 (0.25, 2.72)

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**



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. clodidogrel, n=95) in PLATO. A total of 36 hemorrhagic strokes were reported (ticagrelor, n=23 vs. clodidogrel, n=13). Unknown/no imaging performed was reported for 10 ticagrelor vs. 2 clodidogrel 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
<b>Non-hemorrhagic</b>	100	95	96 (1.0%)	91 (1.0%)
<b>Hemorrhagic</b>	23	13	23 (0.2%)	13 (0.1%)
<b>Unknown/ No Imaging Performed</b>	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**

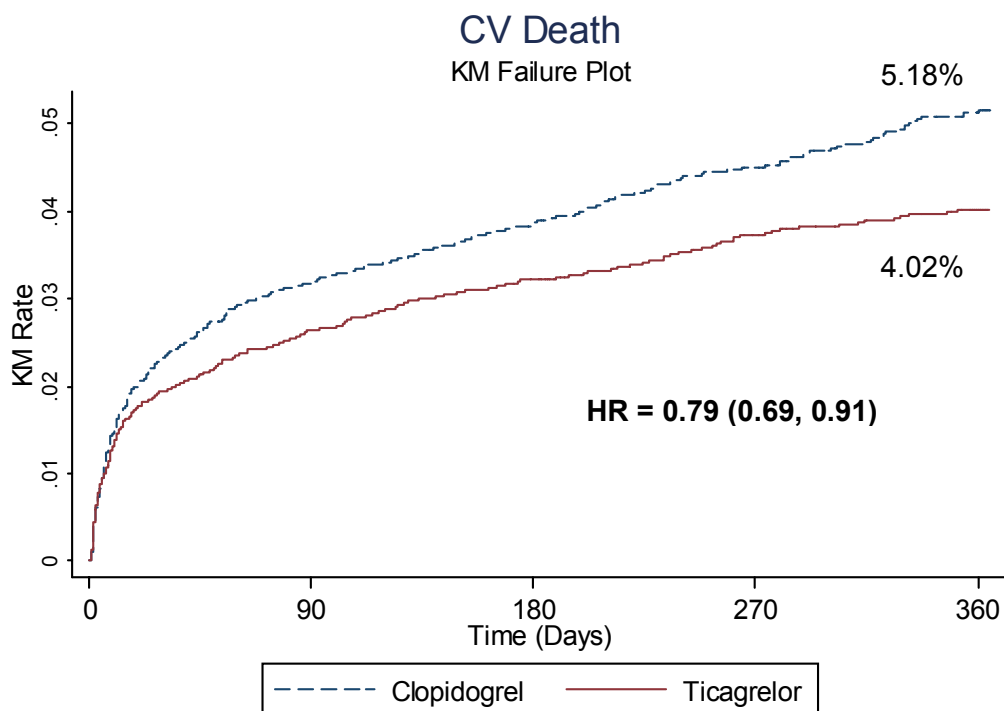
	N Subjects	Ticagrelor n/N	Clopidogrel n/N	HR (95% CI)
<b>Prior Stroke</b>				
<b>Yes</b>	722	7/353	14/369	0.51 (0.20, 1.25)
<b>No</b>	17,892	118/8973	92/8919	1.28 (0.97, 1.68)
<b>Prior TIA</b>				
<b>Yes</b>	499	13/246	5/253	2.52 (0.90, 7.06)
<b>No</b>	18,115	112/9080	101/9035	1.10 (0.84, 1.45)

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)
<b>STEMI</b>	7,026	140/3496 (4.17%)	164/3530 (4.97%)	0.86 (0.69, 1.08)
<b>NSTEMI</b>	7,955	146/4005 (3.90%)	191/3950 (5.31%)	0.75 (0.61, 0.93)
<b>UA</b>	3,112	46/1549 (3.28%)	60/1563 (4.29%)	0.78 (0.53, 1.14)
<b>OVERALL*</b>	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

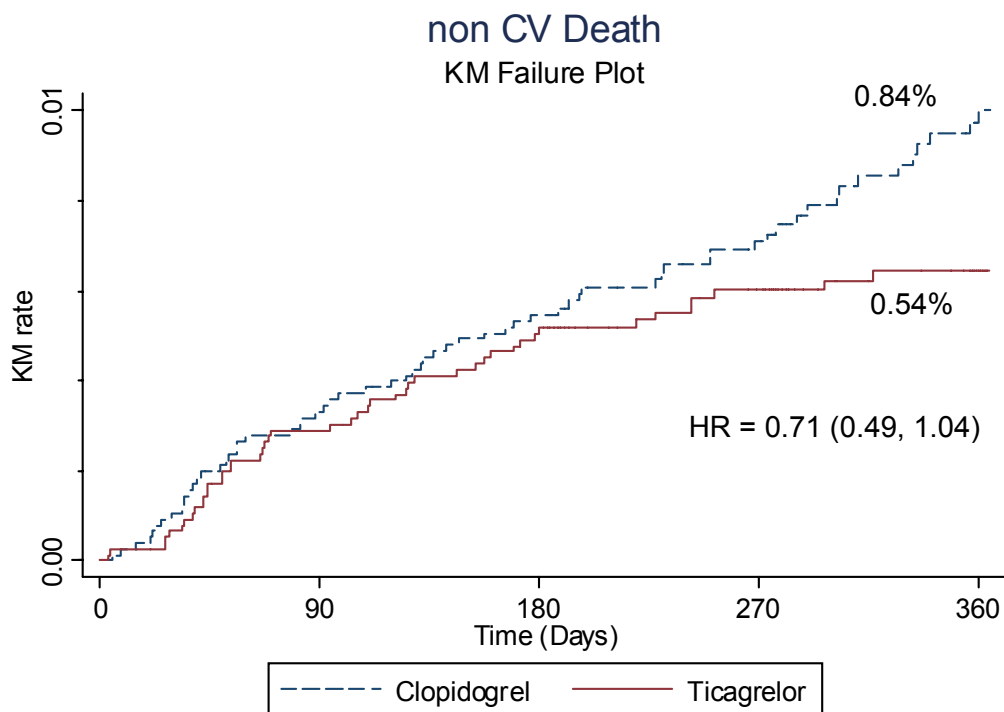
\* Includes "unknown" ACS event type (not shown)

**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**



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)
<b>STEMI</b>	7,026	9/3496 (0.30%)	22/3530 (0.78%)	0.41 (0.19, 0.90)
<b>NSTEMI</b>	7,955	31/4005 (0.84%)	28/3950 (0.84%)	1.09 (0.65, 1.81)
<b>UA</b>	3,112	5/1549 (0.35%)	10/1563 (0.84%)	0.51 (0.17, 1.48)
<b>OVERALL*</b>	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
<ul style="list-style-type: none"> <li>• Index Event hospitalization information</li> <li>• All cardiac biomarker measurements (all CK-MB, Troponin I &amp; T)</li> <li>• Cardiac Ischemic Event</li> <li>• All other hospitalization forms (if applicable)</li> <li>• Procedures and Operations (Cardiac Cath &amp; PCI)</li> <li>• Death Form</li> </ul>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• ECGs: (date and time the ECG was performed must be on each ECG submitted) <ul style="list-style-type: none"> <li>○ Enrolment Visit</li> <li>○ Pre-Discharge (discharge after ACS event if event occurs in separate hospitalization)</li> <li>○ 1 Month</li> <li>○ Peri-endpoint event (ECGs showing changes described in the discharge summary, investigator narrative or reported by site)</li> </ul> </li> <li>• Angiography Report <b>(If done)</b></li> <li>• Reports from any/all the revascularizations that were performed related to the event</li> <li>• Investigator Assessment and Narrative Form if death at home</li> <li>• Autopsy report <b>(if done)</b></li> </ul>

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**

	<b>Ticagrelor N = 9333</b>		<b>Clopidogrel N=9291</b>			
<b>Characteristic</b>	<b>Patients with Events</b>	<b>KM %</b>	<b>Patients with Events</b>	<b>KM %</b>	<b>HR (95%CI)</b>	<b>p- value*</b>
<b>Patients with a History of PCI / Receiving any Stent during the study</b>	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
<b>Patients Receiving any Stent during the study</b>	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
<b>Patients Receiving a Drug- Eluting Stent during the study</b>	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
<b>Patients Receiving a Bare Metal Stent during the study</b>	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)**

	<b>Ticagrelor N = 9333</b>	<b>Clopidogrel N = 9291</b>
<b>Total MIs</b>	13.3% (80/603)	16.6% (113/682)
<b>Patients with Events (1<sup>st</sup> MI)</b>	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**

	<b>Total Events</b>	<b>Subjects with Events</b>	<b>As a proportion of subjects w/ prior PCI or stent placement</b>	<b>Difference (95% CI)*</b>
<b>Clopidogrel (n=9291)</b>	68	60	60 / 6196 (0.97%)	.37% (0.06%, 0.68%)
<b>Ticagrelor (n=9333)</b>	42	37	37 / 6182 (0.60%)	

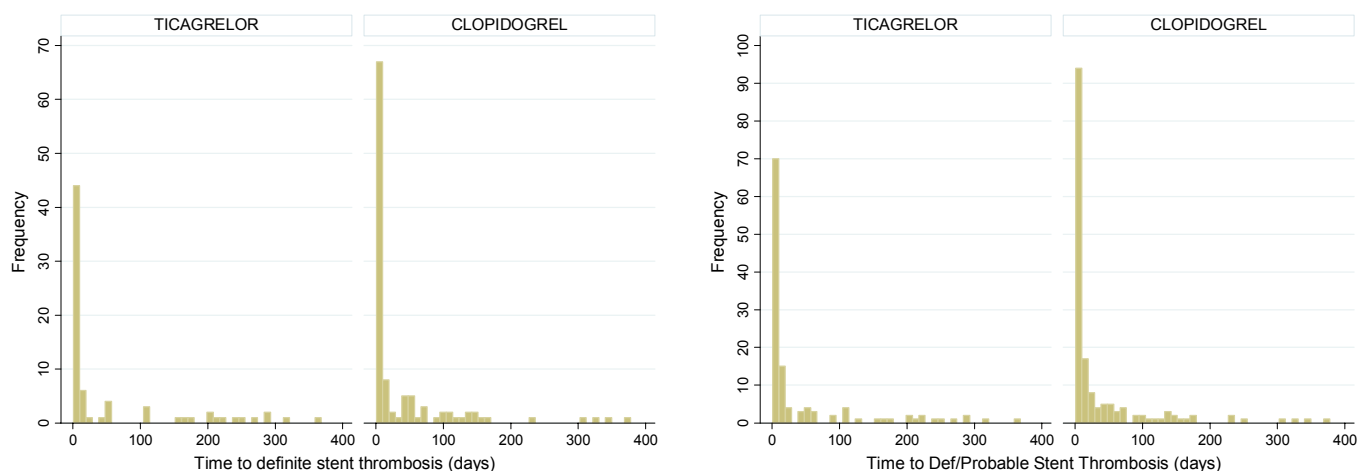
\* derived from a 2-sample test of proportions for descriptive purposes only

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		Total <sup>a</sup>
	Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291	
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%)

<sup>a</sup> 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**

Characteristic	Randomised Treatment				
	Ticagrelor 90 mg bd N = 4465		Clopidogrel 75 mg od N = 4432		Hazard Ratio (95% CI)
	Patients with Events	KM %	Patients with Events	KM %	
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., 2<sup>nd</sup> 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,  $\geq 75$  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)
$\geq 65$ 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)
$\geq 75$ 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)
<b>Male</b>	13,336	9.2% (586/6678)	11.1% (686/6658)	0.85 (0.76, 0.95 )
<b>Female</b>	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**

<b>Ethnicity*</b>	<b># subjects</b>	<b>Ticagrelor (12m KM%)</b>	<b>Clopidogrel (12m KM%)</b>	<b>HR (95% CI)</b>
<b>“Caucasian”</b>	17,077	9.5% (769/8566)	11.2% (893/8511)	0.85 (0.77, 0.94)
<b>“Black”</b>	229	13.0% (14/115)	19.6% (21/114)	0.63 (0.32, 1.23)
<b>“Oriental”</b>	1,096	12.5% (66/542)	14.8% (77/554)	0.87 (0.62, 1.21)
<b>Other</b>	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/m<sup>2</sup>, the hazard ratios were similar across groups.

**Table 47. Primary Endpoint by BMI Subgroups**

<b>BMI</b>	<b># subjects</b>	<b>Ticagrelor (12m KM%)</b>	<b>Clopidogrel (12m KM%)</b>	<b>HR (95% CI)</b>
<b>&lt; 30 kg/m<sup>2</sup></b>	13,354	10.1% (636/6641)	11.9% (747/6713)	0.86 (0.77, 0.95)
<b>≥ 30 kg/m<sup>2</sup></b>	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**

<b>Median Weight Group by Sex</b>	<b># subjects</b>	<b>Ticagrelor (12m KM%)</b>	<b>Clopidogrel (12m KM%)</b>	<b>HR (95% CI)</b>
<b>Males &lt;82kg / Females &lt;71kg</b>	9,001	11.4%	12.5%	0.93 (0.82, 1.05)
<b>Males ≥82kg / Females ≥71kg</b>	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**

	<b>Ticagrelor 90 mg bd N = 9333</b>	<b>Clopidogrel 75 mg od N = 9291</b>
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**

	<b>N</b>	<b>Ticagrelor</b>	<b>Clopidogrel</b>	<b>HR (95%CI)</b>
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”

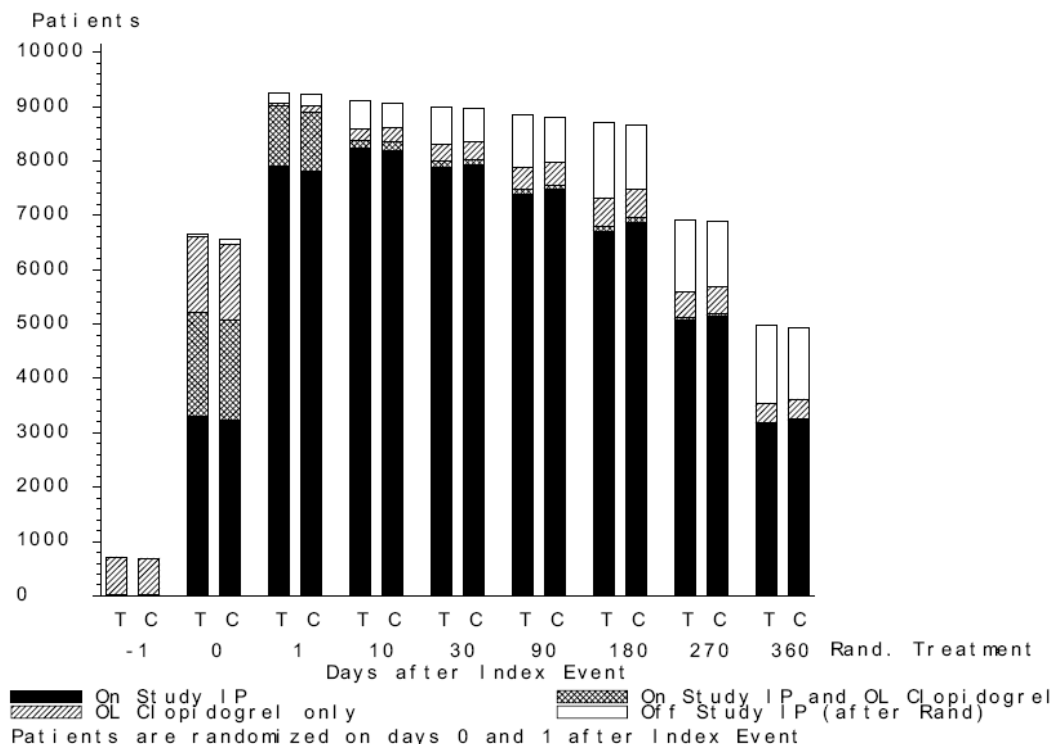
Source: R. Fiorentino, Clinical Reviewer

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**

	<b>Ticagrelor 90 mg bd N=9333</b>	<b>Clopidogrel 75 mg od N=9291</b>
<b>Patients receiving PCI</b>	4736	4736
Clopidogrel OL drug received <sup>a</sup>	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%)

<sup>a</sup> 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**

		<b>Ticagrelor 90 mg bd N = 9333</b>			<b>Clopidogrel 75 mg od N = 9291</b>			
	<b>Group</b>	<b>n</b>	<b>Subjects with Events</b>	<b>KM %</b>	<b>n</b>	<b>Subjects with Events</b>	<b>KM%</b>	<b>HR (95%CI)</b>
<b>Clopidogrel* Loading Dose</b>	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**

	<b>N</b>	<b>HR(95%CI)</b>
<b>No PPI</b>	8,911	0.84 (0.72, 0.97)
<b>PPI</b>	9,690	0.85 (0.76, 0.95)

Source: R. Fiorentino, Clinical Reviewer

Furthermore, there was no 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**

	<b>N</b>	<b>HR(95%CI)</b>
<b>No omeprazole</b>	15,195	0.82 (0.74, 0.91)
<b>Omeprazole</b>	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**

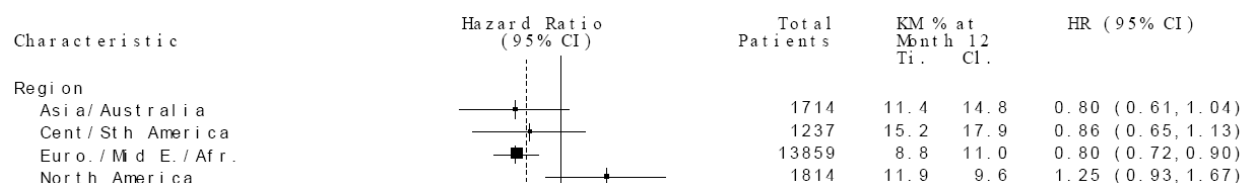
#### **6.1.9.1 Regional Differences**

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
<b>USA</b> <b>N=1413</b>	<b>1.27</b> <b>(0.92, 1.75)</b>	<b>TIC</b> <b>n=707</b>	84 (12%)	64 (9%)	24 (3%)	7 (1%)
		<b>CLOP</b> <b>n=706</b>	67 (9%)	47 (7%)	19 (3%)	4 (1%)
<b>E. Europe</b> <b>N=7645</b>	<b>0.76</b> <b>(0.65, 0.88)</b>	<b>TIC</b> <b>n=3820</b>	299 (8%)	162 (4%)	150 (4%)	41 (1%)
		<b>CLOP</b> <b>n=3825</b>	394 (10%)	242 (6%)	173 (5%)	38 (1%)
<b>W. Europe</b> <b>N=5429</b>	<b>0.84</b> <b>(0.71, 1.00)</b>	<b>TIC</b> <b>n=2725</b>	240 (9%)	157 (6%)	60 (2%)	40 (1%)
		<b>CLOP</b> <b>n=2704</b>	281 (10%)	169 (6%)	101 (4%)	36 (1%)
<b>Asia</b> <b>N=1631</b>	<b>0.77</b> <b>(0.58, 1.01)</b>	<b>TIC</b> <b>n=819</b>	90 (11%)	37 (5%)	56 (7%)	13 (2%)
		<b>CLOP</b> <b>n=812</b>	114 (14%)	45 (6%)	75 (9%)	10 (1%)
<b>L. America</b> <b>N=1237</b>	<b>0.86</b> <b>(0.65, 1.13)</b>	<b>TIC</b> <b>n=621</b>	91 (15%)	48 (8%)	43 (7%)	15 (2%)
		<b>CLOP</b> <b>n=616</b>	104 (17%)	52 (8%)	57 (9%)	13 (2%)
<b>Other</b> <b>N=1269</b>	<b>1.11</b> <b>(0.77, 1.60)</b>	<b>TIC</b> <b>n=641</b>	60 (9%)	36 (6%)	20 (3%)	9 (1%)
		<b>CLOP</b> <b>n=628</b>	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.

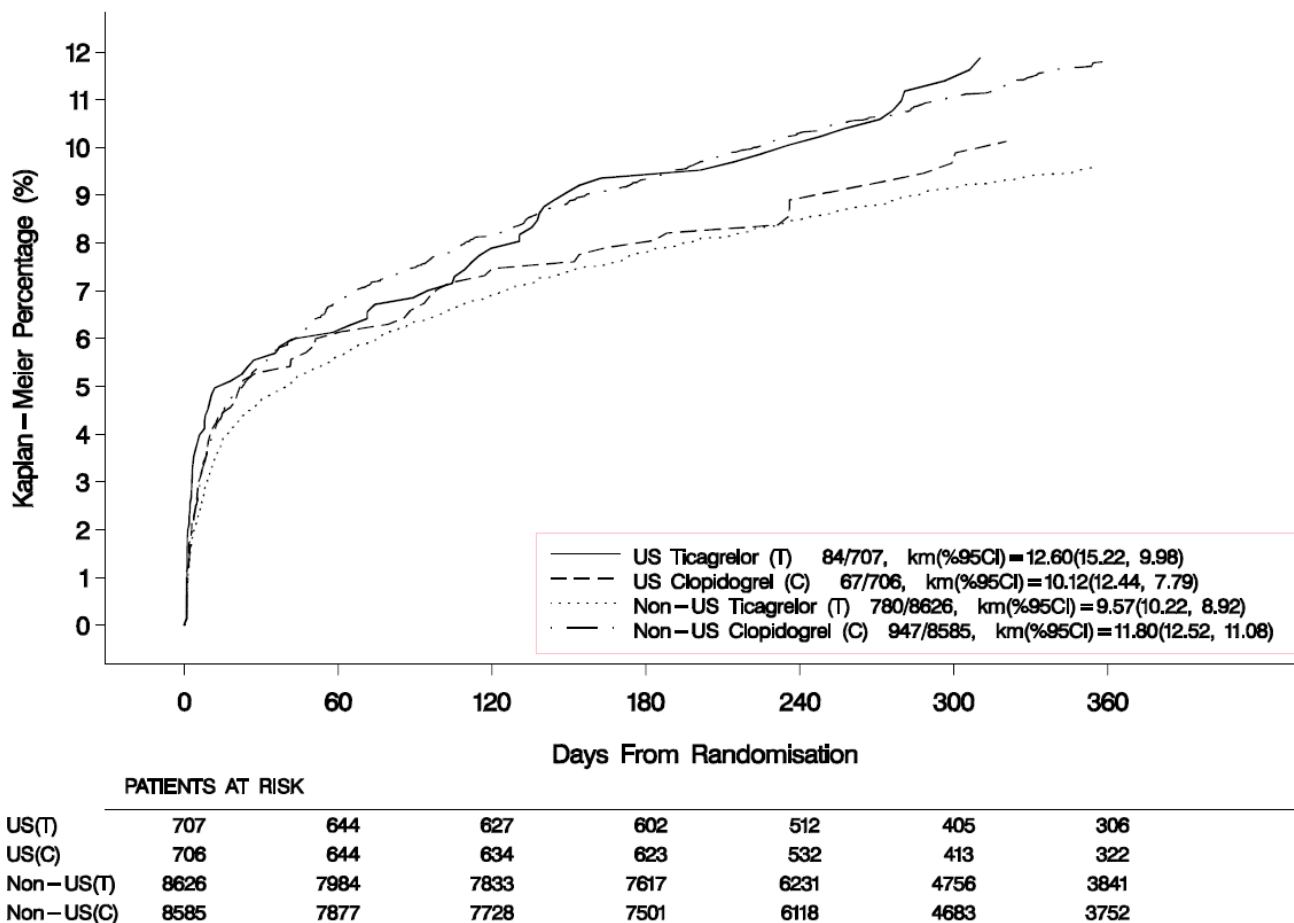
**Table 58. Outcomes by US and non-US**

	<b>Ticagrelor</b>	<b>Clopidogrel</b>	<b>HR (95% CI)</b>	<b>P-value</b>
<b>Overall</b> N=18,624	864/9333 (9.8%)	1014/9291 (11.7%)	0.84 (0.77, 0.93)	p<0.0001
<b>Non-US</b> n=17,211	780/8626 (9.6%)	947/8585 (11.8%)	0.81 (0.74, 0.90)	p<0.0001
<b>US</b> 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**

