



Advisory Committee Briefing Document

Drug Substance Ticagrelor

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Ticagrelor

NDA 22-433

**Briefing Document for Cardiovascular and Renal Drugs Advisory
Committee Meeting**

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EXECUTIVE SUMMARY

Proposed indication

AstraZeneca is seeking approval for a New Drug Application (NDA 22-433) for the use of BRILINTA[™] (ticagrelor) as indicated:

To reduce the rate of thrombotic events (including stent thrombosis) for patients with Acute Coronary Syndromes (ACS) (unstable angina [UA], non-ST segment elevation myocardial infarction [NSTEMI] or ST segment elevation myocardial infarction [STEMI]) who are to be managed medically or are to be managed invasively with percutaneous coronary intervention (PCI [with or without stent]) and/or coronary artery bypass graft (CABG) surgery.

Ticagrelor as compared to clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular (CV) death, myocardial infarction (MI), or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes. Ticagrelor as compared to clopidogrel has also been shown separately to reduce the rate of CV death and MI.

Target disease and patient population

Cardiovascular disease constitutes the single, largest cause of death in the developed world, far outpacing cancer ([World Health Organization 2009](#)). In 2006, the latest year with available statistics ([AHA Statistics 2010](#)), it led to over 1.3 million hospitalizations ([Lloyd-Jones et al 2009](#)). By current estimates, 785000 Americans will have a new ACS event this year, 470000 a recurrent ACS event, and 195000 a silent event ([AHA Statistics 2010](#)).

Clopidogrel, combined with acetylsalicylic acid (ASA), decreases recurrent ACS events. Current US Guidelines ([Antman et al 2008](#)) cite Class Ia evidence provided by the CURE ([Yusuf et al 2001](#)) and COMMIT ([Chen et al 2005](#)) trials, leading to widespread acceptance in clinical use. Clopidogrel, combined with ASA, has become the standard of care for treating ACS patients. Despite this advance, within a year, about 1 in 9 ACS patients has a recurrent ACS event, including death ([Yusuf et al 2001](#)). Within 6 months of an ACS event, 1 in 3 patients will die, have another MI, or require re-hospitalization ([Collinson et al 2000](#), [Turpie 2006](#)).

The reasons behind this substantial residual disease burden are many but are due in part to some important limitations of clopidogrel. Most notable is that clopidogrel is a prodrug. A combination of factors related to absorption and metabolic activation to the active drug, results in highly variable antiplatelet efficacy, which is thought to increase the risk of recurrent events ([Gurbel et al 2003](#), [Mobley et al 2004](#)).

The newest approved thienopyridine, prasugrel, provides better clinical efficacy than clopidogrel predominantly due to reduction in MI, but at the cost of an increase in major bleeding, including life-threatening bleeding ([Effient Prescribing Information 2009](#)). Therefore, an important therapeutic gap remains for an antiplatelet therapy that provides

greater and more consistent efficacy over clopidogrel, but without an increased risk of life-threatening bleeding.

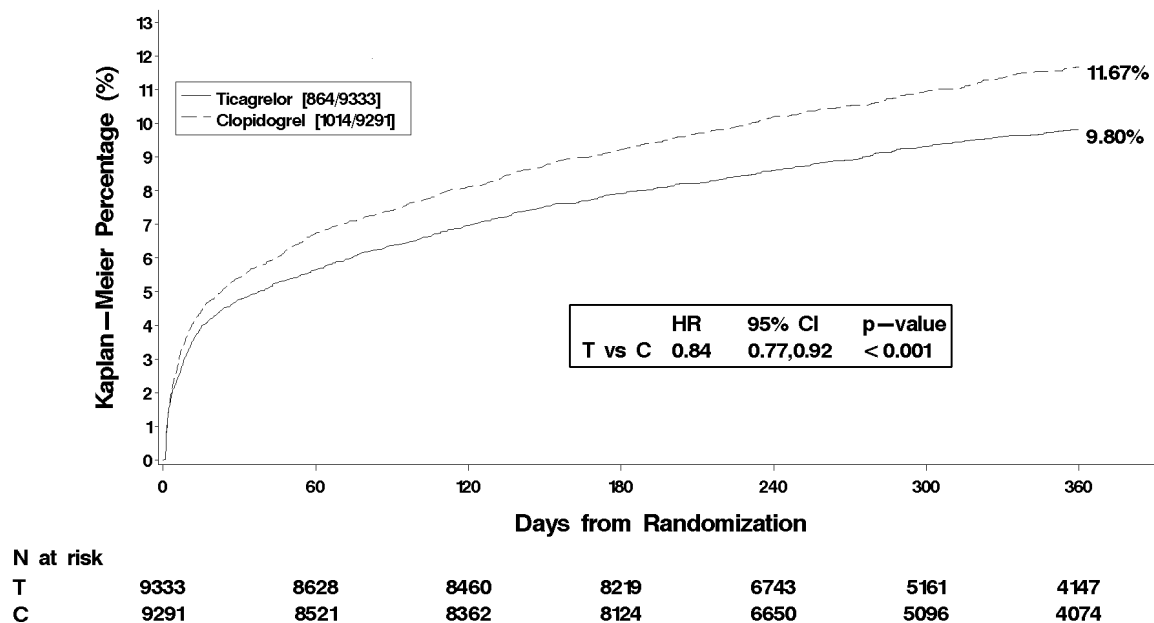
Ticagrelor is the first of a new chemical class of antiplatelet agents called cyclopentyltriazolopyrimidines and has properties that distinguish it from the thienopyridines (ticlopidine, clopidogrel and prasugrel). Ticagrelor is rapidly absorbed following oral administration, does not require metabolic activation, and binds reversibly to the P2Y₁₂ platelet adenosine diphosphate (ADP) receptor. It has a rapid onset of effect, which is important during the early hospitalization period of ACS. Ticagrelor also produces a higher and more consistent inhibition of platelet aggregation than clopidogrel.