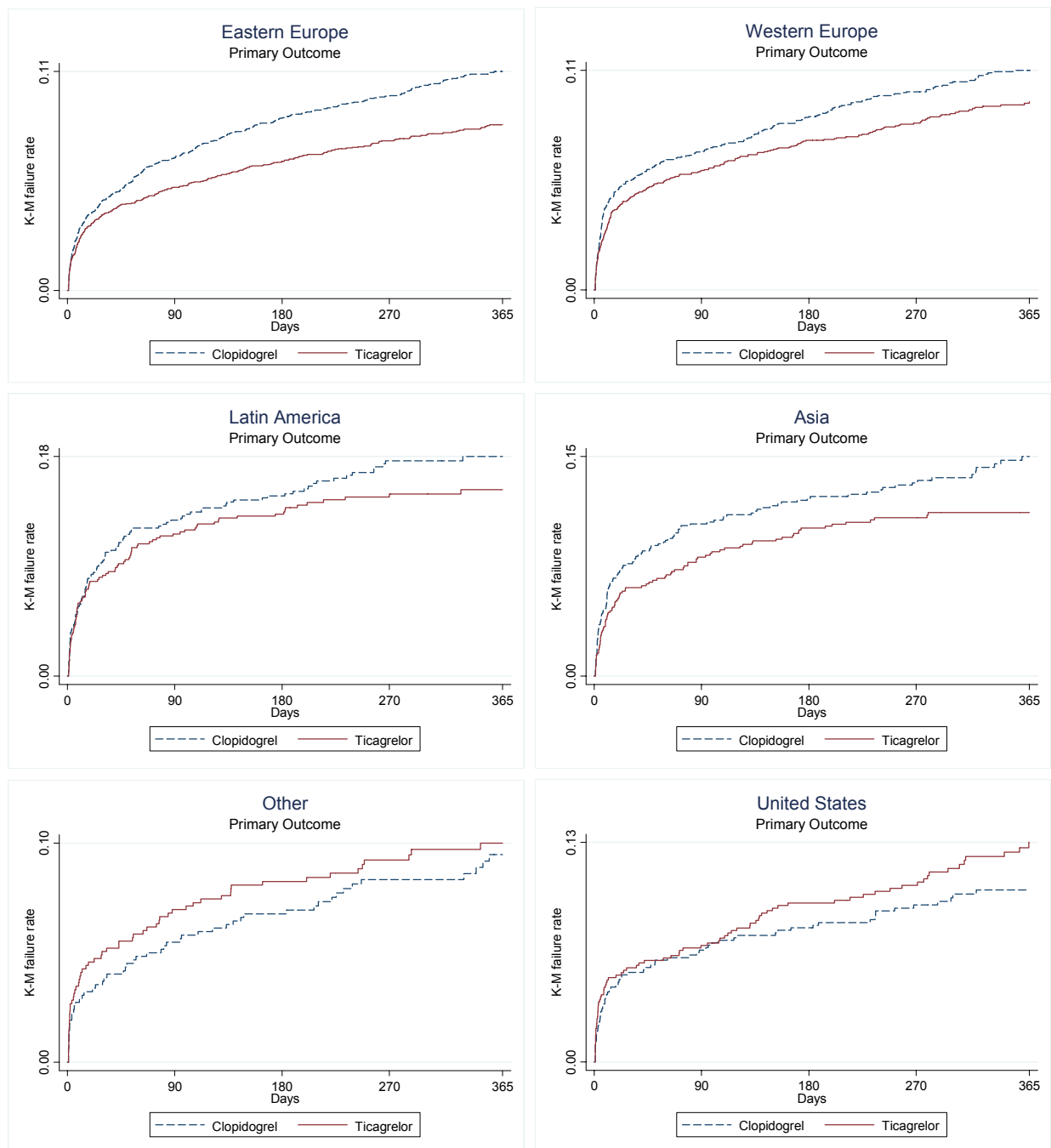


Source: Sponsor, Exploratory Analysis of Treatment Interactions in Plato, p.32, Fig. 4

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**



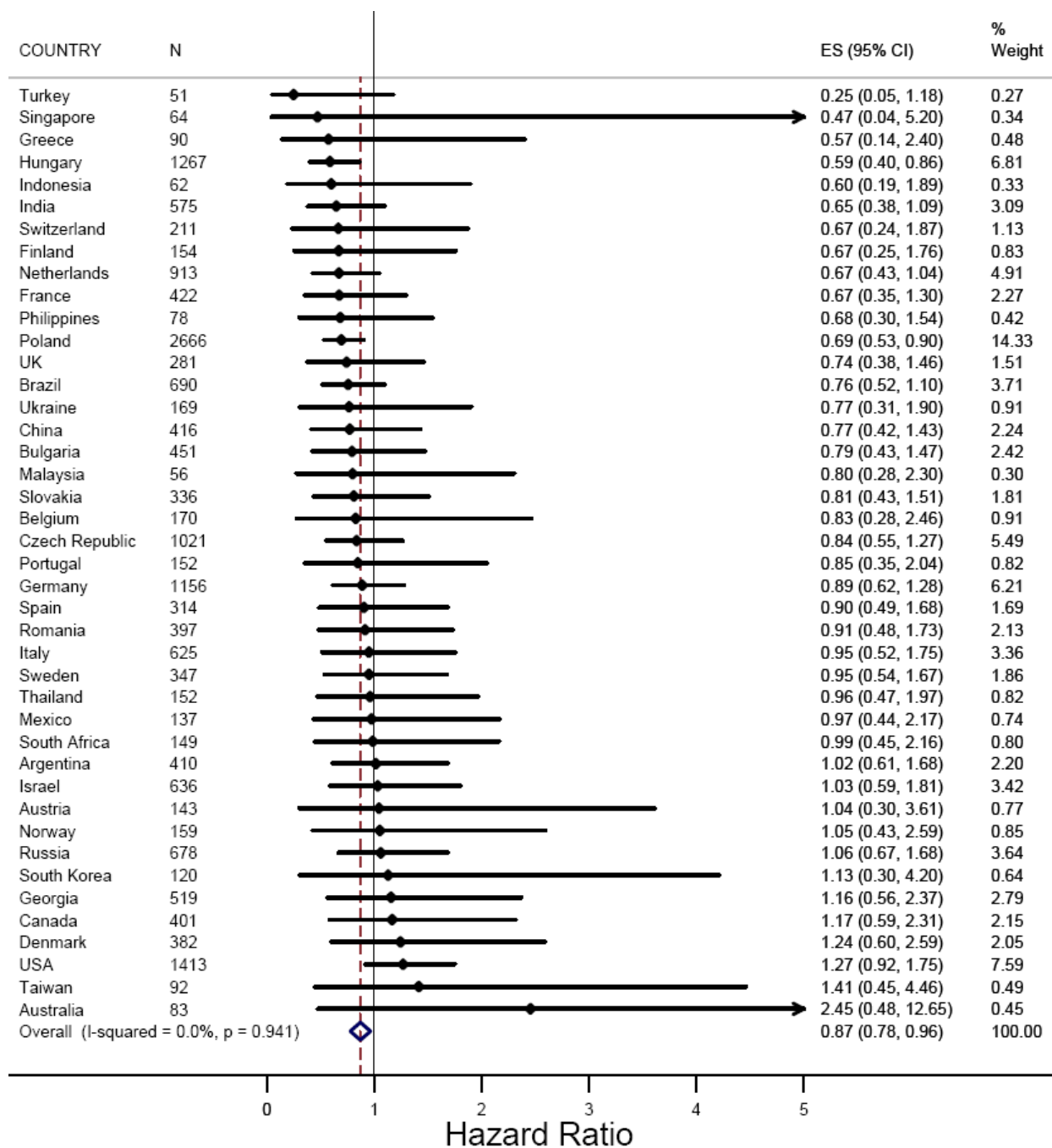
Other = Canada, Israel, South Africa, Australia  
Source: R. Fiorentino, Clinical Reviewer

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**

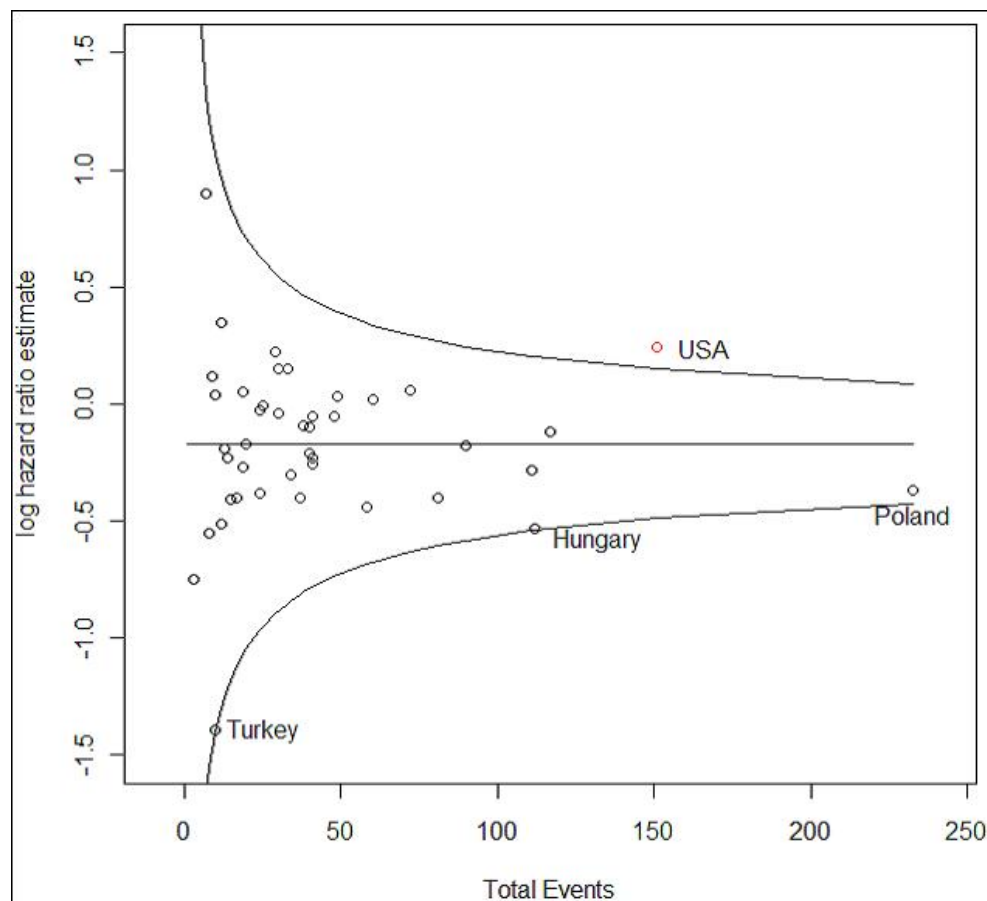


Excludes Hong Kong; weighted by N

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**

		Ticagrelor 90 mg bd N=9333			Clopidogrel 75 mg od N=9291					
EVENT	Region	n	Patients with Events	KM%	n	Patients with Events	KM%	Hazard Ratio (95% CI)	p-value	p-value (Int.)
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	

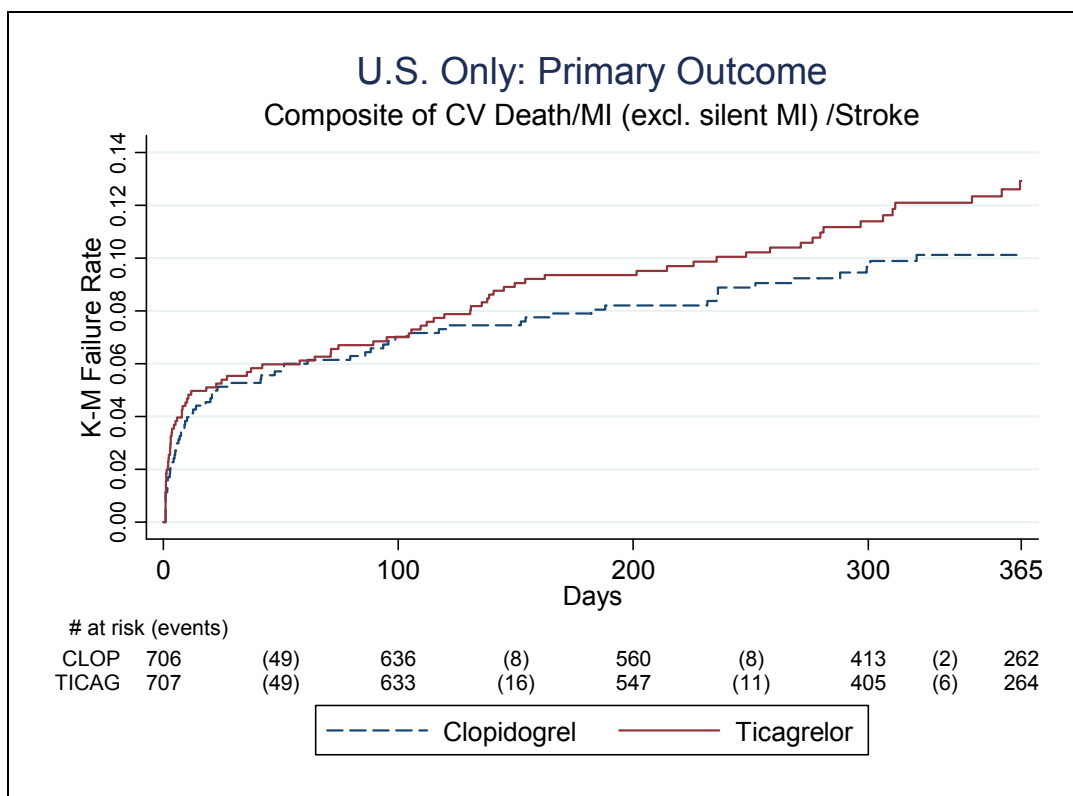
Source: Sponsor, Exploratory Analysis of Treatment Interactions in Plato, p.107, Table 1.7

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.

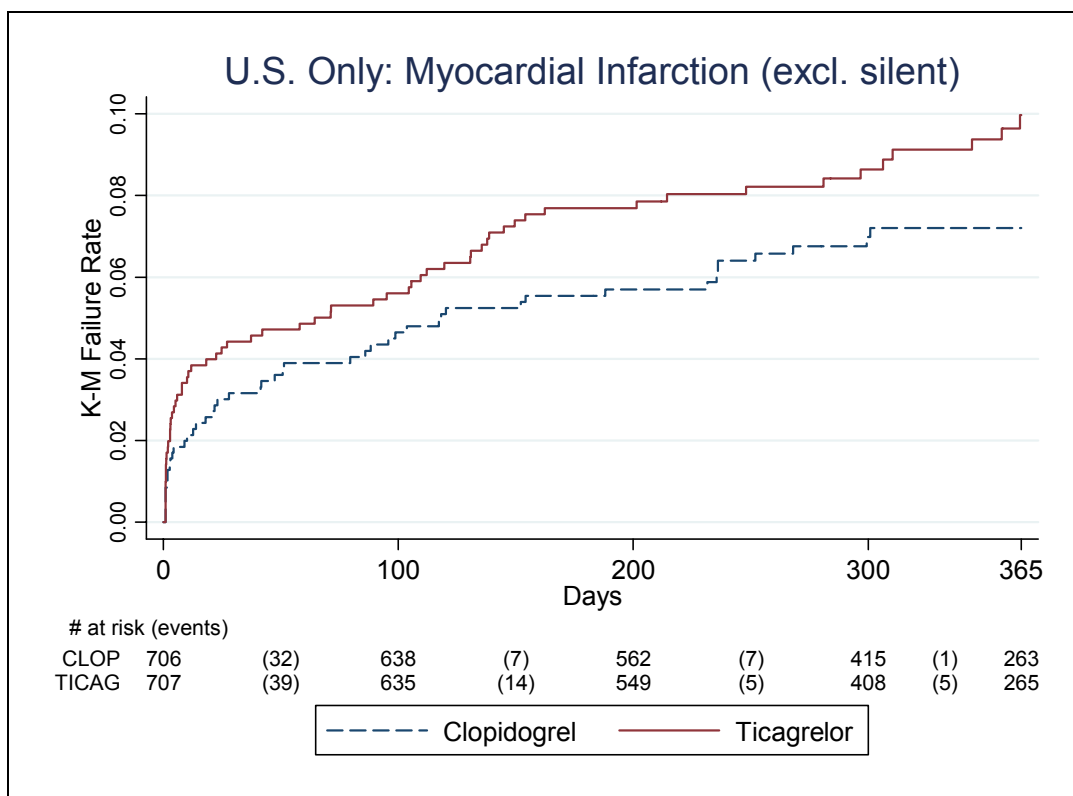
**Figure 25. K-M Curve: US Primary Outcome**



**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).

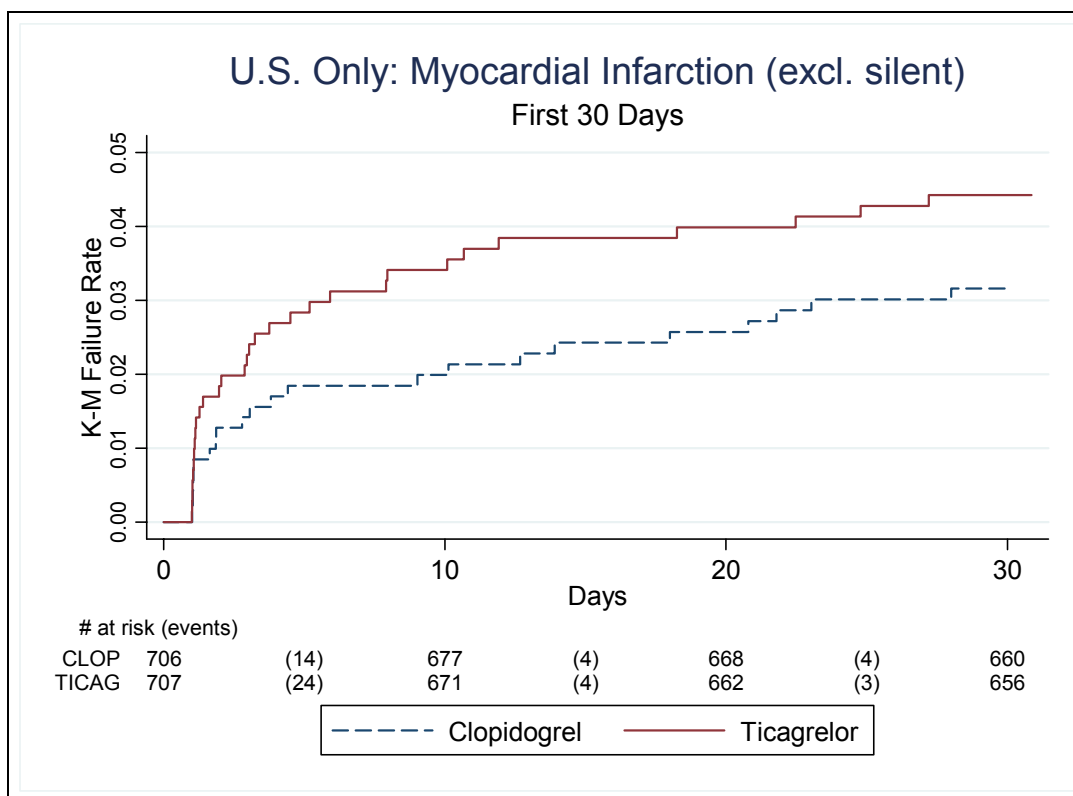
**Figure 26. K-M Curve: U.S. Myocardial Infarctions**



**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.

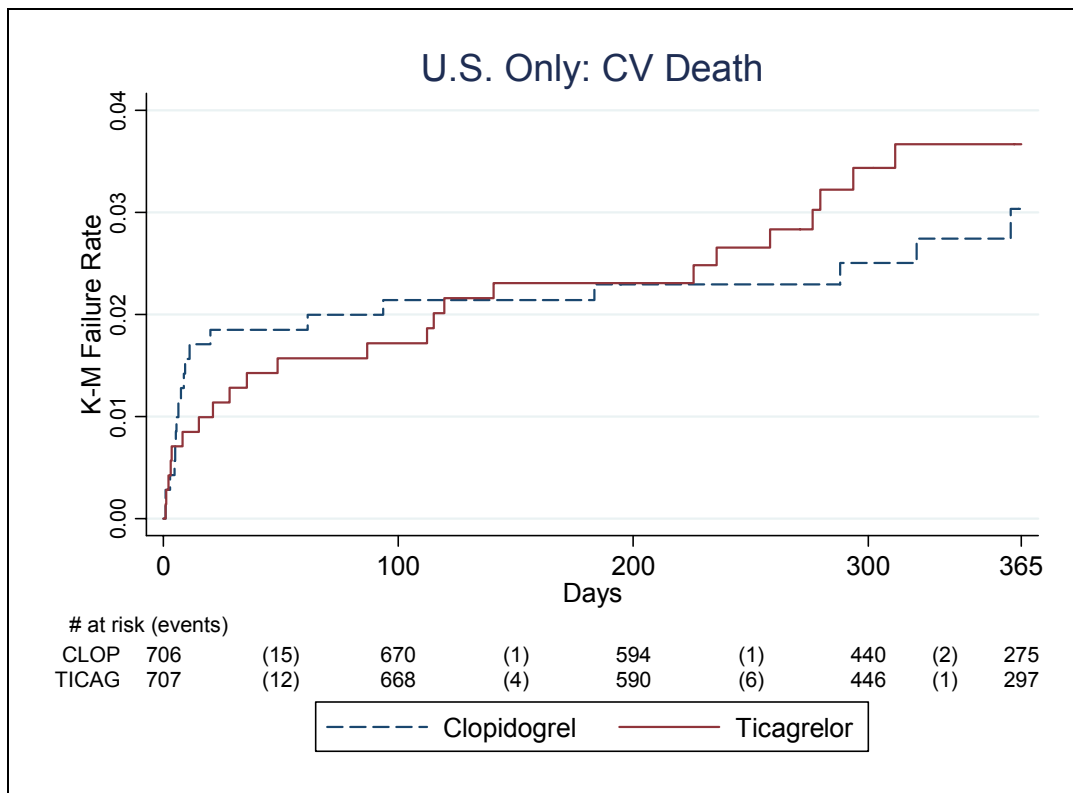
**Figure 27. K-M Curve 30-day Landmark: U.S. Myocardial Infarctions**



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.

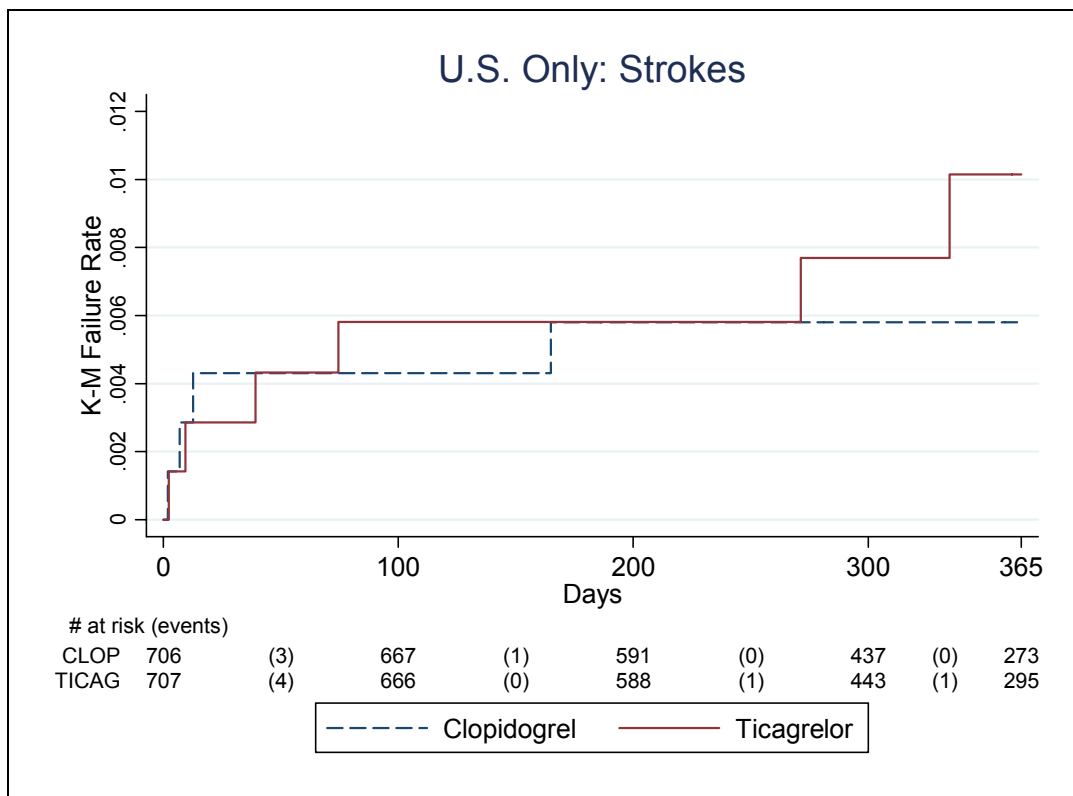
**Figure 28. K-M Curve: U.S. CV Death**



**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**

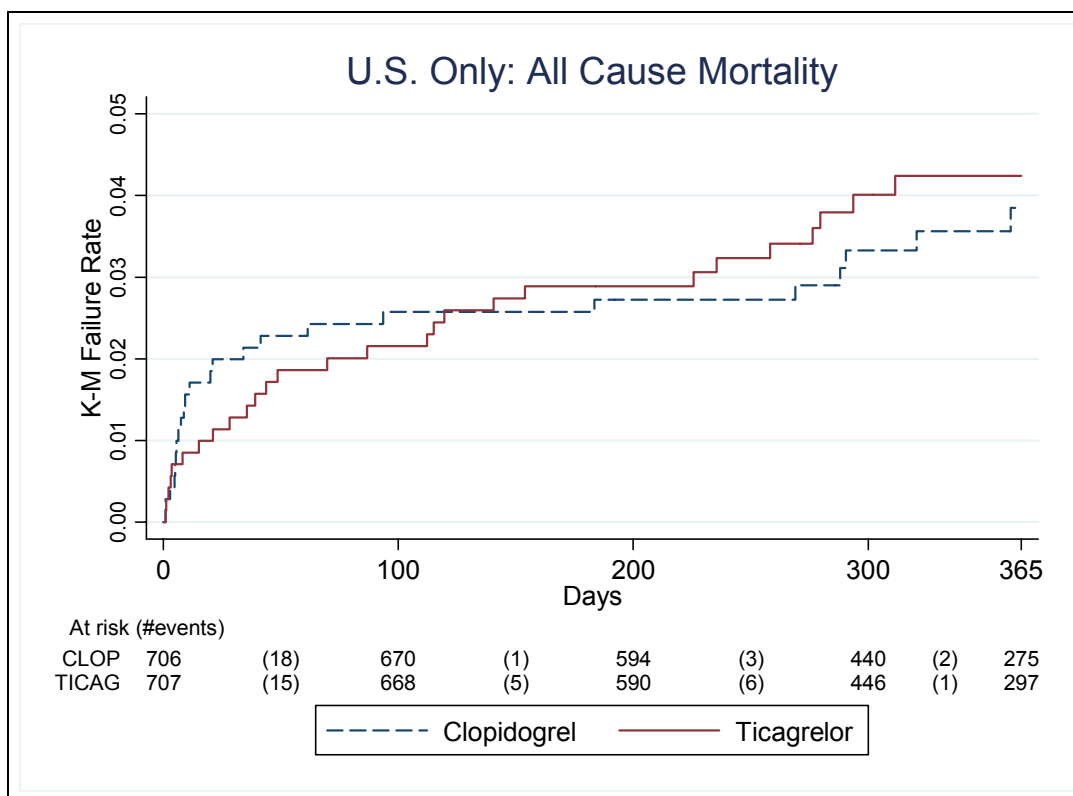


**Source: R. Fiorentino, Clinical Reviewer**

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 heavier (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(%)	653 (46%)	3,339 (19.4%)
Ave. # DES implanted	1.8	1.6
Bare Metal stent, n(%)	331 (23%)	7993 (46%)
Ave. # BMS implanted	1.5	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	325	100.0
Mean	217	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**

<b>Interval Factor (medians)</b>	<b>US (hours)</b>	<b>Non-US (hours)</b>
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**

<b>Interval Factor (median times)</b>	<b>US (hours)</b>	<b>Non-US (hours)</b>
Index Event to PCI	17.6	10.4
Randomization to 1 <sup>st</sup> PCI	1.1	0.97
IP to 1 <sup>st</sup> 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 1 <sup>st</sup> 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 1 <sup>st</sup> 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%
	<b>Total</b>	<b>33.6%</b>	<b>57.2%</b>	<b>8.5%</b>	<b>74.6%</b>	<b>14.7%</b>	<b>25.3%</b>	<b>63.8%</b>	<b>79.9%</b>
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%
	<b>Total</b>	<b>41.5%</b>	<b>47.8%</b>	<b>13.0%</b>	<b>86.8%</b>	<b>14.8%</b>	<b>50.2%</b>	<b>66.5%</b>	<b>78.1%</b>

**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 than 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.

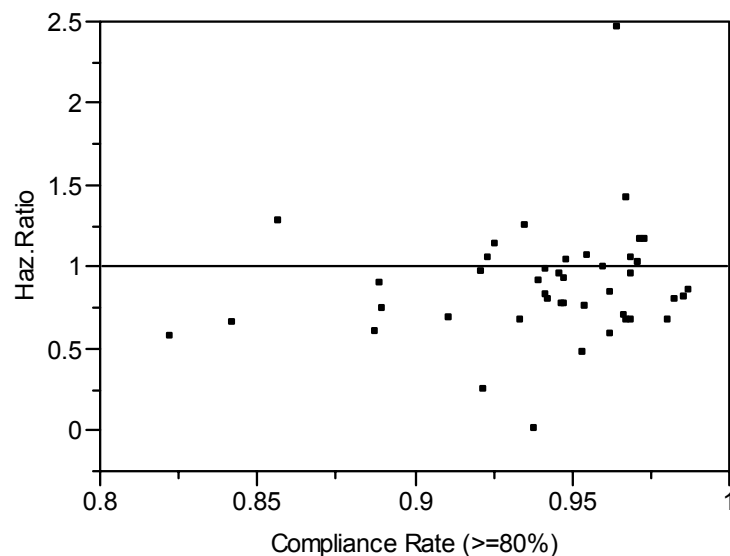
**Table 66. Primary Study Outcome by Compliance**

<b>Compliance ≥80%</b>	<b>N subjects</b>	<b>HR (95%CI)</b>
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%)
<b>Non-US</b>	17,211	16,310	94.8%
<b>US</b>	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
<b>Compliant</b> (n=1210)	68/604	60/606	1.14 (0.81, 1.62)	0.454
<b>Non-compliant</b> (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)
<b>Unstable Angina</b>	142	9/66	8/76	0.73 (0.28, 1.89)
<b>NSTEMI</b>	949	47/471	60/478	1.29 (0.88, 1.89)
<b>STEMI</b>	222	10/117	14/105	1.56 (0.69, 3.52)
<b>Other*</b>	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)
<b>Planned Invasive Strategy</b>				
<b>Yes</b>	1,323	58/664	74/659	<b>1.30</b> (0.92, 1.84)
<b>No</b>	90	9/42	10/48	<b>0.98</b> (0.40, 2.40)
<b>Early PCI (&lt;24hrs)*</b>				
<b>Yes</b>	866	37/437	54/429	<b>1.50</b> (0.99, 2.28)
<b>No</b>	546	30/269	30/277	<b>0.98</b> (0.59, 1.62)
<b>PCI*</b>				
<b>Yes</b>	930	41/472	59/458	<b>1.50</b> (1.01, 2.24)
<b>No</b>	482	26/234	25/248	<b>0.91</b> (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)
<b>PCI<sup>1</sup></b>				
<b>US</b>	930	41/472	59/458	<b>1.50</b> (1.01, 2.24)
<b>non-US</b>	10,920	504/5459	425/5466	<b>0.84</b> (0.74, 0.95)
<b>Overall</b>	11,850	545/5931	484/5924	<b>0.89</b> (0.78, 1.00)
<b>No PCI</b>				
<b>US</b>	482	26/234	25/248	<b>0.91</b> (0.53, 1.58)
<b>non-US</b>	6,281	443/3126	355/3155	<b>0.79</b> (0.69, 0.91)
<b>Overall</b>	6,763	469/3360	380/3403	<b>0.80</b> (0.70, 0.91)

<sup>1</sup> 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 (0.18, 2.46)	T: 42/319	1.46 (0.91, 2.35)	T: 13/88	2.18 (0.87,5.44)
	C: 5/39		C: 29/314		C: 7/101	
No PCI	T: 4/34	0.83 (0.21, 3.31)	T: 18/159	1.01 (0.53, 1.94)	T: 1/17	0.30 (0.03, 2.86)
	C: 4/27		C: 18/157		C: 3/16	
Planned Inv. Treatment	T: 7/67	0.74 (0.27, 2.04)	T: 51/447	1.32 (0.87, 2.00)	T: 14/105	1.56 (0.69, 3.52)
	C: 8/60		C:39/438		C: 10/117	
Planned Med. Mgmt	T: 1/9	0.68 (0.04, 11.0)	T: 9/31	1.25 (0.48, 3.25)	T: 0/0	n/a
	C: 1/6		C: 8/33		C: 0/0	
NON-US						
PCI	T: 45/490	1.12 (0.74, 1.70)	T: 157/1930	0.75 (0.61, 0.92)	T: 215/3004	0.86 (0.72, 1.04)
	C: 44/535		C: 203/1904		C: 248/2986	
No PCI	T: 71/983	0.90 (0.65, 1.23)	T: 215/1597	0.81 (0.67, 0.97)	T: 52/387	0.70 (0.50, 1.00)
	C: 79/962		C: 260/1575		C:79/427	
Planned Inv. Treatment	T: 52/609	0.98 (0.67, 1.42)	T: 191/2117	0.74 (0.61, 0.90)	T: 236/3173	0.84 (0.70, 0.99)
	C: 57/650		C: 245/2043		C: 283/3180	
Planned Med. Mgmt	T: 64/864	0.97 (0.69, 1.37)	T: 181/1410	0.83 (0.68, 1.01)	T: 31/218	0.73 (0.46, 1.16)
	C: 66/847		C:218/1436		C: 44/233	

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	<b>1.22</b> (0.30, 4.88)	T: 2/35	<b>0.36</b> (0.07, 1.78)
		C: 3/27		C: 6/39	
NSTEMI	18.4 hrs	T: 23/232	<b>1.15</b> (0.63, 2.10)	T: 37/246	<b>1.40</b> (0.85, 2.30)
		C: 20/227		C: 27/244	
STEMI	4.7 hrs	T: 6/47	<b>1.55</b> (0.47, 5.08)	T: 8/58	<b>1.53</b> (0.50, 4.69)
		C: 5/61		C: 5/56	

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	<b>1.13</b> (0.77, 1.65)	T: 59/721	<b>0.87</b> (0.62, 1.23)
		C: 49/718		C: 74/779	
NSTEMI	16.3 hrs	T: 167/1763	<b>0.66</b> (0.54, 0.80)	T: 205/1764	<b>0.92</b> (0.76, 1.11)
		C: 242/1711		C: 221/1768	
STEMI	5.0 hrs	T: 104/1670	<b>0.83</b> (0.64, 1.08)	T: 163/1721	<b>0.81</b> (0.66, 1.00)
		C: 125/1673		C: 202/1740	

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 identify 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**

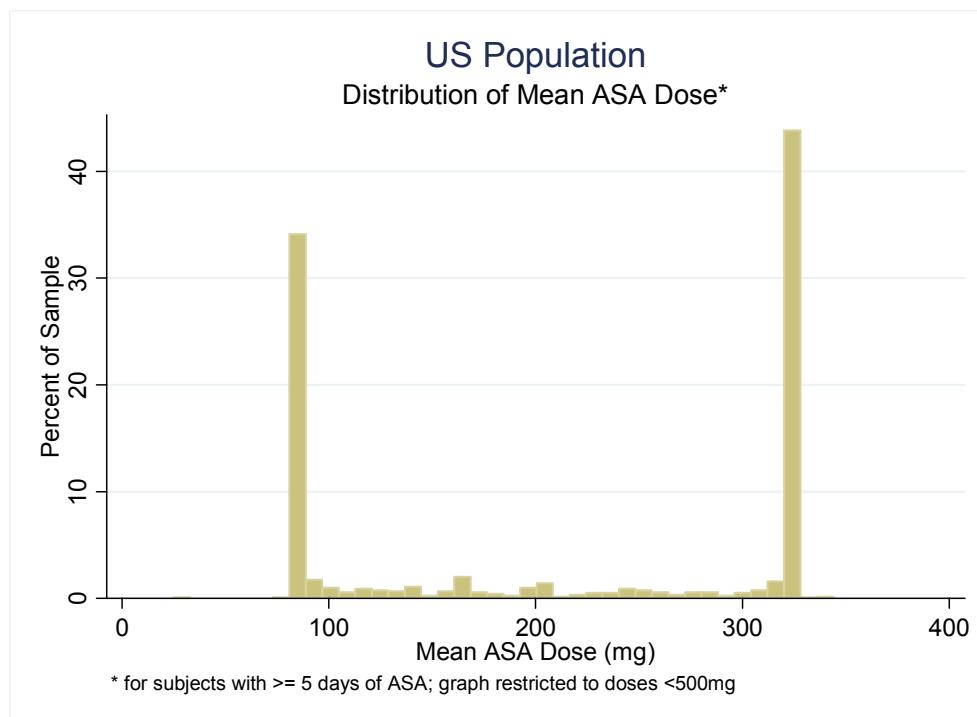
	Median of Median ASA doses	Mean of Original ASA Mean Dose (SD)	Mean of MEDIAN20	Mean of MEDIAN24	Mean of MEDIAN25	Mean of MEDIAN55
<b>US</b>	<b>325</b>	223 (249)	217	219	222	219
<b>Non-US</b>	<b>100</b>	101 (42)	99	101	107	100

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.

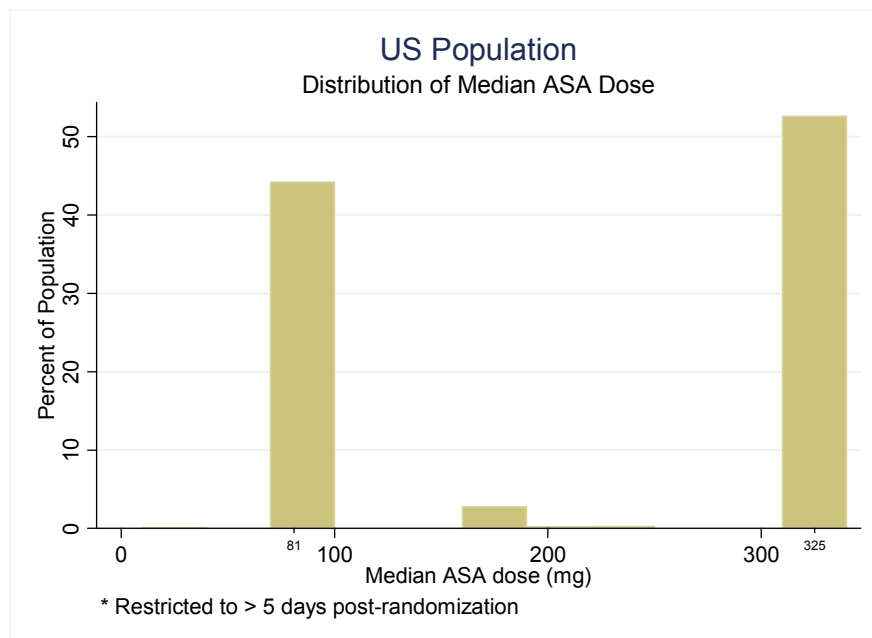
**Figure 32. US: Distribution of Mean Aspirin Use**



Source: R. Fiorentino, Clinical Reviewer

The distribution of median ASA doses in the US follows a similar pattern (Figure 33).

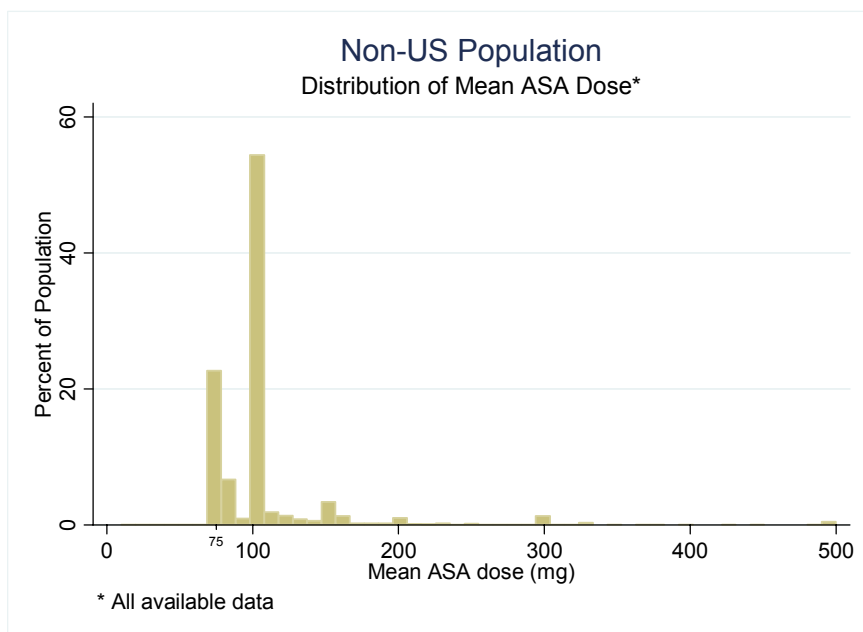
**Figure 33. US: Distribution of Median ASA Dose**



**Source: R. Fiorentino, Clinical Reviewer**

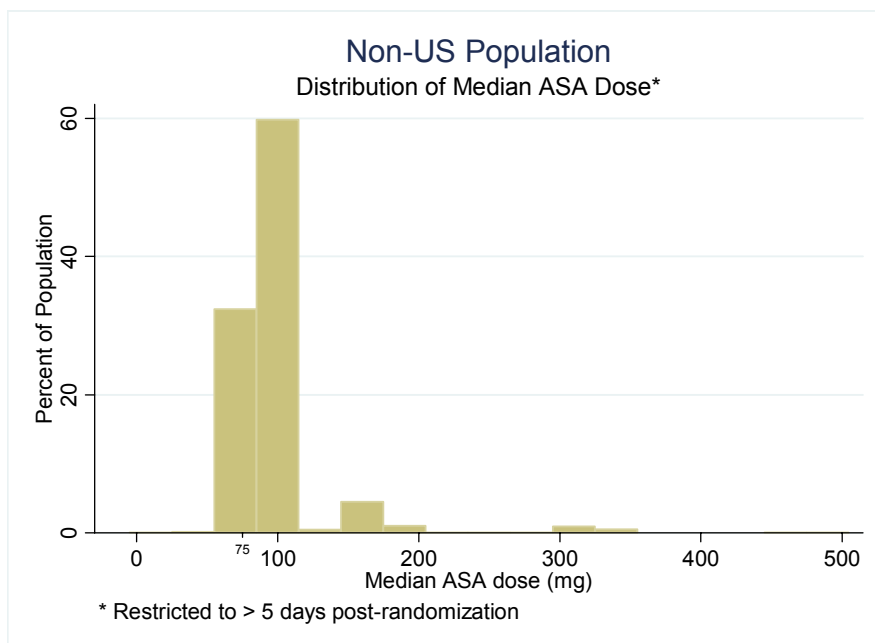
In contrast, the distribution of mean and median ASA doses in the non-US subgroup are predominantly of the 75mg and 100mg doses (Figure 34 & Figure 35).

**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	<b>0.97</b> (0.55, 1.70)	T:17/233	<b>0.80</b> (0.42, 1.52)
	C:24/233		C:21/228	
100 to 300	T:11/120	<b>0.88</b> (0.38, 2.08)	T:6/107	<b>0.80</b> (0.26, 2.45)
	C:10/96		C:6/86	
>300	T:49/345	<b>1.67</b> (1.08, 2.60)	T:61/367	<b>1.68</b> (1.13, 2.51)
	C:33/377		C:40/392	

\* 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	<b>0.96</b> (0.57, 1.63)	T: 19/283	<b>0.76</b> (0.42, 1.40)
	C: 27/272		C: 23/262	
162	T: 2/21	<b>1.51</b> (0.14, 16.7)	T: 2/18	<b>0.76</b> (0.11, 5.41)
	C:1/14		C: 2/13	
325	T: 49/349	<b>1.56</b> (1.01, 2.41)	T: 40/320	<b>1.62</b> (0.99, 2.64)
	C: 34/368		C: 27/347	

\* 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	<b>0.73</b> (0.60, 0.88)
	C: 246/2638	
100 to 300	T: 447/5409	<b>0.83</b> (0.73, 0.94)
	C: 535/5408	
>300	T: 168/644	<b>0.84</b> (0.67, 1.05)
	C: 180/598	

\*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	<b>0.42</b> (0.04, 4.64)
	C:2/17	
75	T:145/2134	<b>0.70</b> (0.57, 0.87)
	C:204/2134	
80/81mg	T:36/464	<b>0.85</b> (0.54, 1.31)
	C:43/469	
100	T:364/4830	<b>0.80</b> (0.70, 0.92)
	C:450/4823	
101-199	T:37/401	<b>0.84</b> (0.54, 1.29)
	C:46/421	
200/250	T:23/99	<b>1.29</b> (0.69, 2.42)
	C:17/90	
300	T:20/90	<b>1.01</b> (0.54, 1.92)
	C:18/82	
325	T:5/43	<b>1.17</b> (0.34, 4.03)
	C:5/50	
>325	T:3/7	n/a
	C:0/8	
unknown	T:144/534	<b>0.80</b> (0.64, 1.00)
	C:162/491	

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)
<b>Age (yrs)</b>	62	60
<b>Body Mass Index (kg/m<sup>2</sup>), median</b>	29	29
<b>Median Weight (kg)</b>	89	88
<b>Female sex</b>	33%	25%
<b>History of MI</b>	27%	29%
<b>History of PCI</b>	28%	31%
<b>Ex-smoker</b>	36%	33%
<b>Habitual smoker</b>	34%	39%
<b>Index event: UA</b>	11%	9%
<b>Index event: NSTEMI</b>	70%	67%
<b>Index event: STEMI</b>	13%	19%
<b>GPI use during index hosp</b>	45%	57%
<b>abciximab</b>	4%	6%
<b>tirofiban</b>	2%	1%
<b>eptifibatide</b>	34%	44%
<b>Heparin Use</b>	60%	70%
<b>Planned Invasive Treatment</b>	90%	96%
<b>PCI during study*</b>	61%	77%
<b>Early PCI during study*</b>	56%	72%
<b>BMS or DES implantation</b>	58%	74%
<b>DES</b>	45%	54%
<b>BMS</b>	19%	29%
<b>Total BMS (mean)</b>	0.27	0.43
<b>Total DES (mean)</b>	0.82	0.99
<b>≥ 80% compliant with IP</b>	91%	90%
<b>Time from Index event to IP (median)</b>	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 (0.42, 1.61)	T: 35/304	1.56 (0.93, 2.60)
	C: 18/236		C: 25/335	
No	T: 3/27	0.55 (0.13, 2.30)	T: 5/16	1.72 (0.33, 9.06)
	C: 5/26		C: 2/12	
Any PCI*				
Yes	T: 11/175	0.84 (0.39, 1.90)	T: 31/238	1.88 (1.06, 3.32)
	C: 12/160		C: 19/274	
No	T: 8/108	0.68 (0.27, 1.70)	T: 9/82	1.00 (0.39, 2.61)
	C: 11/102		C: 8/73	

\* 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**

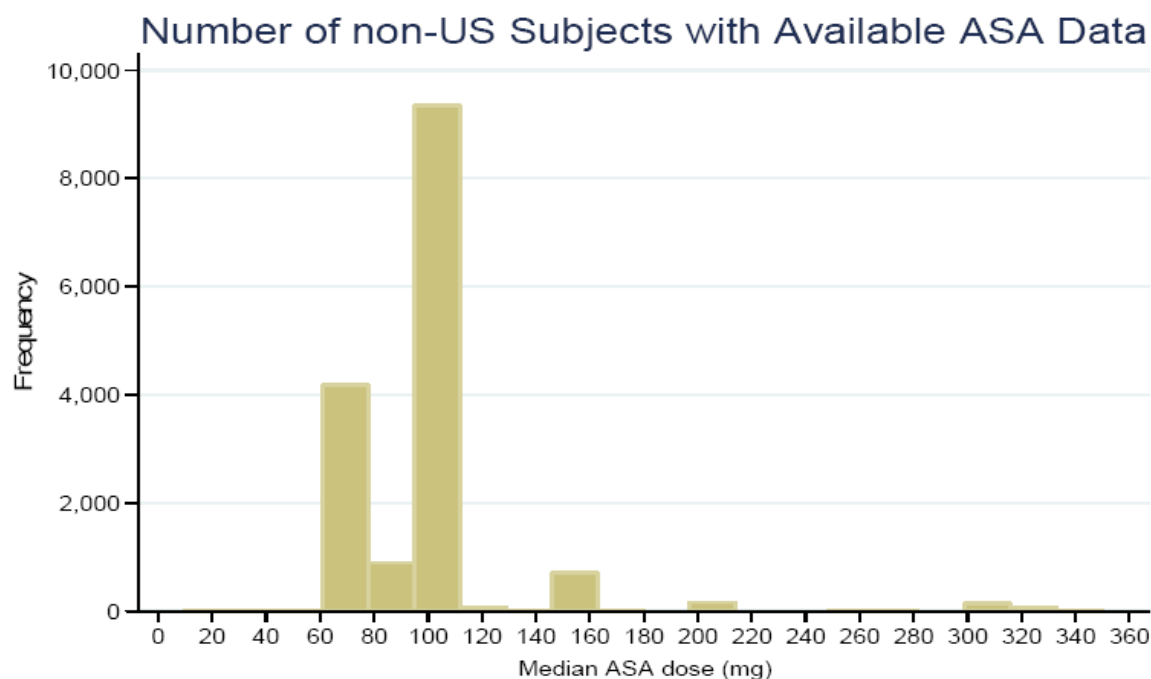
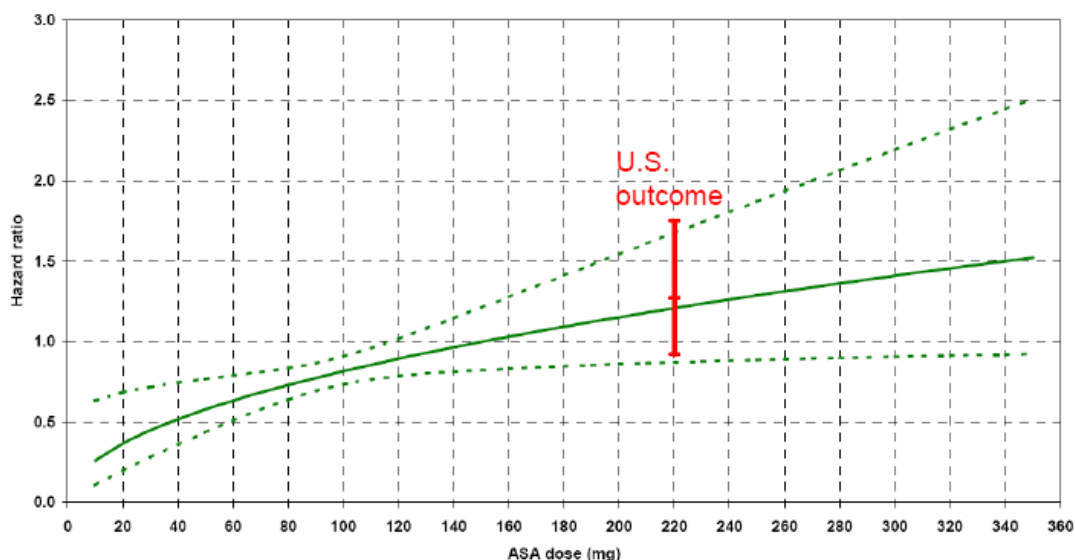
	ASA 81mg		ASA 325mg	
STEMI	T: 3/39	<b>1.19</b> (0.20, 7.15)	T: 7/53	<b>2.45</b> (0.72, 8.38)
	C: 2/32		C: 4/71	
NSTEMI	T: 13/194	<b>0.79</b> (0.38, 1.64)	T: 28/219	<b>1.49</b> (0.84, 2.65)
	C: 16/189		C: 20/226	
UA	T: 3/35	<b>0.45</b> (0.11, 1.90)	T: 5/35	<b>1.10</b> (0.26, 4.62)
	C: 5/27		C: 3/27	

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  $\geq 1$  mm (0.1 mV) in at least 2 contiguous leads and recurrent cardiac ischemic symptoms<sup>g</sup>  $\geq 20$  minutes at rest<sup>h</sup>.