PLATO efficacy results

Clinical evidence for the efficacy and safety of ticagrelor derives from the Phase III study, PLATO (A study of PLAtelet Inhibition and Patient Outcomes). This was a double-blind, parallel-group study in which 18624 patients with ACS (including UA, NSTEMI, and STEMI, if PCI was planned) were randomized within 24 hours of the onset of symptoms to ticagrelor or clopidogrel, each given in addition to aspirin and other standard therapy, for up to 12 months. PLATO initiated antiplatelet therapy early, before the decision on whether to manage invasively or medically was implemented. This approach is in line with current treatment guidelines ([Anderson et al 2007](#), [Antman et al 2008](#)) and allows for broad application of the results to ACS treatment paths.

The primary efficacy endpoint of PLATO was a composite of time to first event of CV death, MI, or stroke. Ticagrelor was shown to be superior to clopidogrel in reducing the rate of the primary efficacy endpoint (relative risk reduction [RRR] 16%, absolute risk reduction [ARR] 1.9%, hazard ratio [HR] 0.84 [95% Confidence Interval (CI) 0.77, 0.92]; p=0.0003) ([Figure 1](#)).

Figure 1 **Kaplan-Meier plot of primary clinical endpoint events - estimate of the risk to the first occurrence of any event in the composite efficacy endpoint – PLATO full analysis set**



C Clopidogrel; CI Confidence interval; HR Hazard ratio; T Ticagrelor.

When the components of the primary endpoint were examined individually, efficacy was demonstrated for CV death and MI, but not for stroke. The reduction in CV death favoring ticagrelor over clopidogrel in PLATO, an active-control trial, is notable both for its clinical importance and its rarity as a trial result. Outside of the reductions in CV mortality that were seen with aspirin over placebo following ACS ([ISIS-2 Collaborative group 1988](#)), and with clopidogrel over placebo following an ST segment elevation myocardial infarction ([Chen et al 2005](#)), no other contemporary trials in ACS patients have shown significant reductions in CV mortality with the use of antiplatelet agents, especially thienopyridines or glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors.

Analyses of secondary efficacy endpoints confirmed superiority of ticagrelor over clopidogrel in the subgroup of ACS patients who received invasive management, in sensitivity analyses which substituted CV death with total mortality in the primary efficacy endpoint, and when the primary composite endpoint included additional vascular events. Total mortality was the last endpoint to be analyzed in the predefined hierarchy, and while nominally positive for ticagrelor, formal statistical testing ceased when significance was not reached for stroke. The data demonstrate that the treatment effect of ticagrelor is established early and maintained over 12 months treatment. For patients receiving intracoronary stenting during the study, ticagrelor demonstrated an advantage over clopidogrel for definite stent thrombosis. A similar numerical benefit for ticagrelor was observed for all subcategories of stent thrombosis (type or

category [[Cutlip et al 2007](#)]) and in patients with a history of PCI receiving any stent during the study.