**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<sup>g</sup>  $\geq 20$  minutes at rest<sup>h</sup>

OR

- ii. One of the following ECG changes:
  - i. New ST elevation of  $\geq 1$  mm (0.1 mV) in at least 2 contiguous leads
  - ii. Development of new pathological Q waves<sup>i</sup> 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<sup>j</sup> 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  $\geq 0.03$  sec in width and  $\geq 1$  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<sup>g</sup> ≥20 minutes at rest<sup>h</sup>
- ii. Development of new pathological Q waves<sup>i</sup> on the ECG
- iii. ECG changes indicative of ischemia<sup>k</sup>

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<sup>l</sup>, 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<sup>i</sup> 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<sup>l</sup>, 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<sup>i</sup> on the ECG (no symptoms are required)
- OR
- ii. CK-MB ≥ 10x local or central laboratory upper normal limit<sup>l</sup> 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<sup>k</sup> and new cardiac ischemic symptoms<sup>g</sup>

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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 and 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<sup>i</sup>, in the absence of cardiac ischemic symptoms<sup>g</sup>

**Definition of Recurrent Cardiac Ischemia**

**Recurrent cardiac ischemia**

Cardiac ischemic symptoms<sup>g</sup> ≥10 minutes at rest<sup>h</sup>, 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<sup>m</sup> (3.1 mmol/L<sup>n</sup>; 0.775 mmol/L<sup>o</sup>)<sup>p</sup>
- 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<sup>m</sup> (1.9 mmol/L<sup>n</sup>; 0.465 mmol/L<sup>o</sup>)<sup>p</sup> to 50 g/L (3.1 mmol/L<sup>n</sup>; 0.775 mmol/L<sup>o</sup>)<sup>p</sup>
- 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<sup>m</sup>; 0.62 mmol/L<sup>n</sup>; 0.155 mmol/L<sup>o</sup> 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:  $\Delta \text{Hb} = [\text{baseline Hb} - \text{post transfusion Hb}] + [\text{number of transfused units} \times \text{conversion factor in Hb}]$ . Conversion factor = Conversion factor = 10 g/L<sup>m</sup>; 0.62 mmol/L<sup>n</sup>; 0.155 mmol/L<sup>o</sup>

### **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; 2344-2351].

**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}):
  - Acute onset of ischemic symptoms at rest
  - New ischemic ECG changes that suggest acute ischemia
  - Typical rise and fall in cardiac biomarkers that represent a spontaneous MI
  - 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.
  - 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.

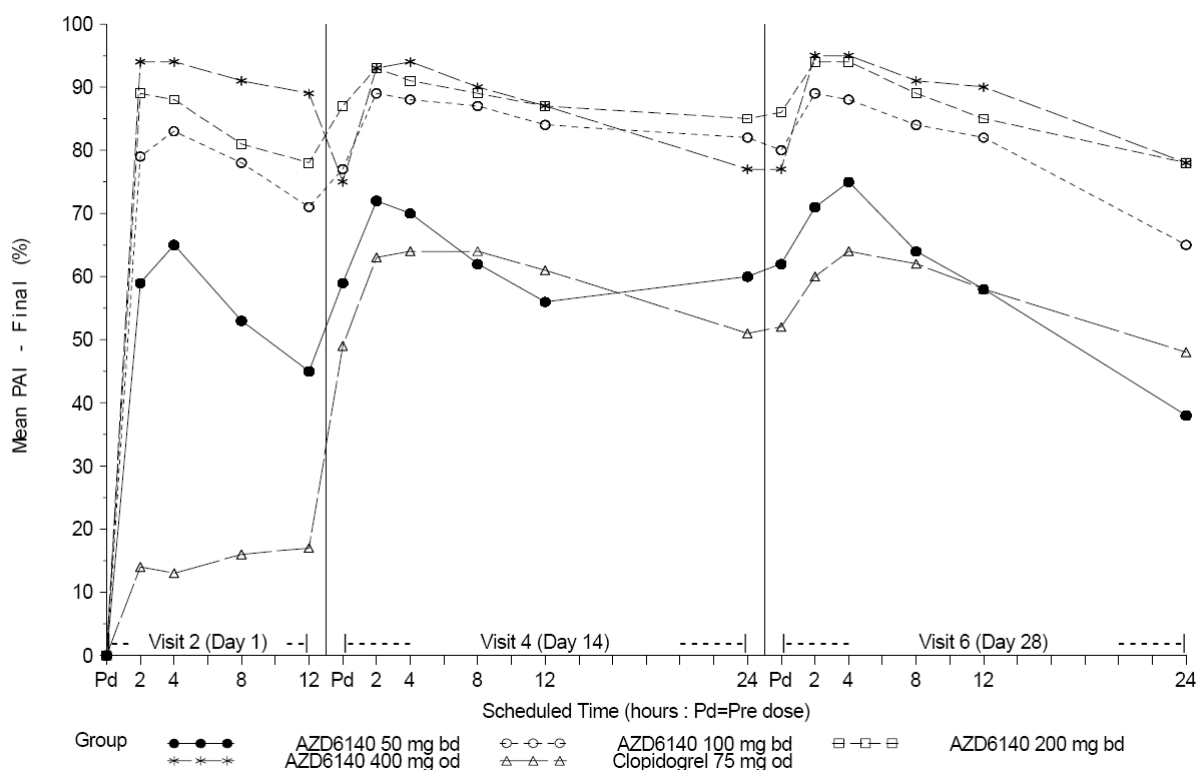
#### **Target subject population and sample size**

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<sub>max</sub> 97% vs. 73%). AZD6140 90 mg bd produced an intermediate effect (IPA<sub>max</sub> 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 <sup>a</sup>	Overall <sup>b</sup>	Week 4 <sup>a</sup>	Overall <sup>b</sup>	Week 4 <sup>a</sup>	Overall <sup>b</sup>
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) <sup>c</sup>	4 (1.2%)	9 (2.7%)	2 (0.6%)	7 (2.1%)	10 (3.1%)	14 (4.3%)
- MI (excluding silent MI) <sup>c</sup>	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) <sup>a</sup>	AZD6140 180 mg bd (n=329) <sup>a</sup>	Clopidogrel 75 mg od (n=327) <sup>a</sup>
<b>Overall study</b>			
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  $\geq 1.0$  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 <sup>a</sup>	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%) <sup>b</sup>	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 <sup>a</sup>	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**

	<b>Lost to follow up or withdrew consent</b>	<b>Died or reached last visit with no premature discontinuation</b>
<b>Non-US (n=17,211)</b>	2101 (12.2%)	15110 (87.8%)
<b>US (n=1,413)</b>	261 (18.5%)	1152 (81.5%)

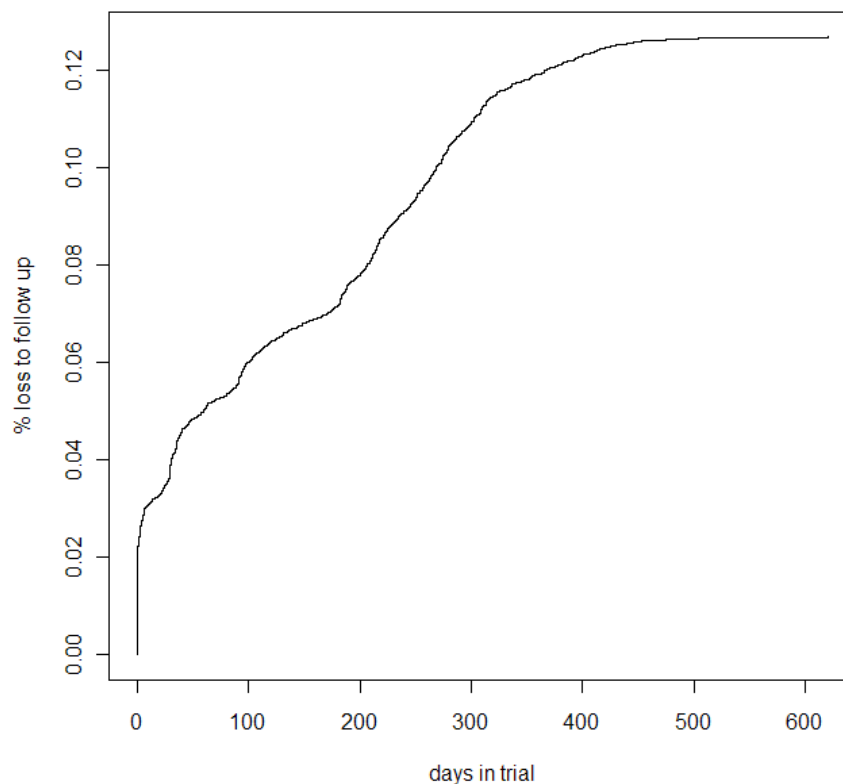
Source: Jialu Zhang, FDA Statistical Reviewer

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

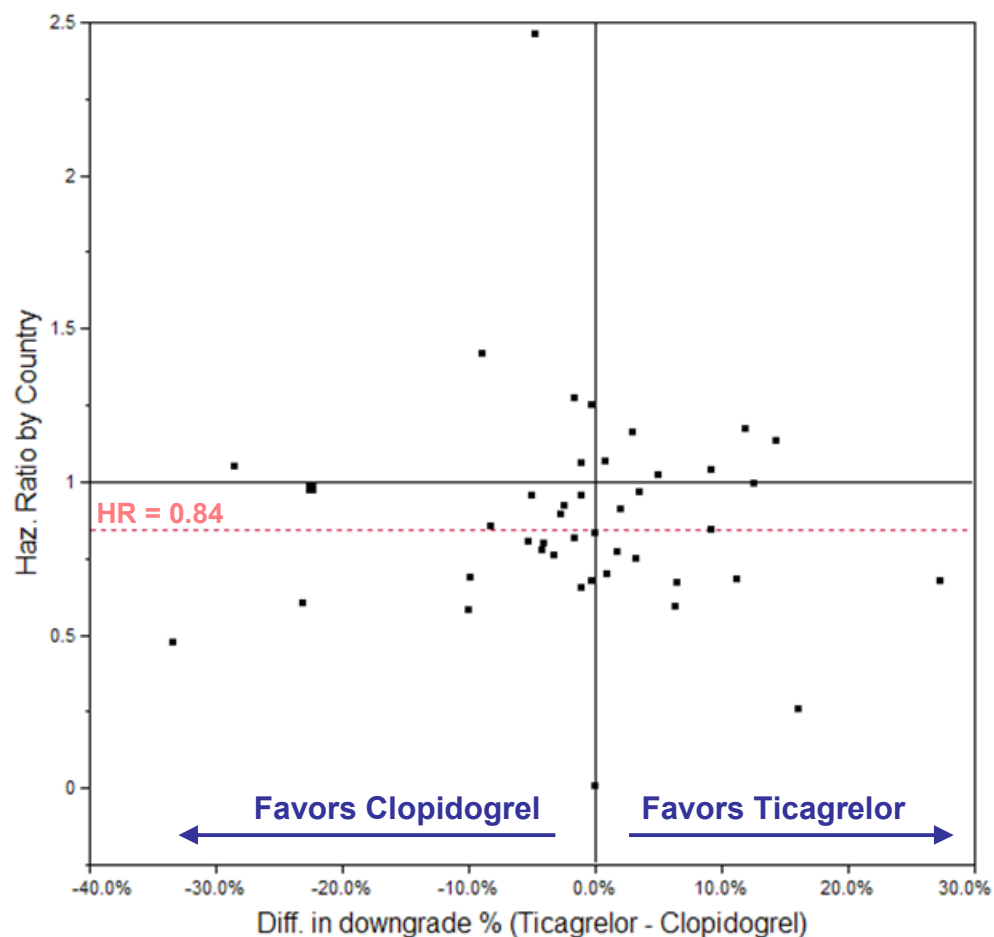
Source: Robert Fiorentino, Clinical Reviewer



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**

<b>Treatment</b>	<b>N</b>	<b>Hospitalization after index event</b>	<b>Hospitalized <i>AND</i> NO primary event</b>
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**

<b>Site MI Event?</b>	<b>Adjudicated MI Event?</b>	<b>Ticagrelor</b> Total: 5280 events submitted for adjudication	<b>Clopidogrel</b> 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**

<b>Category: Number of MI Events (all) submitted for adjudication</b>	<b>Number of Subjects</b>
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**

<b>Treatment</b>	<b>Any Event Submitted for adjudication</b>	<b>Any cardiac ischemic event submitted</b>	<b>Adjudicated Result: MI</b>	<b>MI event in primary analysis</b>
<b>Ticagrelor</b>	98.9%	97.3%	82.8%	75.6%
<b>Clopidogrel</b>	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 3<sup>rd</sup> 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**

	ICAC Adjudicated			
Investigator Reported	Vascular Death	Non-Vascular Death	Other Death	TOTAL
Vascular Death	296	6	9	311
Non-vascular Death	16	44	7	67
Other Death	19	0	20	39
TOTAL	331	50	36	<b>417</b>

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	<b>1536</b>

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**

	ICAC Adjudicated			
Investigator Reported	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	<b>520</b>

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	<b>1650</b>

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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ROBERT FIORENTINO

06/25/2010

Initial clinical efficacy review (pre-AC meeting)



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 22-433 / N\_000

**Drug Name:** Brilinta (ticagrelor)

**Indication(s):** Prevention of Vascular Events in Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS)

**Applicant:** AstraZeneca

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## **1. EXECUTIVE SUMMARY**

### **1.1 Conclusions and Recommendations**

The single phase III trial PLATO randomized 18,624 subjects to compare the efficacy and safety of ticagrelor 90 mg with clopidogrel 75 mg in the prevention of CV death, MI, and stroke in patients with non-ST or ST elevation ACS. One major issue is the regional difference observed between US and non-US. The study reported a hazard ratio estimate of 0.84 [95% CI (0.77, 0.92)] for the overall population favoring ticagrelor. However, for US the hazard ratio estimate was 1.27 [95% CI (0.92, 1.75)], which suggested a 27% greater risk of the clinical event with ticagrelor relative to clopidogrel. The magnitude of this point estimate of hazard ratio in US is quite concerning, especially since US had the second largest enrollment among 43 countries in this trial. The reviewer performed extensive analyses examining many factors or covariates but was not able to find a definitive explanation for the regional difference. However, the US population appeared different from the rest of the world in a number of ways based on the reviewer's analyses even though they did not seem to explain the regional difference. If US population differs sufficiently from the rest of the world, a US trial may be needed to further evaluate the efficacy of ticagrelor in US subjects.

Although play of chance can never be ruled out as a possible explanation, it seems to be a little overstretched, given the magnitude of the difference in hazard ratio estimates between US and non-US. The sponsor attributed the concurrent aspirin (ASA) use to the regional difference if it is not a play of chance. However, even though ASA seems to be the biggest contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the explanatory model used by the sponsor for explaining the regional difference does not appear robust since very few subjects outside US took high dose ASA. Thus, the interpretability of the results that the ASA dose may explain the regional difference remains very much uncertain.

### **1.2 Brief Overview of Clinical Studies**

The application consists of a single phase III trial, PLATO. It was a randomized, double-blind, double-dummy, parallel group, international, multicenter study, compared the efficacy and safety of ticagrelor 90 mg bid with clopidogrel 75 mg od in the prevention of CV death, MI, and stroke 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.

The primary endpoint is time to composite endpoint of CV death, stroke and MI (excluding silent MI). The trial randomized 18624 subjects. A total of 1878 events were included in the primary analysis. The hazard ratio estimate for overall population is 0.84 [95% CI (0.77, 0.92)].



### **1.3 Statistical Issues and Findings**

The big issue in this application is the regional difference observed between US and non-US. The magnitude of the point estimate of hazard ratio in US is quite concerning. The reviewer performed extensive analyses to search for potential explanations.

The hazard ratio estimates in US population stayed consistently above 1 throughout the trial. The probability of observing such results were calculated in several ways assuming that the true hazard ratio is 0.84. If taking the sample size as well as the magnitude of difference between the hazard ratio estimates into account, although play of chance can never be excluded from a possible explanation, it does seem to be a little overstretching if we observe a hazard ratio estimate of 1.27 in a country enrolled 1413 subjects while the rest of the world shows a clear benefit from ticagrelor (HR=0.84).

The sponsor attributed the concurrent ASA dose to the regional difference if it is not a play of chance. However, their finding remains questionable. First of all, most subjects taking 325 mg high dose ASA were from US. Use of high dose ASA may simply be a confounding variable for the region factor (US versus non-US). Secondly, even though ASA seems to be the best contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the Cox proportional hazards model did not appear robust enough due to the small number of subjects taking high dose ASA in the non-US region. The Cox proportional hazards model appeared quite sensitive to the high ASA subjects in non-US region. The model also seemed to be sensitive to whether or not the first day ASA loading dose is included.

The reviewer was also unsuccessful in finding other potential covariates that may explain the regional difference between US and non-US. On the other hand, US population differed from non-US population in a number of ways even though they did seem to explain the regional difference. For example, it took much longer time on average for US subjects to receive first dose of study drug since occurrence of index. More US subjects enrolled in the trial were NSTEMI patients compared to the rest of the world. Other factors include prior history of PCI or MI, number of subjects who went through early PCI, pre-index event antiplatelet therapy, beta blocker usage at randomization, planned treatment approach at randomization, GPI during index hospitalization, and many more.

## **2. INTRODUCTION**

### **2.1 Overview**

The application consists of a single phase III trial, PLATO. It is a randomized, double-blind, double-dummy, parallel group, international, multicentre trial which compared the efficacy and safety of ticagrelor 90 mg bid with clopidogrel 75 mg od for the prevention of CV death, MI, and

stroke 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).

The primary endpoint is time to composite endpoint of CV death, stroke and MI (excluding silent MI). The trial randomized 18,624 subjects. A total of 1,878 events were included in the primary analysis. The hazard ratio estimate for overall population is 0.84 [95% CI (0.77, 0.92)].

## **2.2 Data Sources**

The sponsor's electronic data is stored under the directory  
\\Cdsesub1\evsprod\NDA022433\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\acute-coronary-syndromes\5351-stud-rep-contr\d5130c05262\crt\datasets\.

The sponsor also submitted an updated aspirin data on June 10, 2010 and it is stored under the directory  
\\Cdsesub1\evsprod\NDA022433\0036\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\acute-coronary-syndromes\5351-stud-rep-contr\d5130c05262\crt\datasets\.

## **3. STATISTICAL EVALUATION**

### **3.1 Evaluation of Efficacy**

#### **3.1.1 STUDY PLATO**

##### **3.1.1.1 Study Objectives**

The primary objective is 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 study also assessed the safety and tolerability of ticagrelor compared to clopidogrel.

##### **3.1.1.2 Study Design**

The trial is a randomized, double-blind, double-dummy, parallel group, international, multicentre study. A total of 18,624 patients were randomized in a ratio of 1:1 to either ticagrelor group or clopidogrel group. Patients were randomized within 24 hours of the index event to either ticagrelor (N=9333) or clopidogrel (N=9291) against a background ASA therapy. Patients treated with ticagrelor received a loading dose of 180 mg (with an additional 90 mg if PCI occurred >24 hours after randomization) followed by 90 mg bid. Patients treated with clopidogrel received a loading dose of clopidogrel 300 mg (with an additional 300 mg at PCI at the investigator's discretion) followed by 75 mg od.

### 3.1.1.3 Efficacy Measures

#### (1) Primary Efficacy Endpoint

The primary variable is time to first occurrence of any event from composite of CV death, MI, and stroke.

#### (2) Secondary Efficacy Endpoints

The following secondary efficacy endpoints were analyzed in the order presented using a hierarchical procedure:

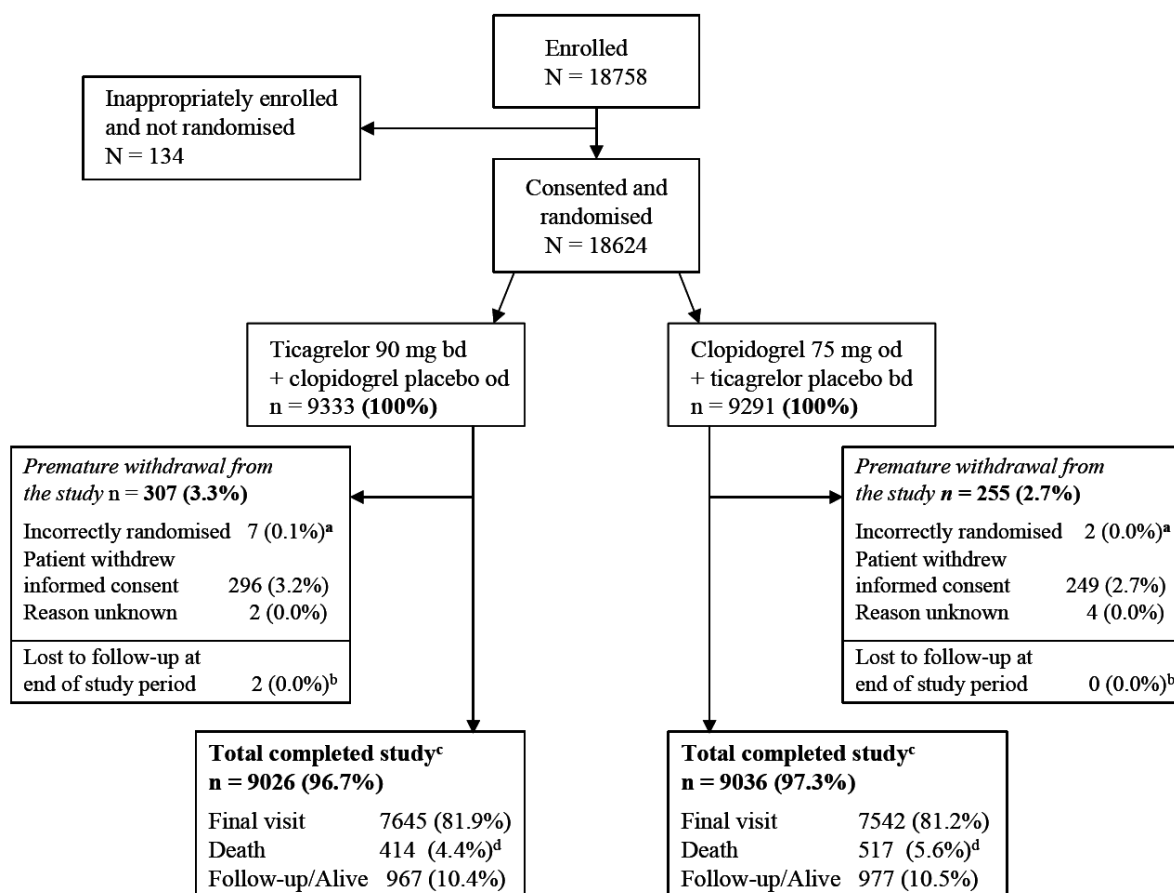
- (i) Time to first occurrence of any event from the composite of CV death, MI and stroke for the subgroup of patients with intent for invasive management at randomization
- (ii) Time to first occurrence of any event from the composite of all-cause mortality, MI, and stroke
- (iii) Time to first occurrence of any event from the composite of CV death, MI (including silent MI), stroke, severe recurrent cardiac ischaemia (SRI), recurrent cardiac ischaemia (RI), transient ischaemic attack (TIA) and other arterial thrombotic events (ATEs)
- (iv) Time to first occurrence of each component of the primary composite efficacy endpoint individually in the order of MI, CV death and then stroke
- (v) Time to occurrence of all-cause mortality.