The efficacy of ticagrelor was consistent in nearly all of the prespecified subgroup analyses with a notable exception of a regional interaction driven by results in the US. Although the US observation may be a chance finding, the implications of this observation may be important. Further analyses of the data suggest that the observation may be due to differences in the level of ASA maintenance dose between regions with the efficacy of ticagrelor highest when co-administered with low maintenance doses of ASA. The majority of patients in PLATO received low maintenance doses of ASA, as recommended in the protocol. The overall PLATO trial result is the best estimate of the true treatment effect, providing clear evidence of a reduction in the combined endpoint of CV death, MI or stroke with ticagrelor compared to clopidogrel. The analyses by region and ASA dose provide guidance for the appropriate usage of ticagrelor in combination with ASA. Although these insights come from post-hoc analyses, these data show a lower event rate for ticagrelor compared to clopidogrel for all patients, both in the US and non-US, when taken with low ASA maintenance doses. This forms the basis for recommending usage of ticagrelor with low dose ASA in ACS patients.

Safety results from PLATO

Despite the clear benefits of antiplatelet and antithrombotic agents in the treatment of CAD, bleeding remains an important safety risk associated with their use.

The 'Total Major' bleeding events on ticagrelor did not differ significantly from that of clopidogrel treatment (Kaplan-Meier [KM] estimate of % events 11.6% vs 11.2%, HR 1.04, [95% CI 0.95, 1.13]; $p=0.4336$) (see Section 9.1.1). In addition, ticagrelor and clopidogrel did not differ significantly in fatal bleeding, or fatal/life-threatening bleeding. Significantly more non-CABG bleeding, including non-procedural bleeding, was reported with ticagrelor treatment. Subgroup analyses do not identify particular patient factors that consistently predict more total bleeding, non-CABG bleeding or, more broadly, non-procedural bleeding with ticagrelor, including low body weight, advanced age, or sex.

There were numerically more intracranial hemorrhages (ICH) among ticagrelor-treated patients compared to clopidogrel-treated patients, and more of these events were fatal in the ticagrelor-treated group. However, there was an excess of fatal extracranial bleeding events in clopidogrel-treated patients.

Overall, there was an increase in the percentage of ticagrelor-treated patients who reported adverse events (AEs), mostly mild to moderate, compared to clopidogrel-treated patients. Dyspnea was reported more commonly by patients taking ticagrelor than clopidogrel; it was usually rated as mild to moderate in intensity. Discontinuations occurred in more patients taking ticagrelor compared to patients taking clopidogrel due to dyspnea and epistaxis. The other most common AEs reported during ticagrelor treatment were headache, dizziness, gastrointestinal (GI) disturbances, and bleeding events.

Other safety considerations observed in patients given ticagrelor include increases in serum creatinine, in ventricular pauses in the acute phase (largely asymptomatic), and in serum uric acid concentrations (see Sections 9.3.2, 9.3.3, and 9.3.4, respectively).

Net benefit of ticagrelor compared with clopidogrel

The net benefit of ticagrelor compared to clopidogrel, the current standard of care, is favorable in a broad patient population with ACS. Results from PLATO demonstrate that ticagrelor provides a clinically significant reduction in major CV events, including CV death, for at least 12 months. In addition, the observed safety and tolerability profile of ticagrelor does not substantially add to the background morbidity of ACS or pose a safety concern considerably different from that of clopidogrel.

The net clinical benefit of ticagrelor is supported by the prespecified exploratory analysis using the PLATO full analysis set which utilized time to first occurrence of any event from the composite of CV death, MI, stroke, and a major bleeding event, excluding non-life-threatening bleeding occurring in the setting of CABG surgery. No adjustment or weighting was applied to differentiate fatal from nonfatal events, ie, a CV death influenced the result to the same extent as a nonfatal, major bleeding event. This efficacy and safety composite demonstrated statistically significant superiority of ticagrelor as compared to clopidogrel for at least 12 months after index ACS events (15.7% vs 17.0%; HR 0.92 [95% CI 0.86, 0.99; p-value=0.0257).

In terms of therapeutic considerations, treating 1000 patients with ticagrelor instead of clopidogrel for a year results in: 14 fewer deaths, 11 fewer MIs, and 6 to 8 fewer cases of stent thrombosis. Those 1000 patients would be expected to experience no increase in overall 'Fatal/Life-threatening' bleeding, but 6 additional 'Major' non-CABG bleeding events and 9 discontinuations due to dyspnea. Overall, the treatment of 54 patients with ticagrelor instead of clopidogrel for a year will prevent 1 major CV event (MI, CV death, or stroke).