### 3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

In total, 18758 subjects enrolled into the study from 43 countries in North America, South America and Central America, Asia and Australia, as well as Europe, the Middle East, and Africa. 18624 subjects were randomized. The first patient enrolled on 11 October 2006 and the last patient completed the study on 27 February 2009.

Patient disposition was similar across the ticagrelor and clopidogrel treatment groups.

Figure 1 Patient disposition



[Source: Figure 5 in sponsor's clinical study report on page 90]

Table 1 summarizes demographic and baseline characteristics of study subjects. There were more male than female subjects in the study. Majority of subjects were Caucasian.

Table 1 Demographic and baseline characteristics at enrollment

<b>Characteristic</b>	<b>Statistic or category</b>	<b>Ticagrelor 90 mg bd N=9333</b>	<b>Clopidogrel 75 mg od N=9291</b>	<b>Total N=18624</b>
Age (years)	N	9332	9290	18622
	Mean (SD)	62.1 (11.21)	62.3 (11.21)	62.2 (11.21)
Sex	Total	9333	9291	18624
	Male	6678 (71.6%)	6658 (71.7%)	13336 (71.6%)
	Female	2655 (28.4%)	2633 (28.3%)	5288 (28.4%)
Race	Total	9332	9291	18623
	Caucasian	8566 (91.8%)	8511 (91.6%)	17077 (91.7%)
	Black	115 ( 1.2%)	114 ( 1.2%)	229 ( 1.2%)
	Asian	542 ( 5.8%)	554 ( 6.0%)	1096 ( 5.9%)
	Other	109 ( 1.2%)	112 ( 1.2%)	221 ( 1.2%)
	Unknown	1 ( 0.0%)	0	1 ( 0.0%)
Weight (kg)	N	9305	9263	18568
	Mean (SD)	80.6 (15.97)	80.3 (16.01)	80.4 (15.99)
BMI (kg/m2)	Total	9291	9241	18532
		27.9 (4.68)	27.8 (4.73)	27.9 (4.70)
Smoking status	Total	9325	9285	18610
	Non-smoker	3592 (38.5%)	3664 (39.5%)	7256 (39.0%)
	Ex-smoker	2373 (25.4%)	2303 (24.8%)	4676 (25.1%)
	Habitual smoker	3360 (36.0%)	3318 (35.7%)	6678 (35.9%)

[Source: Sponsor's clinical study report, confirmed by the reviewer]

### 3.1.1.5 Sponsor's Primary Efficacy Results

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. All efficacy variables were analyzed using the full analysis set.

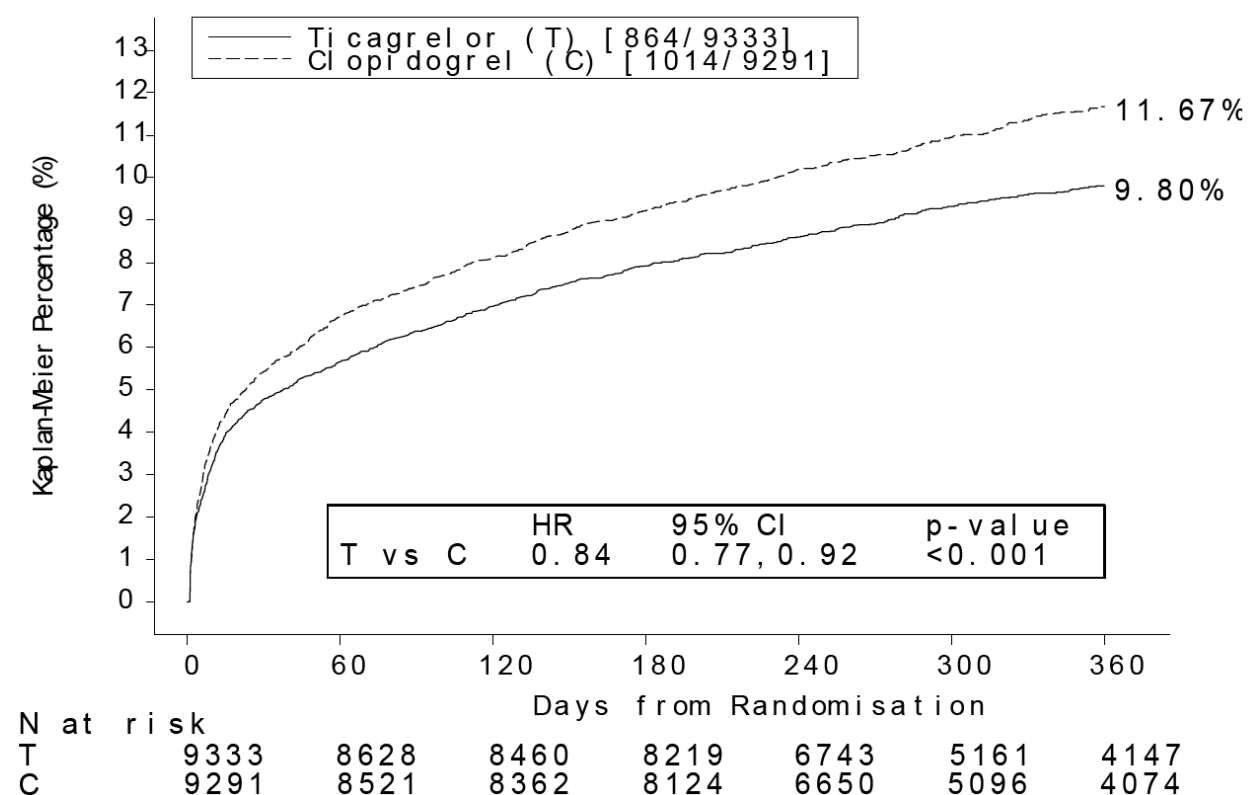
One interim analysis of the primary composite efficacy endpoint was performed when approximately 1200 adjudicated events (2/3rds of the total target number of 1780 events) were observed. The Peto-Haybittle group sequential boundary was used with a critical p-value of 0.001. The critical p-value at the final analysis was 0.0497.

Table 2 Primary efficacy endpoint and its components

	<b>Ticagrelor 90 mg bd</b>	<b>Clopidogrel 75 mg od</b>		
<b>Characteristic</b>	<b>N = 9333</b>	<b>N = 9291</b>	<b>Hazard ratio (95% CI)</b>	<b>p-value</b>
Composite of CV Death/MI (excl. silent MI)/Stroke	864 (9.3%)	1014 (10.9%)	0.84 (0.77, 0.92)	0.0003
CV death	353 (3.8%)	442 (4.8%)	0.79 (0.69, 0.91)	0.0013
MI (excl. silent MI)	504 (5.4%)	593 (6.4%)	0.84 (0.75, 0.95)	0.0045
Stroke	125 (1.3%)	106 (1.1%)	1.17 (0.91, 1.52)	0.2249

[Source: Sponsor's results, confirmed by the reviewer]

Figure 2 Kaplan-Meier Curve of the primary efficacy endpoint



[Source: Figure 13 from sponsor's clinical study report]

### 3.1.1.6 Sponsor's Secondary Efficacy Results

The results of secondary analyses are shown in Table 3. In subjects intended to have invasive procedures (coronary angiography followed by PCI and CABG if indicated), ticagrelor treatment was superior in the primary composite endpoint, compared to clopidogrel. Ticagrelor showed a statistically significant reduction in events for the composite of all-cause mortality, MI, and stroke compared to clopidogrel. Ticagrelor also demonstrated superiority on the composite of CV death, total MI (including silent MI), stroke, SRI and RI, TIA, and other ATEs.

Ticagrelor also showed statistical significance to clopidogrel in primary endpoint components MI (excluding silent MI) and CV death. No statistically significant difference was observed between ticagrelor and clopidogrel for the efficacy component stroke. Thus further formal testing of secondary endpoints was stopped. However, ticagrelor did show a nominally significant reduction in all-cause mortality compared to clopidogrel (nominal p-value=0.0003).

Table 3 Summary of Secondary Endpoints in PLATO

Secondary objective	Ticagrelor 90 mg bd (N = 9333)	Clopidogrel 75 mg od (N = 9291)	Hazard ratio (95% CI)	p-value
<b>(i)</b> Composite of CV death/MI (excl. silent MI)/stroke - intent to invasively manage	569 (8.5%)	668 (10.0%)	0.84 (0.75, 0.94)	0.0025
<b>(ii)</b> Composite of all-cause mortality/MI (excl. silent MI)/stroke	901 (9.7%)	1065 (11.5%)	0.84 (0.77, 0.92)	0.0001
<b>(iii)</b> Composite of CV Death/Total MI/Stroke /SRI/RI/TIA/Other ATE	1290 (13.8%)	1456 (15.7%)	0.88 (0.81, 0.95)	0.0006
<b>(iv)</b> Each component of primary efficacy endpoint:				
MI (excl. silent MI)	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)	0.2249
<b>(v)</b> All-cause mortality	399 (4.3%)	506 (5.4%)	0.78 (0.69, 0.89)	0.0003

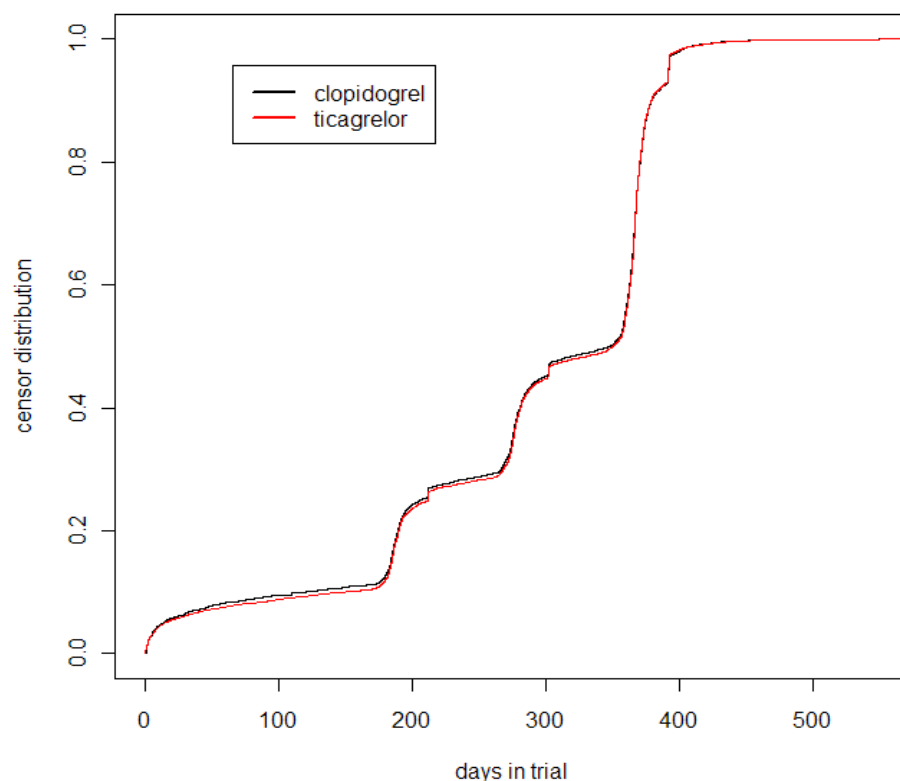
[Source: Sponsor's results, confirmed by the reviewer]

### 3.1.1.7 Reviewer's Results

During the review, question was brought up with regard to the censoring rules. Subject who discontinued the study early but did not withdraw consent was censored 30 days after the date when the End of Treatment visit should have occurred. In other words, the censoring dates of those subjects were projected. The sponsor clarified that "censoring rules were needed to allow counting events that were discovered following the final patient contact." Figure 3 shows the cumulative distribution of censored subjects; there are three sharp increments during the trial. This is consistent with the fact that majority of subjects finished the treatment within 6-month, 9-month or 12-month periods. The length of the treatment was determined by the time when the subject was enrolled in the study. Subjects that entered towards the end of the enrolment period would have the shortest duration of treatment. Figure 3 also showed three vertical "jumps" in the

middle of the three increments. Those “jumps” represent the patients who had projected censoring dates. The censoring distribution of subjects in clopidogrel group overlaps very well with the censoring distribution of subjects in ticagrelor group. Therefore, although the projected censoring dates may still be a concern, it is reassuring to see that the two groups are well balanced in this aspect.

Figure 3. Censor distribution for all subjects



The reviewer also performed a sensitivity analysis on the primary endpoint. In the sensitivity analysis, subjects no longer have the projected censor dates. Subjects who did not have a primary event were censored at the last real visit. HR estimate came out to be 0.86 with 95% CI (0.78, 0.94) in overall population in the sensitivity analysis. US population had HR=1.21 with 95% CI (0.88, 1.67). So the conclusion remains unchanged by different censoring rule. Figure 4 shows the cumulative percentage of subjects who did not make it to the expected last visit (excluding subjects who died).



Figure 4 Cumulative percentage of subjects who lost to follow up

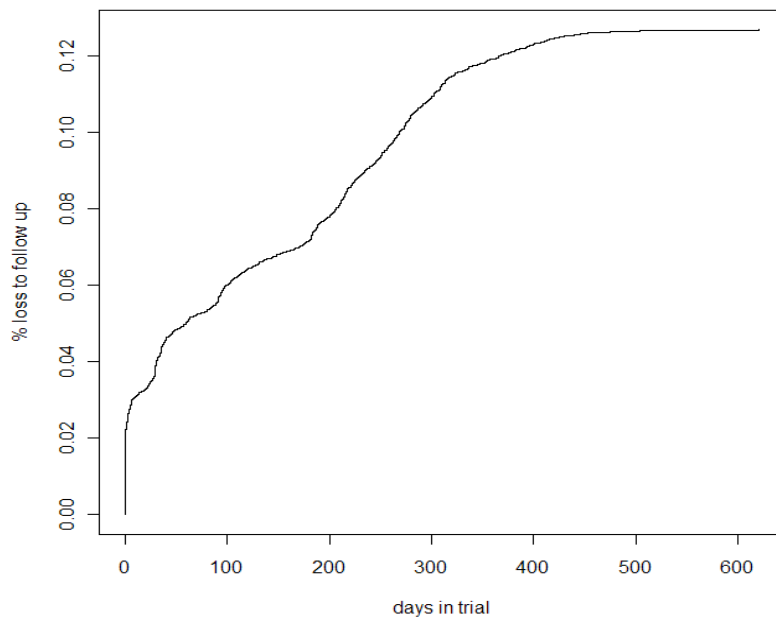
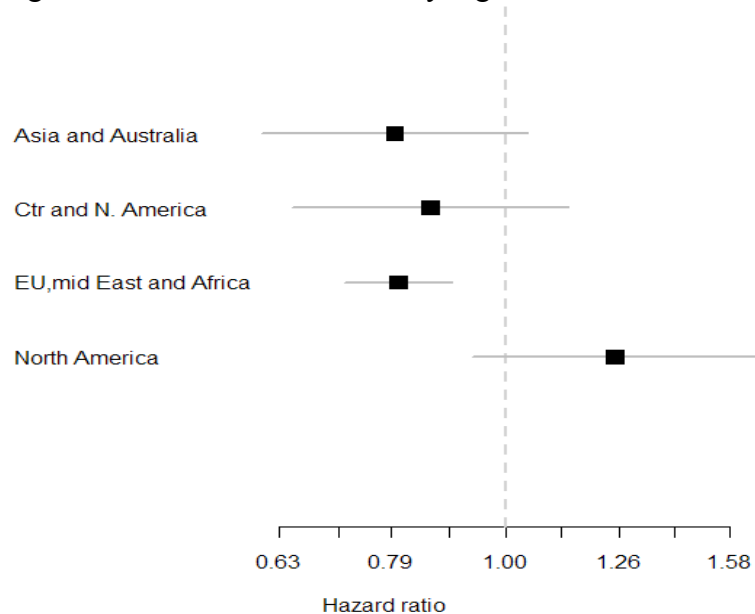


Figure 5 shows the hazard ratio estimates by region. Region was prospectively defined as Europe, Middle East and Africa; North America; Asia and Australia; and Central and South America. The hazard ratio point estimate for the primary endpoint numerically favored clopidogrel in the North America region and favored ticagrelor in the rest of 3 other regions.

Figure 5 Hazard ratio estimates by region



The major issue in this application is the regional difference observed between US and non-US. It is even more concerning that ticagrelor treatment appears to have a nominally negative effect on US subjects that almost reached nominal statistical significance itself (HR=1.27 with 95% CI (0.92, 1.75)).

In the following analyses, the reviewer performed extensive analyses to search for all potential explanations for the regional difference between US and non-US. For clarification, the treatment-by-region interaction referred below by the reviewer is based on models comparing US versus non-US (by combining all non-US countries into one region).

Table 4 Primary event rate in countries with top 10 largest enrollments

COUNTRY	ticagrelor			clopidogrel		
	N	event	rate (%)	N	event	rate (%)
Poland	1337	96	7.2	1329	137	10.3
USA	707	84	11.9	706	67	9.5
Hungary	632	42	6.6	635	70	11.0
Germany	580	55	9.5	576	62	10.8
Czech Republic	510	41	8.0	511	49	9.6
Netherlands	457	33	7.2	456	48	10.5
Brazil	347	49	14.1	343	62	18.1
Russia	340	37	10.9	338	35	10.4
Israel	320	25	7.8	316	24	7.6
Italy	312	20	6.4	313	21	6.7

Table 4 shows the primary event rate in each treatment group for the countries with top 10 largest enrollments. The overall event rates are 10.9% for clopidogrel group and 9.3% for ticagrelor group. Looking at the primary event rate in US, the ticagrelor group appeared to have a higher event rate while the clopidogrel group had a lower event rate than average.

Due to the observed treatment-by-region interaction, the reviewer focused on exploratory analyses in this section to examine any potential factors (such as play of chance, baseline factors, trial conduct matters, and patient characteristics, etc) that may explain the observed regional difference between US and non-US.

The reviewer examined the data from three aspects:

1. Is the difference between US and non-US a play of chance?
2. Is the difference between US and non-US caused by aspirin?
3. Is the difference between US and non-US caused by some other factors?

### **1. Is the regional difference due to a play of chance?**

Figure 6 Funnel Plot

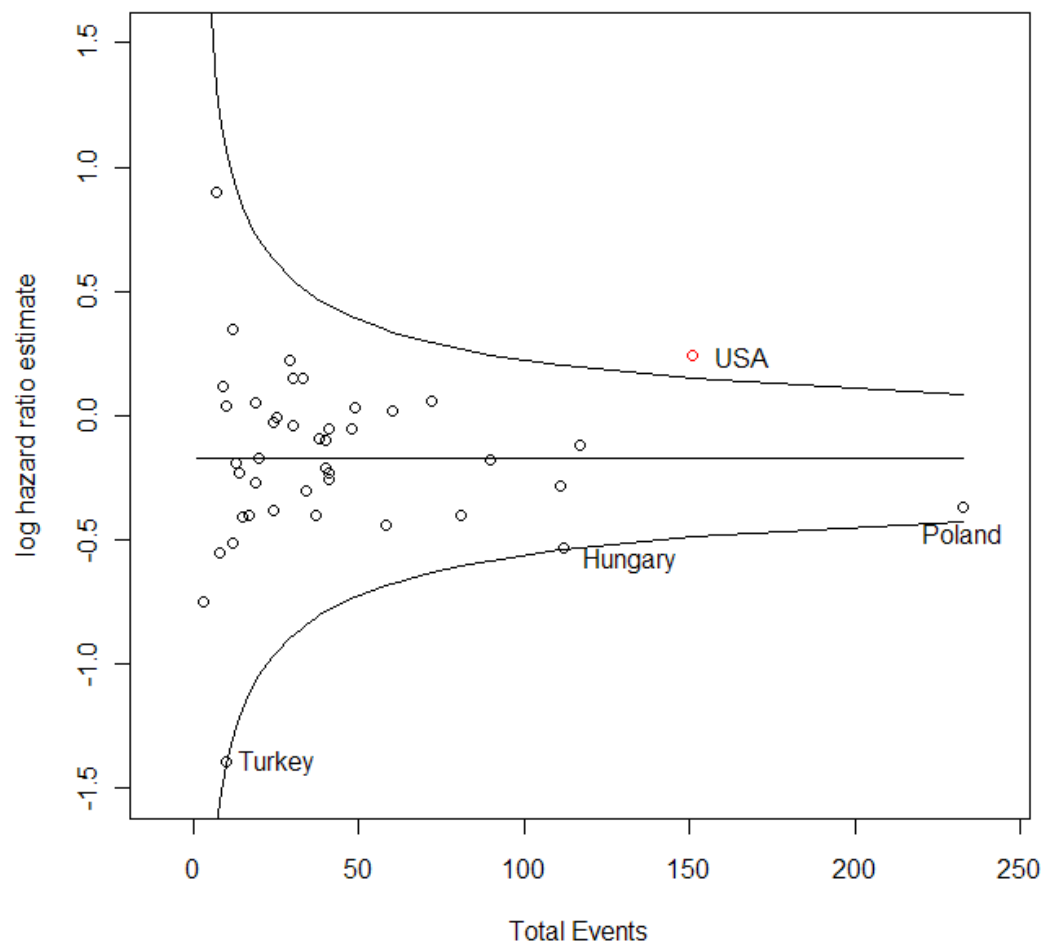


Figure 6 is a funnel plot to show potential outliers. USA is the only country out of the approximated 95% CI boundary. Hungary, Poland and Turkey are close to the bound. In fact, given that there are 43 countries in the trial, observing one country lying outside the bound should not be too surprising.

Since both Hungary and Poland enrolled large number of subjects, they may drive the study result to favor ticagrelor. The reviewer excluded all three countries (Turkey, Hungary and Poland) and re-analyzed the primary endpoint as a sensitivity analysis. The hazard ratio estimate is 0.90 with 95% confidence interval (0.81, 0.99). Even by excluding the big centers which showed big treatment effect favoring ticagrelor over clopidogrel (Poland and Hungary), the overall result still favors ticagrelor. The efficacy results seem robust.

The reviewer examined the data by plotting the hazard ratio estimate along the time (Figure 7). The hazard ratio estimate was calculated after every 10 events occurred in the trial. The grey area shows how the primary events accumulated in the ITT population. As more subjects enrolled into the trial, more events occurred and the confidence interval of the hazard ratio estimate became narrower as shown in the plot. It is noteworthy that the hazard ratio estimate stayed under 1 throughout the trial and the upper bound of the confidence interval was below 1 and

stayed below 1 in the second half of the trial. This result again showed the robustness and consistence of the overall efficacy results.

Figure 8 is the plot on nominal p-value corresponding to the hazard ratio estimates in Figure 7.

On the other hand,

Figure 9 and Figure 10 showed similar plot but this time based on US subjects only. Contrary to the hazard ratio plot in overall population, the hazard ratio estimates in US population stayed consistently above 1 throughout the trial. Although the hazard ratio estimates decreased gradually toward one, the estimates seemed to be stabilized after June 2008. The result in US subjects itself seemed consistent as well.