Conclusion

The PLATO study demonstrated that ticagrelor is superior to clopidogrel in reducing the rate of the primary efficacy endpoint of CV death, MI, or stroke in patients with ACS without an increase in 'Total Major' bleeding events. An increase in non-procedural bleeding in both the 'Major' and less severe categories was observed. Another important safety consideration included dyspnea, which was reported more frequently by ticagrelor patients leading to more discontinuations among those patients.

The overall benefit to ACS patients treated with ticagrelor is driven by a reduction in both CV mortality and MI, distinguishing PLATO from other trials in ACS that show benefit in preventing recurrent MI. When efficacy and safety were analyzed together, ticagrelor provided a net clinical benefit over clopidogrel. Therefore, AstraZeneca is seeking approval of ticagrelor to reduce the rate of fatal and nonfatal CV events for patients with ACS.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Briefing Document:

Abbreviation or special term	Explanation
ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndromes
ADP	Adenosine diphosphate
AE	Adverse event
AHA	American Heart Association
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
AR-C124910XX	Active metabolite of ticagrelor
ARR	Absolute risk reduction/12 months post ACS event
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AV	Atrioventricular
bid	Twice daily
BB	Beta blocker
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events
CCB	Calcium channel blocker
cECG	Continuous electrocardiogram
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance
CHF	Congestive heart failure
CI	Confidence interval
C _{max}	Peak plasma concentration
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial

Abbreviation or special term	Explanation
COPD	Chronic obstructive pulmonary disease
CRUSADE	Can Rapid Risk stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA guidelines
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events trial
CV	Cardiovascular
CYP	Cytochrome P ₄₅₀
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
D _L CO	Single breath diffusing capacity for lungs using carbon monoxide
DSMB	Data and Safety Monitoring Board
EC ₅₀	Concentration at which 50% of maximum effect is reached
eCRF	Electronic case report form
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
E _{max}	Maximum effect of inhibition
FDA	Food and Drug Administration (US Department of Health and Human Sciences)
FEF ₂₅₋₇₅	Mean forced expiratory flow 25% and 75% of the FVC
FEV ₁	Forced expiratory volume in 1 second
FPI	Full prescribing information
FVC	Forced vital capacity
GI	Gastrointestinal
GPIIb/IIIa	Glycoprotein IIb/IIIa
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial
HLGT	High-level group term
Holter monitoring	3-lead digital continuous ECG [cECG] recording
HR	Hazard ratio
IC ₅₀	Concentration at which 50% of inhibitory effect is reached
ICAC	Independent Central Adjudication Committee
ICH	Intracranial hemorrhage
IPA	Inhibition of platelet aggregation

Abbreviation or special term	Explanation
ITT	Intention-to-treat
KM	Kaplan-Meier
LFT	Liver function test
LMWH	Low molecular weight heparin
MDR1	Multi-drug resistance gene, also known as ABCB1; codes for P-glycoprotein enzyme
MDRD	Modification of Diet in Renal Disease
MedDRA [™]	Medical Dictionary for Regulatory Activities
mg	milligrams
MI	Myocardial infarction
NA	North America
NDA	New drug application
NNT	Number needed to treat
Non-responder	Patient with IPA <10% 2 hours after administration of single dose of 300 mg clopidogrel (definition used for RESPOND study)
Non-ST segment elevation	ACS that lacks ST segment elevation (comprised of NSTEMI and Unstable Angina)
NSTEMI	Non-ST segment elevation myocardial infarction
NSAID	Non-steroidal anti-inflammatory drug
NT pro-BNP	N-terminal pro-brain natriuretic peptide
P2Y ₁₂	A subtype of adenosine diphosphate receptor found on platelets
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PFT	Pulmonary function test
PGI ₂	Prostacyclin
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PLATO	Phase III - A study of <u>PLA</u> Telet inhibition and Patient <u>O</u> utcomes
PPI	Proton pump inhibitor
PT	Preferred term
qd	Once daily
REMS	Risk Evaluation and Mitigation Strategy
Responder	Patient with IPA ≥10% 2 hours after administration of single dose of