Figure 7 Hazard Ratio Plot for All Subjects in the Trial

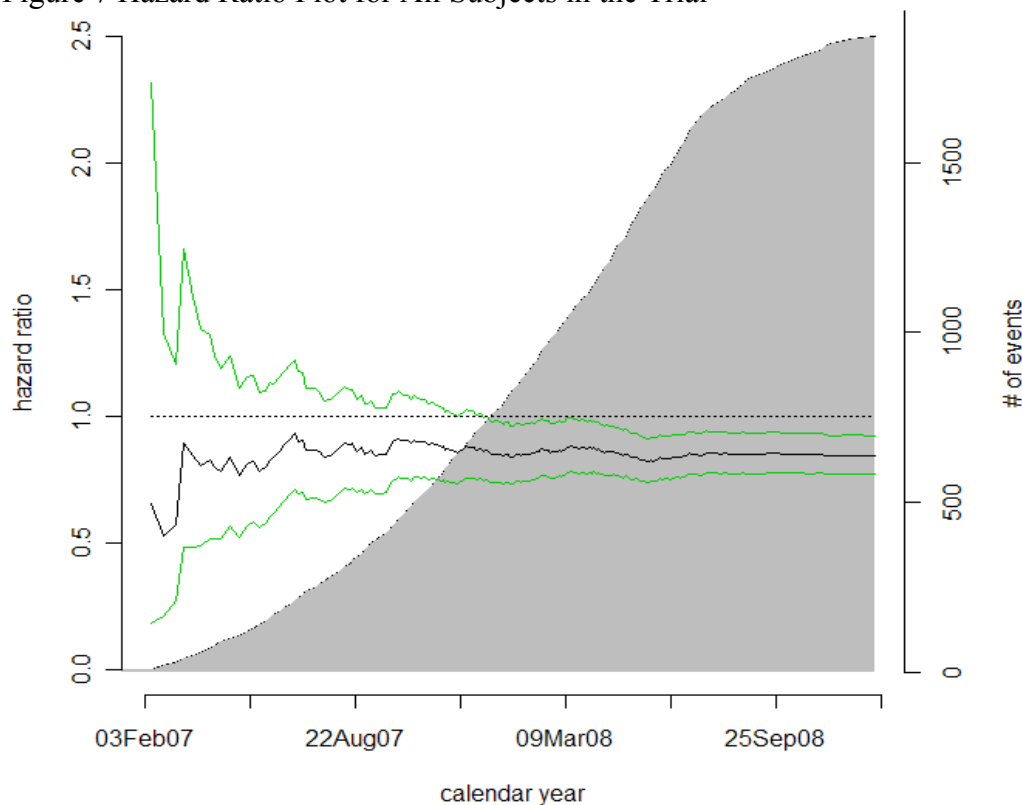


Figure 8 P-value Plot for All Subjects in the Trial

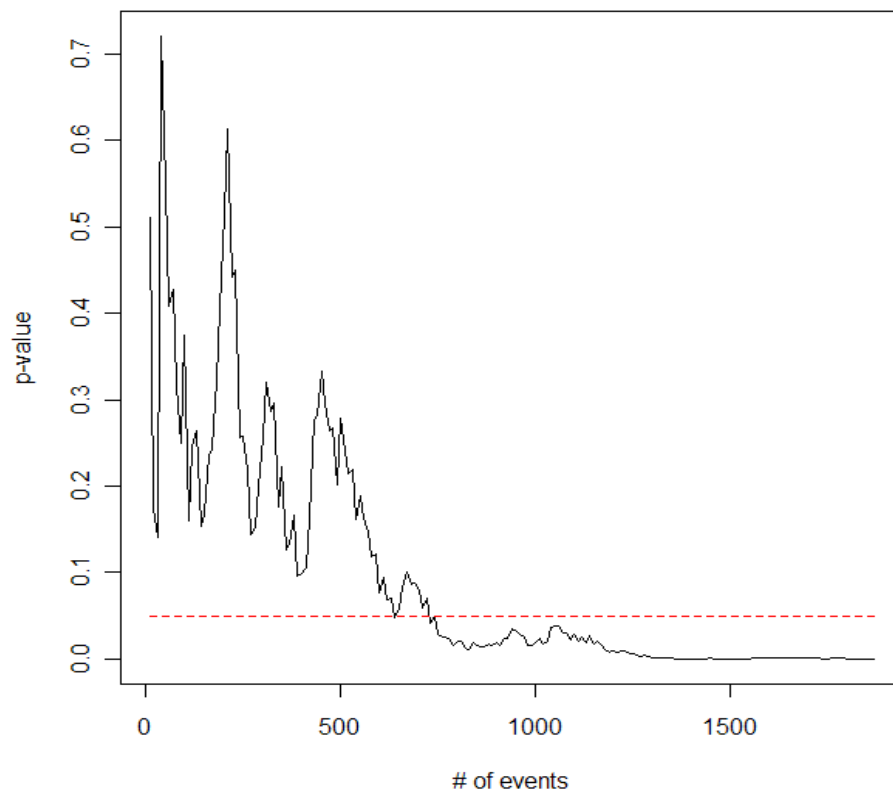


Figure 9 Hazard Ratio Plot for Subjects in US only

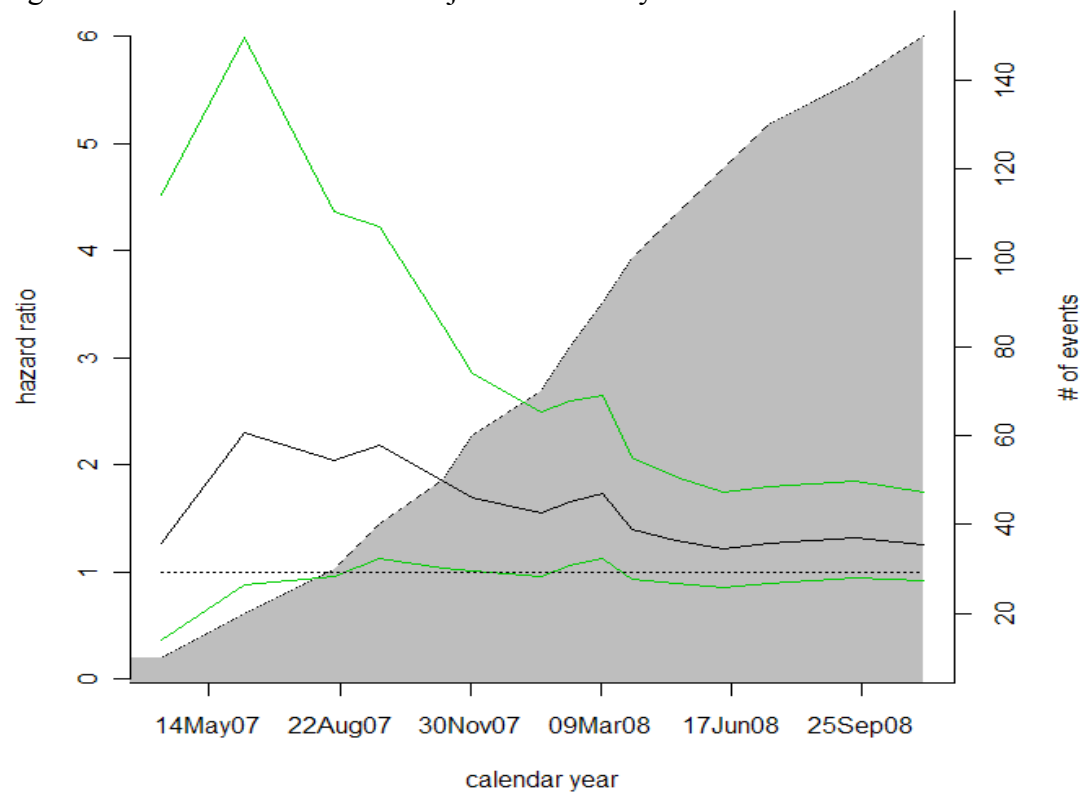
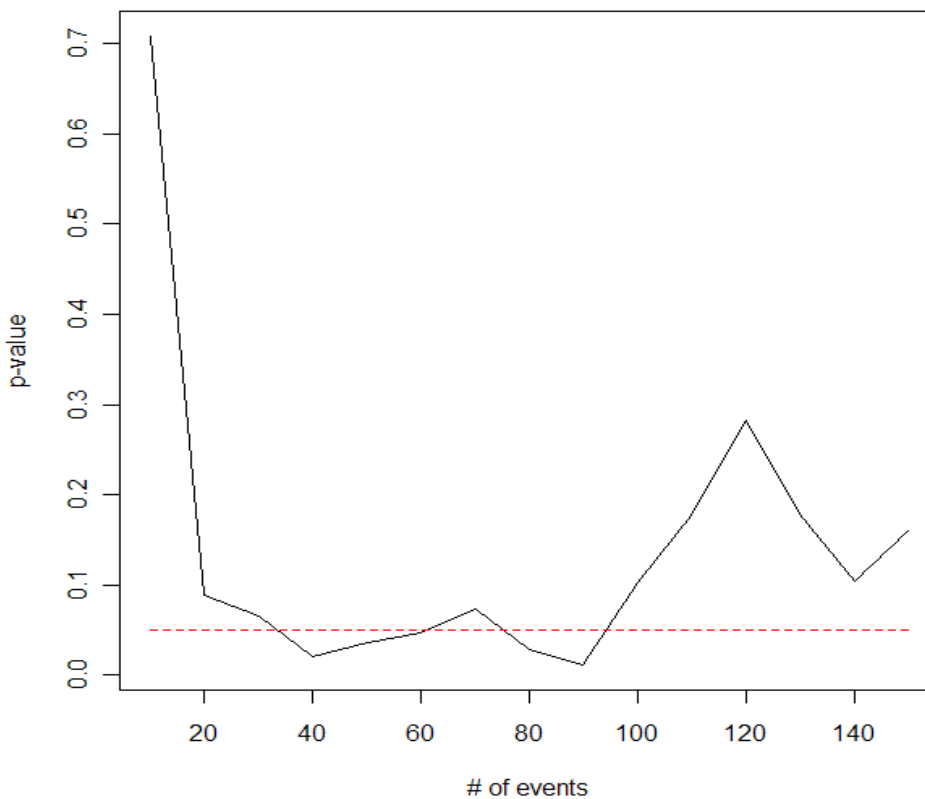


Figure 10 P-value plot for Subjects in US Only



The sponsor calculated the probability of observing such results in several ways, which were confirmed by the reviewer.

First of all, given the distribution of patients and events across the 4 pre-specified regions and assuming a common overall HR across regions of 0.84 as observed in PLATO, the probability of observing a result numerically favoring clopidogrel in the North America region while numerically favoring ticagrelor in the other 3 regions is 10%. However, this did not take into the account of the magnitude of the difference observed in hazard ratio estimates between US and non-US.

Secondly, 12 countries were found to have a HR >1 and 3 countries to have a HR >1.25. While it is not uncommon to observe a country with HR estimate going to the opposite direction from the overall HR in multi-regional trial with such large scale, the magnitude of difference in the HR estimate (HR=1.25 in US versus HR=0.84 in the rest of the world) is concerning, especially when US had the largest number of subjects enrolled among the 12 countries which had HR estimate above 1. Two other countries which had HR>1.25 are Australia (N=92) and Taiwan (N=83).

Another calculation was to compute the probability of observing a HR >1.25 if the true HR across all regions was 0.84. It was estimated to be <1% given the number of events in the US.

These calculations in general oversimplify the real situation. Nevertheless, it can shed some light on how likely the difference between US and non-US is due to a play of chance.

In the three calculations mentioned above, only the last one took the number of events in the US as well as the magnitude of difference between the hazard ratio estimates into account. Even though it may underestimate the probability of observing such a HR estimate in US due to the post-hoc nature of this calculation that does not account for multiplicity in the analyses, the estimate may be relatively closer to real probability in this reviewer's point of view. In other words, although play of chance can never be ruled out of possible explanations, it seems a little overstressing if we observed a hazard ratio estimate of 1.25 in a center enrolled 1413 subjects while the rest of the world showed a clear benefit from ticagrelor (HR=0.84).

## **2. Can the regional difference be explained by the aspirin usage?**

The sponsor analyzed over 30 factors including pre-specified covariates and post-hoc covariates and discovered that the concurrent ASA use contributed significantly to the observed treatment-by-region interaction. So the concurrent ASA dose was considered a strong candidate for explaining the regional difference if it is not due to a play of chance. However, the sponsor also acknowledged that "there are no data from preclinical pharmacology studies that could explain why specifically ticagrelor could be less effective than clopidogrel with concomitant administration of high dose ASA".

Figure 11 and Figure 12 show the distribution of median aspirin dose for non US subjects and US subjects in the trial, respectively. As shown in the figures, most subjects taking high dose

ASA (median ASA dose  $\geq 300$ mg) were from US. A total of 676 subjects in US took high ASA dose, while only 280 subjects in the rest of the world took high ASA dose (the numbers are based on variable MEDIAN55, a derived median ASA dose by the sponsor). So use of high dose ASA may simply be a confounding variable for the region factor (US versus non-US).

Figure 11 Distribution of Median Aspirin Dose for Non-US Subjects

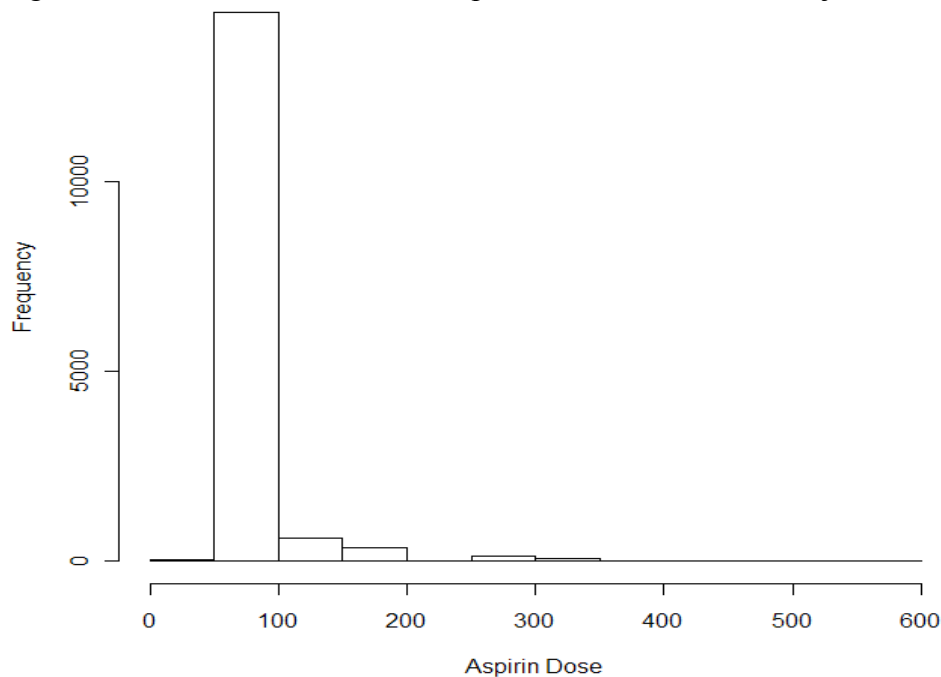
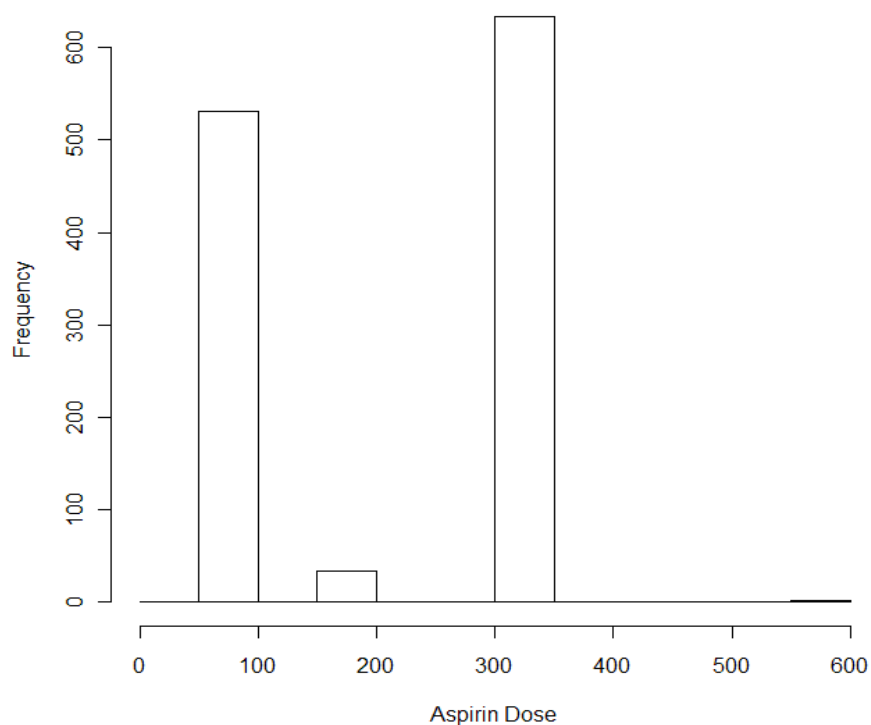


Figure 12 Distribution of Median Aspirin Dose for US Subjects



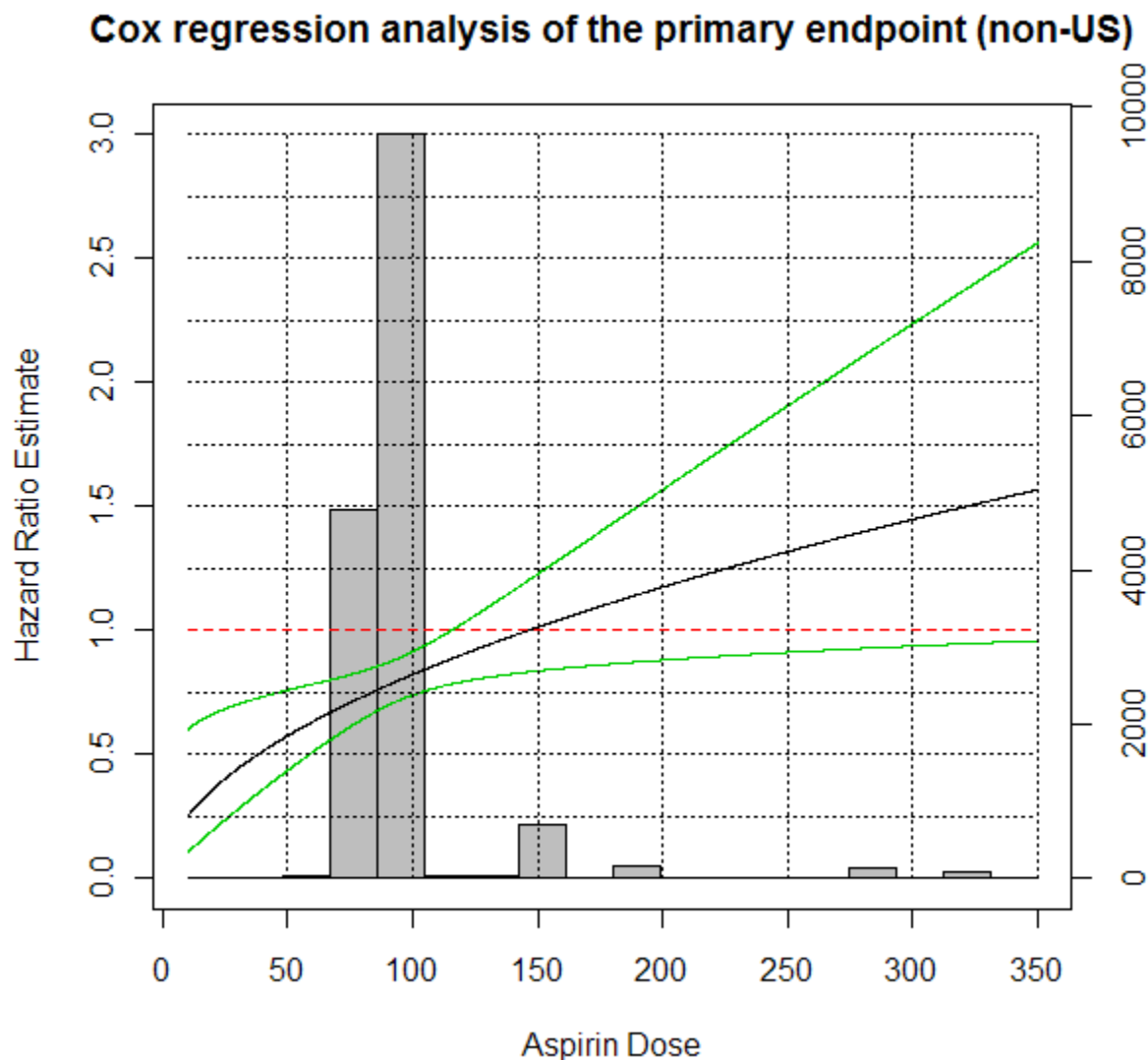


The sponsor also performed analysis using Cox Proportional Hazards model in the non-US population. The model included treatment, log(median ASA dose) and interaction between treatment and log(median aspirin dose) as shown in Figure 13. The black curve is the estimate of hazard ratio of ticagrelor over clopidogrel and the confidence interval boundaries are marked in green. It appears that the hazard ratio estimate increases as the ASA dose increases.

This is further verified by using the average of the median ASA doses in US subjects in the model to calculate a “hypothetical” hazard ratio estimate for US. The average of the median ASA dose in US subjects is 217.6 mg. Based on the covariate coefficient estimates in the Cox proportional hazard model from the non-US region as shown in Figure 13, the corresponding “hypothetical” hazard ratio estimate for US is 1.23 with 95% CI (0.89, 1.69). This is quite close to the hazard ratio estimate in US based on real data (1.27 with 95% CI (0.92, 1.75)).

However, the reviewer has some concerns on the analysis. The most important one is that the majority of subjects in the non-US region took either 75mg or 100 mg ASA so the model may not be robust due to the limited data on the high end of ASA dose in the non-US region. This can also be seen in the widening confidence band as the ASA dose increases.

Figure 13 Hazard Ratio Estimate Using Cox Proportional Hazards Model Including Aspirin-Treatment Interaction



It is unknown whether the median ASA dose is sufficient to capture the information. After all, each subject used a single value to represent the whole course of ASA treatment during the trial in these analyses.

Table 5 lists all subjects who took any daily ASA dose  $\geq 1000$  mg. Some doses taken are very large. According to the sponsor, “a further review of the database revealed 33 patients whose recorded aspirin dose was something other than ‘mg’: namely ‘ $\mu\text{g}$ ’, ‘g’, ‘mL’ or ‘IU’; and the dose was equal to the subject’s median aspirin dose. In most of the cases, the dose appears to be a valid aspirin dose or a multiple of a valid dose.” Since the number of subjects is small and the median ASA dose is not sensitive to extreme values, it is probably not a big concern.