Abbreviation or special term	Explanation
	300 mg clopidogrel (definition used for RESPOND study)
RMP	Risk Management Plan
RRR	Relative risk reduction
RV	Residual volume
SA	Sinoatrial
SAE	Serious adverse event
SD	Standard deviation
SpO ₂	Blood oxygen saturation measured by pulse oximetry
SMQ	Standardized MedDRA queries
SOC	System organ class
STEMI	ST segment elevation myocardial infarction
ST segment	The part of the ECG trace between the end of the QRS complex and the start of the T wave of a heart beat
t _{1/2}	Apparent terminal half-life
TAM	Ticagrelor active metabolite
TIA	Transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
TLC	Total lung capacity
t _{max}	Time to reach peak or maximum concentration following drug administration
TRITON	TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition
TXA ₂	Thromboxane
UA	Unstable angina
ULN	Upper limit of normal
Ventricular pause (Holter-detected)	An ECG finding showing the absence of ventricular electrical activity (QRS complex) for ≥3 seconds as a result of sinus node dysfunction (SA node pause), atrial fibrillation with slow ventricular response, or sinus or other supraventricular rhythm with high degree A-V block (AV node pause) or other mechanism (other pause) (TIMI definition).

1. INTRODUCTION

AstraZeneca has submitted a New Drug Application (NDA 22-433) for the use of ticagrelor to reduce the rate of thrombotic events (including stent thrombosis) for patients with Acute Coronary Syndromes (ACS) (unstable angina [UA], non-ST segment elevation myocardial infarction [NSTEMI] or ST segment elevation myocardial infarction [STEMI]) who are to be managed medically or are to be managed invasively with percutaneous coronary intervention (PCI [with or without stent]) and/or coronary artery bypass graft (CABG) surgery. The Division of Cardiovascular and Renal Products of the US Food and Drug Administration (FDA) has scheduled an Advisory Committee meeting for 28 July 2010 as part of its ongoing review.

This briefing document summarizes key aspects of the ticagrelor development program and NDA, including:

- Limitations of current antiplatelet therapy in ACS
- Pharmacokinetic (PK) and pharmacodynamic (PD) properties of ticagrelor, the first of a new chemical class of antiplatelet agents
- Efficacy data from the Phase III study, PLATO (A study of PLAtelet Inhibition and Patient Outcomes), including exploratory analyses of treatment-by-region interactions in PLATO and impact of acetylsalicylic acid (ASA) maintenance dosing
- Safety data from PLATO, including topics extensively evaluated in the ticagrelor development program
- Risk management and the Risk Evaluation and Mitigation Strategy
- Overall risk/benefit profile of ticagrelor.

1.1 Pharmacologic class and mode of action

The first of a new chemical class of antiplatelet agents called cyclopentyltriazolopyrimidines, ticagrelor has properties that distinguish it from the thienopyridines. Ticagrelor, formerly AZD6140, substantially reduces platelet aggregation, blocking the pathophysiologic process leading to intracoronary thrombosis in ACS. Ticagrelor possesses the following properties:

- Is rapidly absorbed following oral administration
- Does not require metabolic activation
- Binds reversibly to the P2Y₁₂ platelet adenosine diphosphate (ADP) receptor

- Has a rapid onset of effect, important in the acute setting, a period of high risk for the ACS patient
- Achieves both a higher and more consistent inhibition of platelet aggregation (IPA) than clopidogrel.

Ticagrelor is metabolized mainly via cytochrome P₄₅₀ (CYP) 3A4/5, leading to the generation of an active metabolite (AR-C124910XX), the inactive metabolite AR-C124913XX and other minor metabolites. The active metabolite is at least as potent as ticagrelor at blocking the P2Y₁₂ receptor *in vitro*.

Ticagrelor's reversible binding to the P2Y₁₂ receptor enables the return of platelet aggregation upon cessation of therapy, without requiring the generation of new platelets or platelet transfusions. Ticagrelor is eliminated mainly via metabolism and excretion through bile.

1.2 Proposed indication and dose

Ticagrelor is indicated to reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina [UA], non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be managed medically or are to be managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG. Ticagrelor as compared to clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular (CV) death, myocardial infarction (MI), or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes. Ticagrelor as compared to clopidogrel has also been shown separately to reduce the rate of CV death and MI.

Ticagrelor treatment should be initiated with a single 180 mg loading dose (2 tablets of 90 mg) and then continued at 90 mg twice daily (bid). Patients taking ticagrelor should take low maintenance doses of ASA daily unless specifically contraindicated.