Table 5 Subjects with daily dose of ASA  $\geq$  1000mg

SUBJECT	Days with ASA $\geq$ 1000mg	Minimum (mg)	Maximum (mg)
E1202063	1	2500	2500
E1317013	30	1500	1500
E1417031	2	1500	1600
E1421021	6	3000	3000
E1639007	12	1950	2600
E1639012	6	2600	2600
E1643005	1	1850	1850
E1643006	1	1950	1950
E1710002	1	10000	10000
E2115005	32	3000	3000
E2132005	5	2250	3000
E2133021	1	3000	3000
E2133033	1	3000	3000
E2309031	1	1500	1500
E2309059	1	1500	1500
E2309130	1	1500	1500
E2309165	1	1500	1500
E2309196	1	1500	1500
E2309249	1	1500	1500
E2309261	1	1500	1500
E2309274	1	1500	1500
E2313049	1	1500	1500
E2318008	27	1100	3000
E2341001	1	1500	1500
E2341004	1	1500	1500
E2349005	1	1200	1200
E2610032	1	5000	5000
E2901083	5	1200	1800
E3318002	30	2400	2400
E3340007	1	1200	1200
E3604043	7	1800	1800
E3624100	1	3000	3000
E3706016	1	1500	1500
E3913022	1	2050	2050
E4208050	1	1600	1600
E4404004	2	1200	1200
E4409025	2	1300	1500
E4414004	5	3000	3000
E5335001	367	6325	6325
E5514004	37	25200	25200

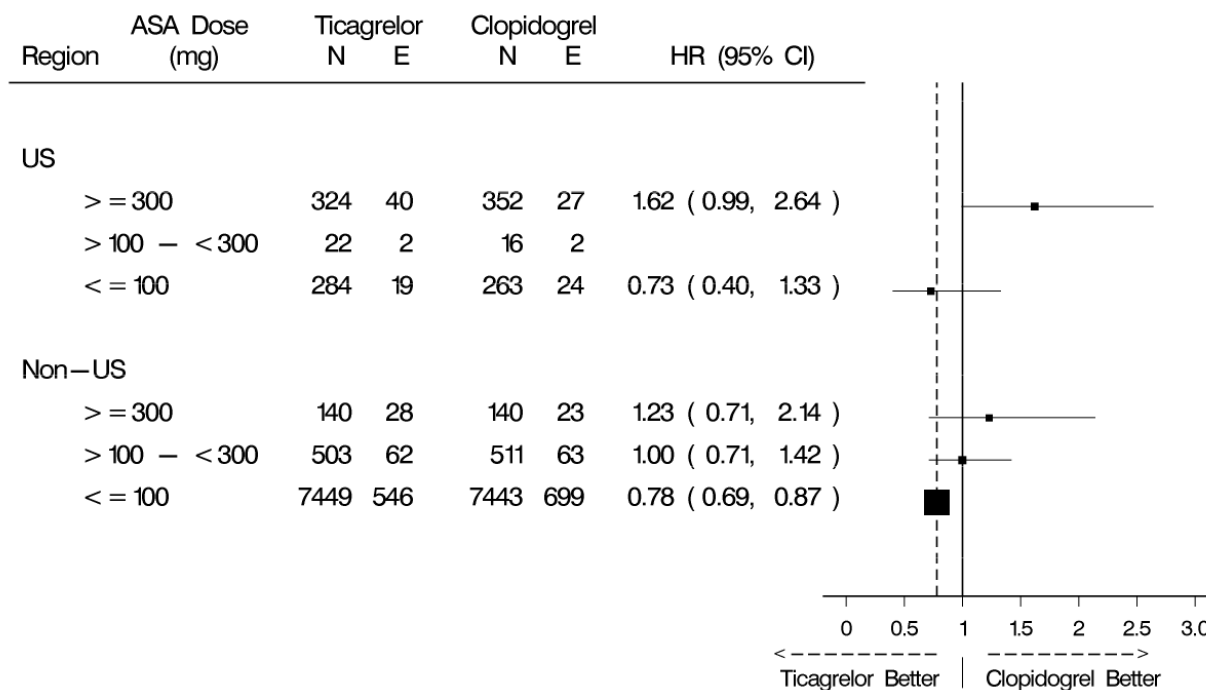
The sponsor also performed sensitivity analyses with regard to the median ASA dose. Median ASA dose was originally defined as the median of all of a patient's aspirin doses taken during the study drug period, regardless of whether and when the patient had an event. In addition, the original definition excluded patients who took less than 5 doses of aspirin. This is to avoid the possibly confounding influence of high ASA loading dose following the index event since some

patients took high dose for 1 day and had an immediate event. Taking the feedback from outside experts into consideration, the sponsor conducted a number of sensitivity analyses. They reported that “both analyses (MEDIAN24 and MEDIAN55) lead to similar conclusions, supporting a potential role for ASA maintenance dose in the treatment-by-region interaction observed in PLATO.”

The sponsor defined in a number of ways to calculate the median. MEDIAN55 excludes the loading dose of ASA in the calculation completely. MEDIAN24 excludes subjects who had only 1 day of ASA (presumably, only the loading dose). MEDIAN20 excludes subjects who had less than 5 days of ASA and MEDIAN25 includes all doses (loading dose as well) in the calculation. Nevertheless, the sponsor tried to assess how sensitivity the model is to the different definition of the median ASA. It appears reasonable to this reviewer that the ASA doses after a subject had a primary event should be excluded in calculating the median ASA dose.

In the sensitivity analysis, the variable MEDIAN55 represents the median summary of ASA doses, excluding Day 1 loading dose, and up until the day of the event. Given the fact that all the sensitivity analyses are exploratory, MEDIAN55 was preferred by the sponsor because it “appears more relevant in addressing the input of clinical experts and the FDA, and in separating maintenance dosing from loading dose”. Interestingly, HR point estimate in US subjects decreased to 0.73 for low dose ASA (below 100 mg) by the new definition MEDIAN55 shown in Figure 14. In the sponsor’s original analysis, the hazard ratio estimate in subjects who took low ASA dose ( $\leq 100$ mg) in US was 0.99.

Figure 14 Hazard ratio estimates by different ASA dose using MEDIAN55



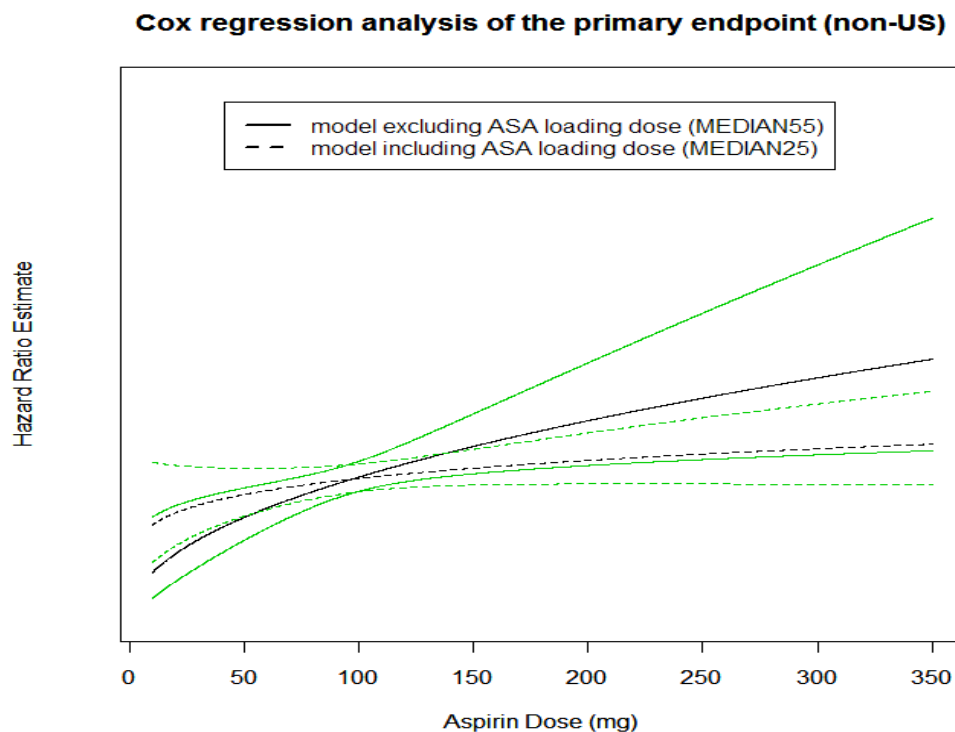
[Source: Figure 9 on sponsor’s correspondence submitted on 6/16/2010]

MEDIAN24 represents the median summary of ASA doses, excluding patients with less than 2 days of aspirin. It includes all aspirin during the study drug period for patients who did not have an event. The results are similar to MEDIAN55.

The sponsor also used MEDIAN25 which included all aspirin during the study drug period for patients who did not have an event. It includes all aspirin up to the time of the event for subjects who had a primary event.

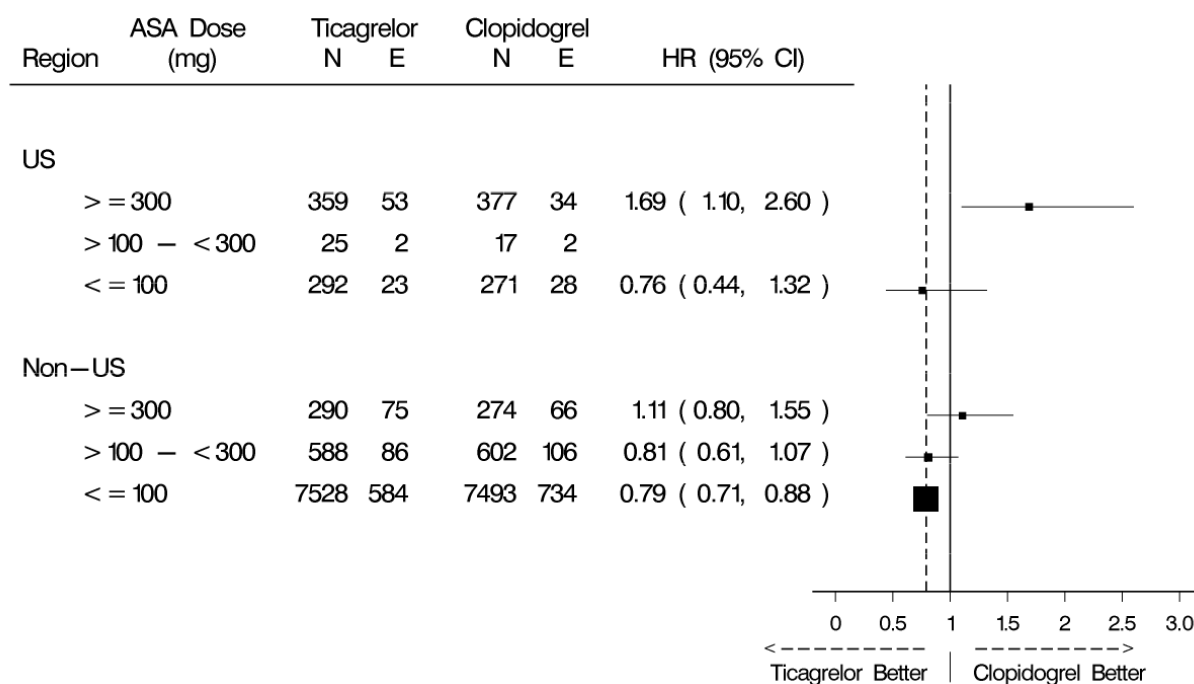
The Cox proportional hazards model seems to be sensitive to whether or not the first day ASA loading dose is included. Just by including the first day loading dose, the relationship between the hazard ratio estimate and median ASA dose becomes much flatter (Figure 15). It is also interesting to find that the treatment\*region interaction does not seem to be affected by the total ASA dose taken during the trial.

Figure 15 Comparison of models excluding or including 1<sup>st</sup> day ASA loading dose



Looking further to compare Figure 14 and Figure 16, which show the subgroups by region and by median ASA dose using different median ASA measurements, the biggest difference between the two is that there are considerably more subjects in the high ASA dose group in the non-US region if the calculation of median ASA includes the loading dose. It again puts the small number of high dose ASA subjects in the non-US region into a crucial position. Those subjects appeared to have a huge leverage on the Cox proportional hazards model.

Figure 16 Hazard ratio estimates by different ASA dose using MEDIAN25



[Source: Figure 7 on sponsor's correspondence submitted on 6/16/2010]

The reviewer went further to investigate how sensitivity the model is to the high dose ASA data. The reviewer simply used the median ASA variable MEDIAN55 preferred by the sponsor in the following sensitivity analyses. In fact, there were only 472 subjects whose median daily ASA dose were above 200 mg out of a total of 16186 subjects in non-US region took at least two days of ASA during the study period. Among those 472 subjects, 280 subjects had median daily ASA dose equal or above 300 mg. In order to show how much leverage those 472 subjects had on the Cox proportional hazards model, the reviewer applied the same model in the non-US excluding these subjects with high median ASA dose. Although the relationship between ASA dose and hazard ratio estimate still seemed to exist, the model appeared quite sensitive to these subjects (Figure 17 and Figure 18). The curve can swing up and down considerably by excluding either all subjects who had median ASA no less than 300 mg or subjects who had median ASA no less than 200 mg. It casts doubt on how real the relationship is since less than 3% subjects can make such big impact on the model.

There are a number of other factors which showed a significant interaction with treatment within US population and differed between US and non-US populations, for example, use of GPI during index hospitalization and whether subjects went through early PCI. However, these factors did not show any significant interaction with treatment in the non-US populations and were not considered as important contributors to the regional difference. Therefore the robustness of the Cox proportional model on the non-US population is crucial. A few more or less events in that high ASA dose subpopulation in the non-US region may make a huge impact on the Cox proportional hazards model and therefore influence the interpretation.

Figure 17 Sensitivity analyses on median ASA dose (1)

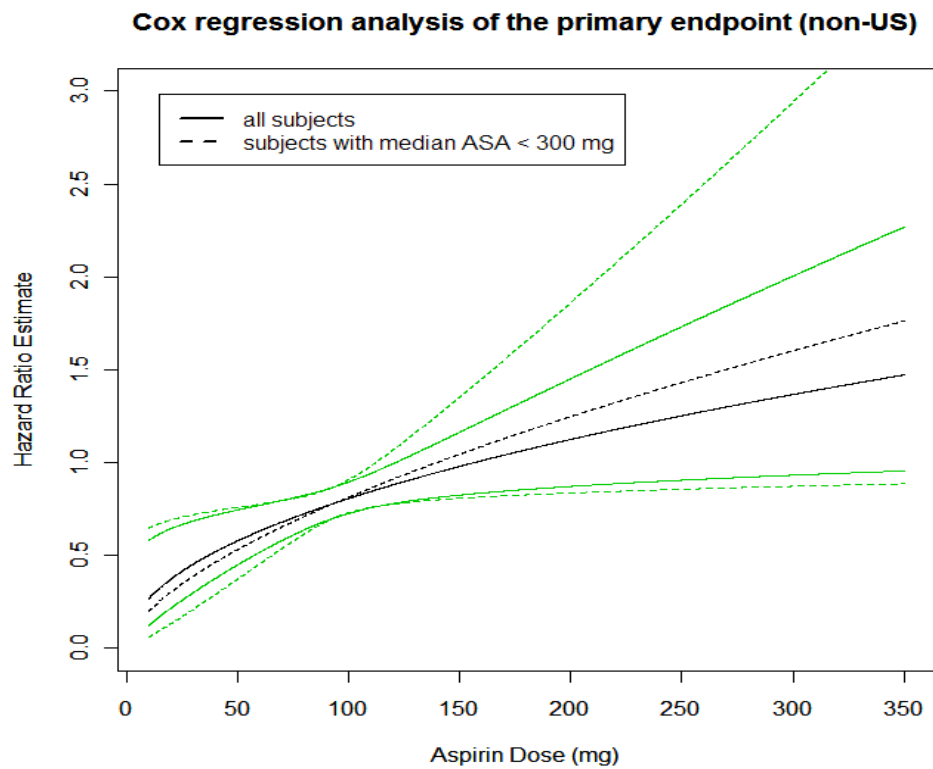
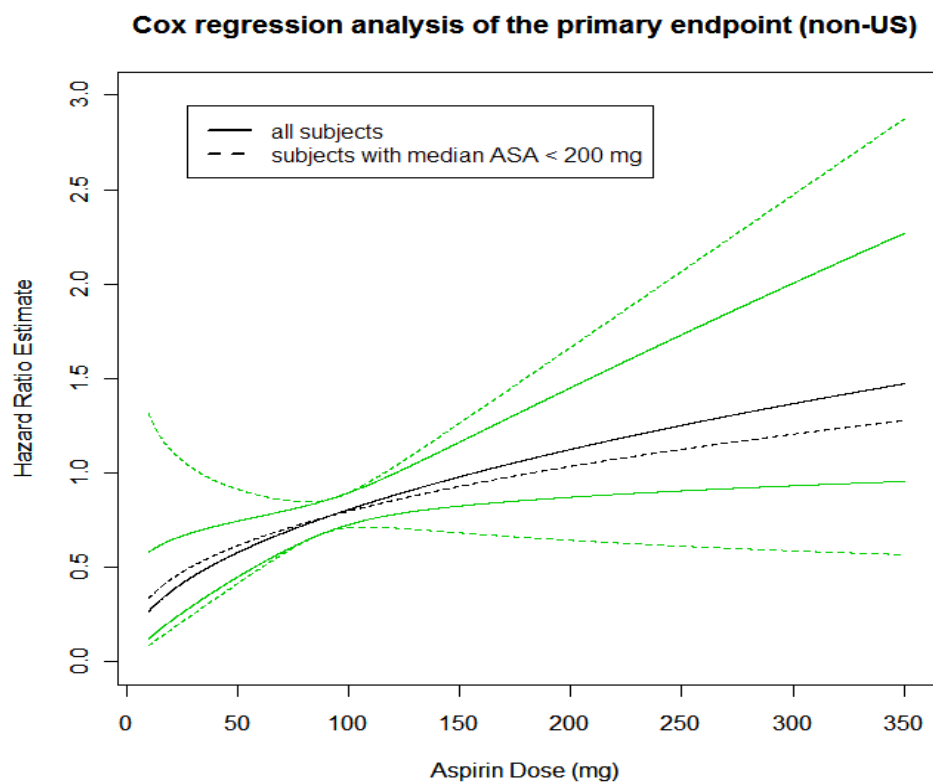


Figure 18 Sensitivity analyses on median ASA dose (2)



Therefore, the finding that ASA may contribute to the regional difference remains questionable. First of all, as the reviewer mentioned before, as most subjects taking high dose ASA were from US, high dose ASA may simply be a confounding variable. Even though ASA seemed to be the best contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the Cox proportional hazards model did not appear robust enough due to the small number of subjects taking high dose ASA in the non-US region. A few more or less events in that subpopulation in the non-US region can make a huge impact on the Cox proportional hazards model and therefore influence the interpretation.

### **3. Is the difference caused by other factors?**

While the sponsor performed pre-specified analyses of 31 baseline factors to explore interactions with treatment for the primary efficacy endpoint, the reviewer also explored certain other factors as well as models.

Here is a list of pre-specified factors explored by the sponsor.

1. Gender (male, female)
2. Race (Caucasian, Black, Oriental, Other)
3. Waist circumference (<100 cm, ≥100 cm)
4. Troponin I (positive, negative)
5. Index event characteristic (unstable angina; NSTEMI; STEMI; other)
6. Pre-index event antiplatelet therapy (none, clopidogrel, ASA, clopidogrel + ASA, other)
7. ASA on day of randomization (yes, no)
8. History of diabetes (yes, no)
9. Prior MI (yes, no)
10. Prior PCI (yes, no)
11. Prior CABG (yes, no)
12. Intent at time of randomization for medical management versus invasive management (yes, no)
13. Moderate CYP3A inhibitor usage at randomization (yes, no)
14. Any use of GP IIb/IIIa inhibitor between index event and end of index hospitalisation (yes, no)
15. Unfractionated heparin, low molecular weight heparin, fondaparinux (fondaparinux), or bivalirudin between index event and end of index hospitalisation (yes, no)
16. Lipid-lowering drugs on day of randomization (yes, no)
17. β-blockers on day of randomization (yes, no)
18. ACE inhibitors on day of randomization (yes, no)
19. ARBs on day of randomization (yes, no)
20. Calcium channel blockers on day of randomization (yes, no)
21. Age (years) as a continuous factor
22. Weight (kg) as a continuous factor
23. BMI as a continuous factor
24. Time from start of index event to initiation of study therapy as a continuous factor
25. At least 80% compliance with assigned study medication at all visits (yes, no)



26. Concomitant median ASA dose (mg) as a continuous variable
27. Having PCI (yes, no)
28. Use of DES or BMS (yes, no)
29. PPI use on day of randomization (yes, no)
30. Angiography quartiles in terms of access to catheterisation laboratory (high access, medium-high access, medium-low access, low access)
31. Randomized treatment

Nine more factors were identified and included in the analyses by the sponsor.

The following additions or changes in definitions of factors were adopted for some analyses.

1. Age as a continuous factor
2. Weight as a continuous factor
3. BMI as a continuous factor
4. Geographic region was categorized as US and non-US. The analyses were also conducted for NA (United States and Canada) and ROW
5. Time from start of index event to initiation of study therapy as a continuous factor
6. In addition to the use (yes/no) of GP IIb/IIIa, the type of GP IIb/IIIa was analysed, if available in the dataset.
7. At least 80% compliance with assigned study medication at all visits (yes/no)
8. Cumulative 24-hour clopidogrel loading dose instead of the dose within a 4-hour window: none, 1 to 450 mg, >450 mg
9. Angiography for non-ST elevation myocardial infarction (NSTEMI) patients

The reviewer also examined a number of variables by US and Non US as shown in Table 6 and Table 7.

Table 6 Comparisons of categorical covariates in US and non-US

Factors		Non-US		US	
		N	Percentage	N	Percentage
ACE use at randomization	No	7364	42.8	738	52.2
	Yes	9847	57.2	675	47.8
pre-index event antiplatelet therapy	None	11403	66.3	744	52.7
	clopidogrel	254	1.5	35	2.5
	ASA	4542	26.4	482	34.1
	clopidogrel+ASA	956	5.6	152	10.8
	Other	56	0.3		
ARB use at randomization	No	15751	91.5	1230	87.0
	Yes	1460	8.5	183	13.0
ASA use at randomization	No	839	4.9	88	6.2
	Yes	16372	95.1	1325	93.8
Beta blocker at randomization	No	4377	25.4	187	13.2
	Yes	12834	74.6	1226	86.8
Prior CABG	No	16341	94.9	1177	83.3
	Yes	870	5.1	236	16.7
CCB use at randomization	No	14684	85.3	1204	85.2

	Yes	2527	14.7	209	14.8
History of diabetes	No	13021	75.7	941	66.6
	Yes	4190	24.3	472	33.4
Index event characteristic	Unstable Angina	2970	17.3	142	10.1
	NSTEMI	7006	40.8	949	67.3
	STEMI	6804	39.6	222	15.7
	Other	391	2.3	98	6.9
GPI during index hospitalization	No	12858	74.7	704	49.8
	Yes	4353	25.3	709	50.2
Heparin during index hospitalization	No	6222	36.2	474	33.5
	Yes	10989	63.8	939	66.5
Prior PCI	No	15134	87.9	998	70.6
	Yes	2077	12.1	415	29.4
Lipid lowering agent at randomization	No	3459	20.1	309	21.9
	Yes	13752	79.9	1104	78.1
Previous MI	No	13774	80.0	1026	72.6
	Yes	3437	20.0	387	27.4
Race	caucasian	15815	91.9	1262	89.3
	Black	92	0.5	137	9.7
	Oriental	1087	6.3	9	0.6
	Other	216	1.3	5	0.4
Gender	Male	12329	71.6	1007	71.3
	Female	4882	28.4	406	28.7
Early PCI	No	8818	51.2	546	38.7
	Yes	8388	48.8	866	61.3
Habitual smoker	No	11048	64.2	898	63.6
	Yes	6163	35.8	515	36.4
Use of DES or BMS	No	6810	39.6	525	37.2
	Yes	10401	60.4	888	62.8
Indicator of 1st PCI	No	6281	36.5	482	34.1
	Yes	10925	63.5	930	65.9
Prior stroke?	No	16991	98.7	1402	99.2
	Yes	220	1.3	11	0.8
Troponin I>ULN 24 hr Post Index Event	Positive	13913	80.8	1176	83.2
	Negative	2797	16.3	171	12.1
	missing	501	2.9	66	4.7
Waist circumference	<100cm	9067	52.7	560	39.6
	>=100cm	7289	42.4	689	48.8
	unknown	855	5.0	164	11.6
Cyp3A strong inducer	No	17057	99.2	1398	99.1
	Yes	133	0.8	13	0.9
Cyp3A strong inhibitor	No	16947	98.6	1390	98.5
	Yes	243	1.4	21	1.5
Subject flag	NSTEMI	9976	59.5	1091	83.1
	STEMI	6804	40.5	222	16.9
Planned treatment approach at randomization	medical management	5126	29.8	90	6.4

	invasive management	12085	70.2	1323	93.6
TIMI risk score(STEMI)	0-2	3755	55.2	134	60.4
	3-6	2799	41.1	85	38.3
	>6	250	3.7	3	1.4
TIMI risk score(NSTEMI)	0-2	685	6.9	45	4.1
	3-6	4987	50.0	501	45.9
	>6	4304	43.1	545	50.0

Table 7 Comparisons of continuous covariates in US and non-US

	US				Non US			
	N	Median	Mean	STD	N	Median	Mean	STD
hours between hosp admission to early PCI	702	11.1	12.0	9.9	7663	1.8	5.6	8.4
hours between index event to early PCI	866	16.8	16.5	10.4	8388	6.6	10.5	10.9
hours between index event to randomization	1412	15.3	14.7	8.7	17202	10.1	11.5	9.0
hours between index event to hospitalization	1141	2.8	4.4	4.8	15052	2.8	4.5	4.9
hours between 1st dose IP to early PCI	858	0.2	1.3	9.1	8376	0.3	1.5	5.9
hours between randomization to early PCI	866	1.0	2.7	4.9	8388	0.6	2.1	4.7
hours between randomization to 1st IP	1356	0.6	11.0	76.1	17064	0.3	1.2	20.1
hours from Index Event to 1st Study Drug	1355	16.7	25.8	77.0	17055	10.8	12.7	22.0
hours between hospital admission and 1st dose	1096	12.5	21.9	78.9	14931	3.8	12.8	495.9
days on ASA	1342	272.0	229.0	141.5	16780	275.0	243.3	132.6
mean ASA dose (mg)	1342	268.3	227.1	274.7	16779	100.0	108.2	97.1
median ASA dose (mg)	1203	325.0	217.6	213.6	15656	100.0	99.3	43.3
ticagrelor study drug (mg) before 1st PCI	406	180.0	180.0	24.5	3964	180.0	179.5	15.1
clopidogrel study drug (mg) before 1st PCI	425	300.0	288.5	163.1	4176	300.0	230.6	160.6
clopidogrel open label (mg) before 1st PCI	314	300.0	291.5	213.2	4325	375.0	418.2	187.4
clopidogrel total dose (mg) before 1st PCI	595	300.0	359.9	194.4	6409	375.0	432.5	185.0
Clop Load Cumulative between IE and Rand+24h	920	300.0	348.8	191.3	12613	300.0	388.2	181.2
Clop Load Max in Any 4h IE to Rand+24h	920	300.0	306.5	173.0	12613	300.0	351.7	165.8
weight (KG)	1410	87.0	89.2	20.6	17158	80.0	79.7	15.3
Age	1413	61.0	61.1	11.6	17209	62.0	62.3	11.2
number of BMS stent	1413	0.0	0.4	0.8	17211	0.0	0.7	0.9
number of DES stent	1413	0.0	0.8	1.2	17211	0.0	0.3	0.8

US population differs from non-US population in a number of ways. For example, it took much longer time on average for US subjects to receive first dose of study drug since occurrence of index events (median=16.7 hours in US, median =10.8 hours in non-US). More US subjects enrolled in the trial were NSTEMI patients compared to the rest of the world (67.3% in US and 40.8% in non-US). If a subject had stents inserted, US subjects tended to have drug eluting stents and non-US subjects tended to have bare metal stents. Other factors including prior history of PCI or MI, number of subjects who went through early PCI, pre-index event antiplatelet therapy, beta blocker usage at randomization, planned treatment approach at randomization, GPI during index hospitalization, and many more (Table 8). So it appears that the US population in the trial

differs from the population outside of US in many ways. The reviewer further broke down the US population and non-US population by each covariate and looked at the hazard ratio estimate by each subgroup. Figure 19, Figure 20 and Figure 21 shows the subgroup analyses in US and non-US populations side by side.

Table 8 Comparison of US and Non-US characteristics

	US			non-US		
	N	# of subjects	Percentage	N	# of subjects	Percentage
Use of ACE at randomization	1413	675	47.8	17211	9847	57.2
Use of ARB at randomization	1413	183	13	17211	1460	8.5
beta blocker use at randomization	1413	1226	86.8	17211	12834	74.6
Prior CABG	1413	236	16.7	17211	870	5.1
History of diabetes	1413	472	33.4	17211	4190	24.3
Index event (NSTEMI)	1413	949	67.3	17211	7006	40.8
GPI during index hospitalization	1413	709	50.2	17211	4353	25.3
Prior PCI	1413	415	29.4	17211	2077	12.1
Prior MI	1413	387	27.4	17211	3437	20
Black	1413	137	9.7	17211	92	0.5
early PCI	1413	866	61.3	17211	8388	48.8
Planned invasive management at randomization	1413	1323	93.6	17211	12085	70.2
Use of bare metal stents	1413	331	23.4	17211	7993	46.4
Use of drug eluting stents	1413	653	46.2	17211	3339	19.4
	N	Mean	Median	N	Mean	Median
weight (KG)	1413	89.2	87	17158	79.7	80
median ASA dose (mg)	1261	219	325	16186	100.1	100
hours from index event to 1st study drug	1355	25.8	16.7	17055	12.7	10.8
hours from index event to early PCI	866	16.5	16.8	8388	10.5	6.6
hours from index event to randomization	1412	14.7	15.3	17202	11.5	10.1

US and non-US populations appear to be affected differently by some covariates as shown in the forest plots. The reviewer then included each individual covariate and covariate\*treatment interaction into the Cox proportional hazards model with presence of treatment\*region interaction term. However, not a single covariate seems to contribute much to the treatment\*region interaction.

Figure 19 Analysis by various subgroups (1)

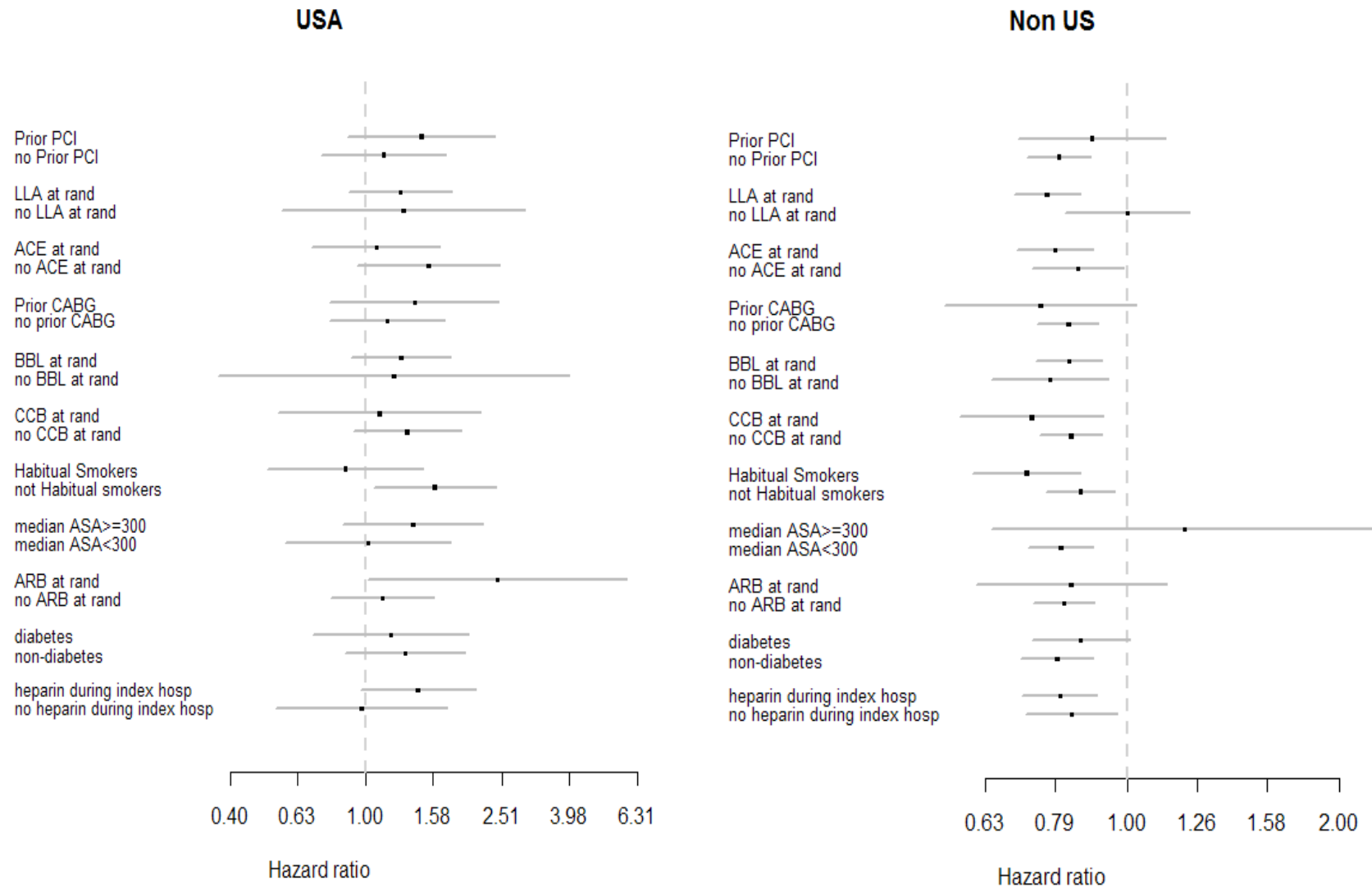


Figure 20 Analysis by various subgroups (2)

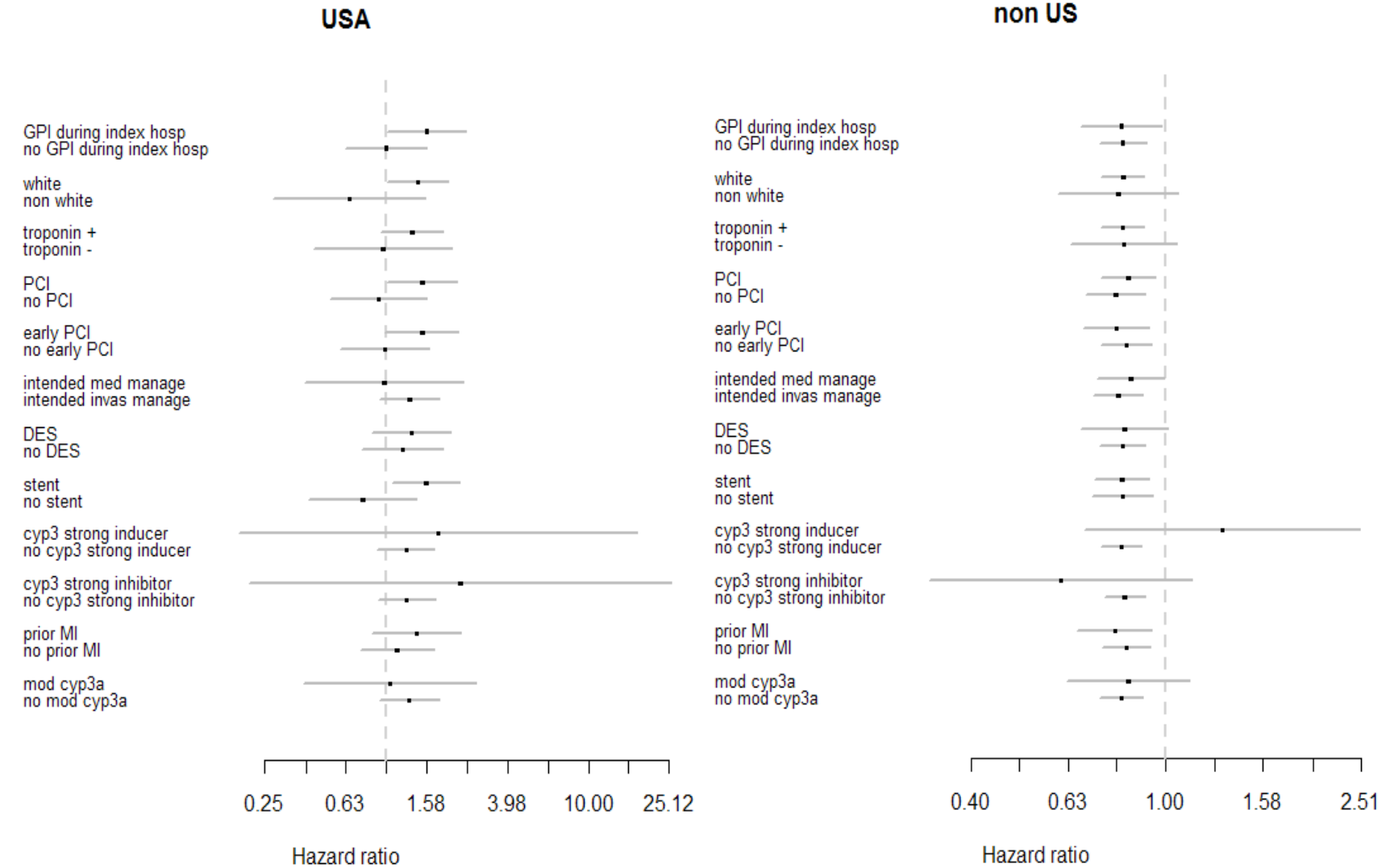
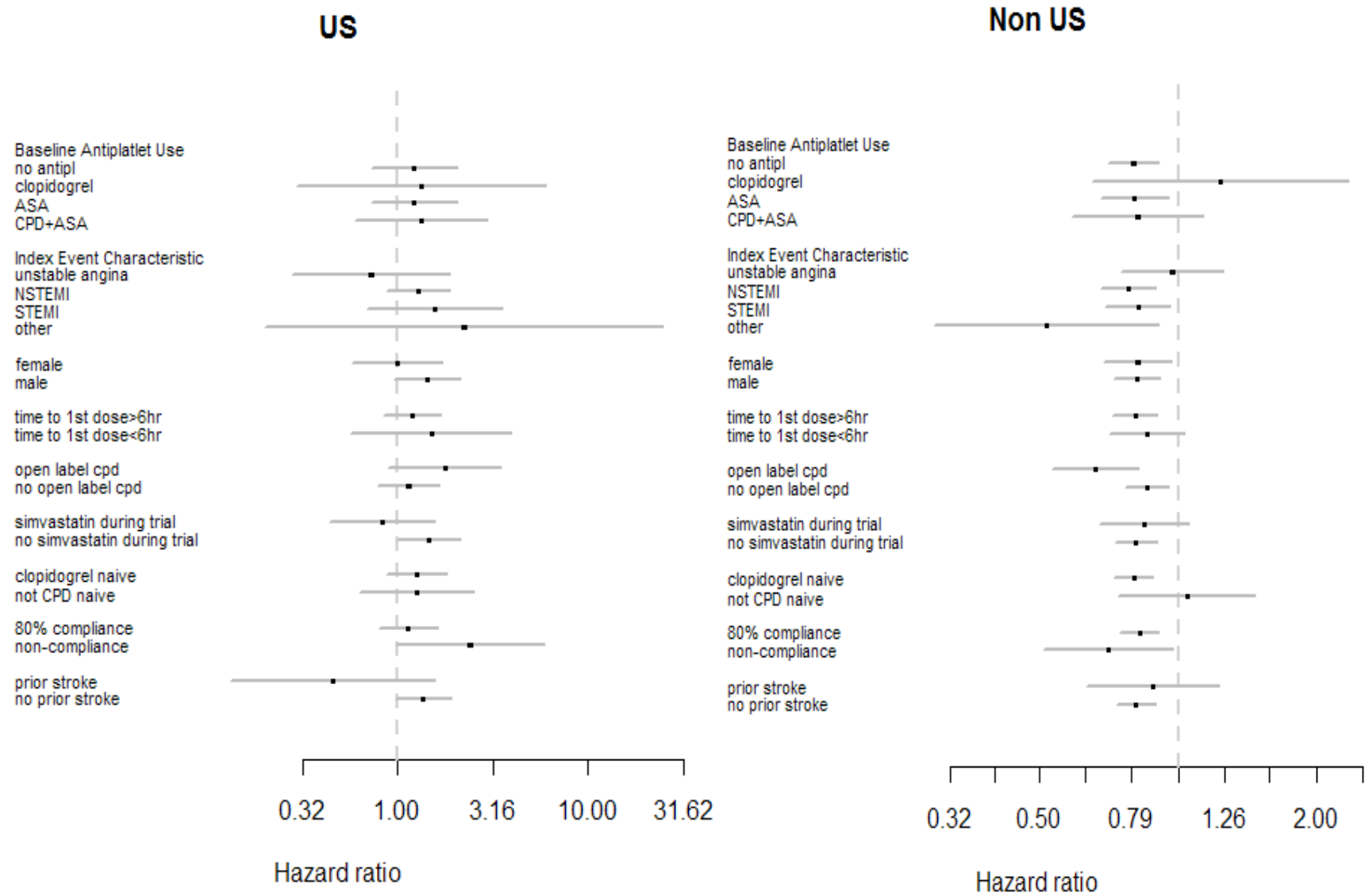


Figure 21 Analysis by various subgroups (3)



The reviewer also performed multivariate analyses based on the non-US population and compute the estimates of covariate coefficients. Due to some missing values, only 14258 subjects were included in the model. The covariates include

1. age
2. use of ARB at randomization
3. use of ASA at randomization
4. use of beta blocker at randomization
5. BMI
6. history of previous CABG
7. use of calcium channel blocker at randomization
8. use of modest CYP3A at randomization
9. history of diabetes
10. use of GPI during index hospitalization
11. use of heparin during index hospitalization
12. history of previous MI
13. race (white versus non-white)
14. use of DES or BMS
15. weight (kg)
16. planned treatment approach at randomization
17. use of CYP3A strong inducer during the study
18. use of CYP3A strong inhibitor during the study
19. PCI received during the study
20. habitual smoker
21. hours between index event to the first dose of study drug
22. statin use during the study
23. total number of bare metal stents inserted
24. total number of drug eluting stents inserted
25. early PCI received during the study
26. use of simvastatin during the study
27. whether took clopidogrel before index event (clopidogrel naïve)
28. use of lipid lowering agents at randomization
29. index event characteristic (NSTEMI, unstable angina, or other)
30. use of antiplatelet at randomization (ASA, clopidogrel or other)
31. days in hospital
32. hours between index event to hospital admission
33. history of previous stroke
34. 80% compliance

The treatment, covariates and covariate\*treatment interactions were included in the model for the non-US population. Then a “hypothetical” estimate of hazard ratio on the US population was calculated based on the covariate coefficient estimates from the non-US model using the average of the corresponding covariates in the US population. If this multivariate model includes some factors contributing to the difference in treatment effect between US and non-US, the “hypothetical” hazard ratio estimate for US would be close to the hazard ratio estimate we



observed in the study for US population. The “hypothetical” hazard ratio estimate comes out to be 0.794. From this prospective, the covariates listed above do not seem to contribute significantly to the regional difference we observed.

#### 3.1.1.8 Conclusions

The big issue in this application is the regional difference observed between US and non-US. The magnitude of the point estimate of hazard ratio in US is quite concerning. The reviewer performed extensive analyses to search for potential explanations.

Although play of chance can never be ruled out as a possible explanation, it seems to be a little overstretched if we observe a hazard ratio estimate of 1.25 in the US with 1413 subjects randomized while the rest of the world shows a clear benefit from ticagrelor (HR=0.84).

The sponsor attributed the concurrent ASA dose to the regional difference if it is not a play of chance. However, their finding remains questionable. First of all, most subjects taking 325 mg high dose ASA were from US. Use of high dose ASA may simply be a confounding variable for the region factor (US versus non-US). Secondly, even though ASA seems to be the best contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the Cox proportional hazards model did not appear robust enough due to the small number of subjects taking high dose ASA in the non-US region. A few more or less events in that subpopulation in the non-US region can make a huge impact on the Cox proportional hazards model and therefore influence the interpretation.

The reviewer was also unsuccessful in finding other potential covariates that may explain the regional difference between US and non-US.

## 3.2 Evaluation of Safety

Please refer to the clinical review for safety evaluation.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Age, Gender and Ethnic group

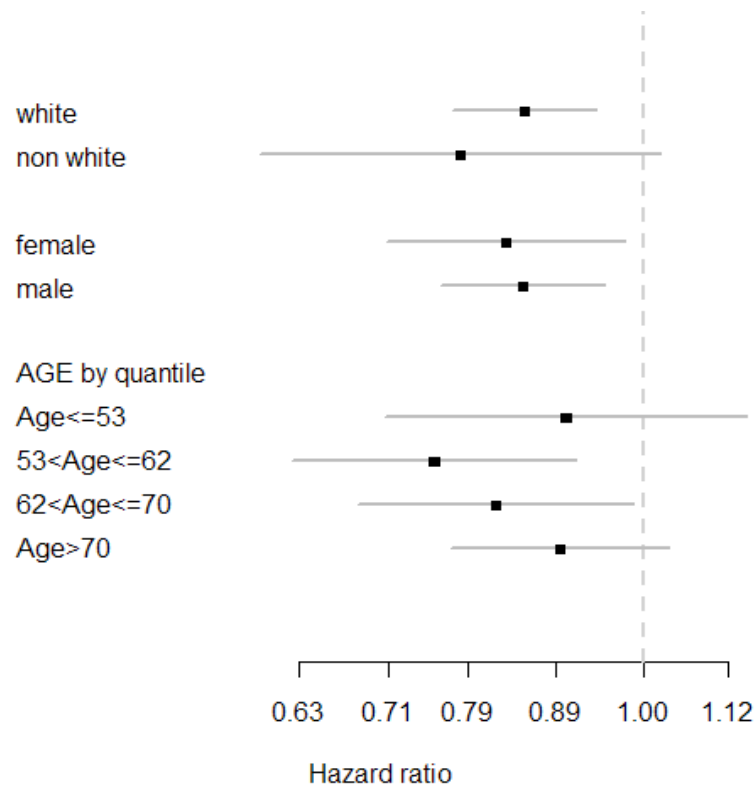
Over 90% subjects enrolled in the study are Caucasian. Gender, age and ethnic group are all well balanced between the two treatment groups (Table 9).

Table 9 Demographic Information on Age, Gender and Ethnic Group

Characteristic	Statistic or category	Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291	Total N=18624
Age (years)	N	9332	9290	18622
	Mean (SD)	62.1 (11.21)	62.3 (11.21)	62.2 (11.21)
Sex	Total	9333	9291	18624
	Male	6678 (71.6%)	6658 (71.7%)	13336 (71.6%)
	Female	2655 (28.4%)	2633 (28.3%)	5288 (28.4%)
Race	Total	9332	9291	18623
	Caucasian	8566 (91.8%)	8511 (91.6%)	17077 (91.7%)
	Black	115 ( 1.2%)	114 ( 1.2%)	229 ( 1.2%)
	Asian	542 ( 5.8%)	554 ( 6.0%)	1096 ( 5.9%)
	Other	109 ( 1.2%)	112 ( 1.2%)	221 ( 1.2%)
	Unknown	1 ( 0.0%)	0	1 ( 0.0%)

Figure 22 shows the hazard ratio estimates by the individual subgroups. Numerically, treatment effect of ticagrelor appears to be consistent across gender, race and age.

Figure 22 Hazard ratio estimates by race, gender and age



## 4.2 Other Subgroup Populations

Please refer to Section 3.1.1.7 for reviewer's analyses on regional difference.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The big issue in this application is the regional difference observed between US and non-US. The magnitude of the point estimate of hazard ratio in US is quite concerning. The reviewer performed extensive analyses to search for potential explanations.

The hazard ratio estimates in US population stayed consistently above 1 throughout the trial. The probability of observing such results were calculated in several ways assuming that the true hazard ratio is 0.84. If taking the sample size as well as the magnitude of difference between the hazard ratio estimates into account, although play of chance can never be excluded from a possible explanation, it does seem to be a little overstretching if we observe a hazard ratio estimate of 1.27 in a country enrolled 1413 subjects while the rest of the world shows a clear benefit from ticagrelor (HR=0.84).

The sponsor attributed the concurrent ASA dose to the regional difference if it is not a play of chance. However, their finding remains questionable. First of all, most subjects taking 325 mg high dose ASA were from US. Use of high dose ASA may simply be a confounding variable for the region factor (US versus non-US). Secondly, even though ASA seems to be the best contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the Cox proportional hazards model did not appear robust enough due to the small number of subjects taking high dose ASA in the non-US region. The Cox proportional hazards model appeared quite sensitive to the high ASA subjects in non-US region. The model also seemed to be sensitive to whether or not the first day ASA loading dose is included.

The reviewer was also unsuccessful in finding other potential covariates that may explain the regional difference between US and non-US. On the other hand, US population differed from non-US population in a number of ways even though they did seem to explain the regional difference. For example, it took much longer time on average for US subjects to receive first dose of study drug since occurrence of index. More US subjects enrolled in the trial were NSTEMI patients compared to the rest of the world. Other factors include prior history of PCI or MI, number of subjects who went through early PCI, pre-index event antiplatelet therapy, beta blocker usage at randomization, planned treatment approach at randomization, GPI during index hospitalization, and many more.

## 5.2 Conclusions and Recommendations

The single phase III trial PLATO randomized 18,624 subjects to compare the efficacy and safety of ticagrelor 90 mg with clopidogrel 75 mg in the prevention of CV death, MI, and stroke in patients with non-ST or ST elevation ACS. One major issue is the regional difference observed between US and non-US. The study reported a hazard ratio estimate of 0.84 [95% CI (0.77, 0.92)] for the overall population favoring ticagrelor. However, for US the hazard ratio estimate was 1.27 [95% CI (0.92, 1.75)], which suggested a 27% greater risk of the clinical event with ticagrelor relative to clopidogrel. The magnitude of this point estimate of hazard ratio in US is quite concerning, especially since US had the second largest enrollment among 43 countries in this trial. The reviewer performed extensive analyses examining many factors or covariates but was not able to find a definitive explanation for the regional difference. However, the US population appeared different from the rest of the world in a number of ways based on the reviewer's analyses even though they did not seem to explain the regional difference. If US population differs sufficiently from the rest of the world, a US trial may be needed to further evaluate the efficacy of ticagrelor in US subjects.

Although play of chance can never be ruled out as a possible explanation, it seems to be a little overstretched, given the magnitude of the difference in hazard ratio estimates between US and non-US. The sponsor attributed the concurrent aspirin (ASA) use to the regional difference if it is not a play of chance. However, even though ASA seems to be the biggest contributing factor out of over 30 factors which the reviewer and the sponsor have been looking into, the explanatory model used by the sponsor for explaining the regional difference does not appear robust since

very few subjects outside US took high dose ASA. Thus, the interpretability of the results that the ASA dose may explain the regional difference remains very much uncertain.

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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06/29/2010

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06/29/2010