1.3 Overview of the ticagrelor clinical development program

The clinical development program focused on:

- Characterizing the PK and PD properties of ticagrelor
- Determining whether ticagrelor plus ASA is superior to clopidogrel plus ASA in the reduction of thrombotic events in patients with ACS
- Quantifying the bleeding risks that accompany ticagrelor's antiplatelet effect
- Establishing the overall safety profile of ticagrelor to assess benefit and risk, thereby defining an appropriate risk management plan.

This briefing document is based largely on the PLATO trial. The PLATO study design encompassed clinically relevant aspects of ACS and its current, guideline-recommended treatment, ie:

- Enrollment included patients across the entire spectrum of ACS: UA, STEMI, and NSTEMI. PLATO provided for all ACS treatment strategies, including PCI, CABG surgery, and medical management.
- Dual antiplatelet treatment began within 24 hours of the index event to help protect patients early during the initial high risk period. Investigators had discretion to provide an additional loading dose of the comparator, clopidogrel, as practiced in some regions depending on treatment strategy.
- Patients receiving chronic clopidogrel therapy could enroll, as could patients given open-label clopidogrel upon admission to hospital prior to randomization.
- Investigators were advised to use the currently recommended 75 mg to 100 mg ASA dose as maintenance treatment although they were allowed to provide up to 325 mg ASA for up to 6 months, as recommended by guidelines in the United States (US) after stent placement ([King et al 2008](#), [Antman et al 2008](#)).

This application consists of an additional 41 Phase I placebo-controlled or active-comparator (clopidogrel) controlled studies and 4 Phase II studies (Section 4; [Table 1](#)). The Phase II program provided important design information and evidence supporting the dosing regimen taken forward. The Phase II program also achieved its goals of identifying several potential safety concerns associated with ticagrelor administration, among them dyspnea, ventricular pauses, and increases in serum uric acid, which were explored in depth in the pivotal study.

2. RATIONALE FOR PRODUCT DEVELOPMENT

2.1 Current standard of care in acute coronary syndromes

Cardiovascular disease constitutes the single, largest cause of death in the developed and developing world, far outpacing the mortality rates for cancer ([World Health Organization 2009](#)). Cardiovascular disease is also responsible for considerable morbidity, including hospitalizations. Despite the widespread adoption of intensive monitoring and prompt treatment of cardiac electrical instability, thrombolytic therapy, acute invasive interventions, and dual antiplatelet therapy with ASA and thienopyridines, approximately 1 in 3 ACS patients dies, has a repeat MI, or requires re-hospitalization within 6 months ([Collinson et al 2000](#), [Turpie 2006](#)).

In 2006, the incidence of ACS in the US was 45 cases per 10000 individuals per year, accounting for over 1.3 million unique hospitalizations ([Lloyd-Jones et al 2009](#)). Final mortality data in 2006, indicated that CV disease accounted for the nearly 2.5 million deaths, or 1 of every 2.9 deaths in the US that year ([AHA Statistics 2010](#)). According to 2010 AHA

Heart Disease & Stroke Statistics, it is estimated that 785000 Americans will have a new coronary attack and 470000 will have a recurrent attack, while an additional 195000 silent heart attacks are expected to occur ([AHA Statistics 2010](#)).

Patients presenting with signs and symptoms of ACS receive early antiplatelet treatment with ASA and, in many instances, the platelet ADP-receptor antagonist clopidogrel. Current guidelines include recommendations for initiation of therapy with clopidogrel plus ASA as early as possible for all ACS patients during an event, including prior to angiography ([Anderson et al 2007](#)). Patients whose initial electrocardiogram (ECG) indicates an ST elevation MI usually receive accelerated care, including cardiac catheterization, leading to PCI, CABG surgery, or management with medication alone. For them, time from presentation to re-establishing coronary flow impacts survival ([Antman et al 2008](#)). Those with non-ST segment elevation ACS have the same treatment options; however, interventions are less time-critical. Non-ST elevation ACS patients will less urgently be diagnosed with either a documented MI (NSTEMI), or UA. Whether or not a patient with ACS undergoes coronary angiography, PCI, CABG surgery, or none of these, guidelines worldwide specify dual antiplatelet therapy consisting of ASA and an ADP receptor antagonist for all patients, during and following the index event ([Anderson et al 2007](#), [Antman et al 2008](#), [King et al 2008](#)).

Following the initial ACS event, patients should receive dual antiplatelet therapy for at least 1 month and ideally up to 1 year ([Anderson et al 2007](#), [Antman et al 2008](#)). After drug-eluting stent implantation, therapy should continue for at least 12 months ([Antman et al 2008](#), [King et al 2008](#)).

2.2 Limitations of current antiplatelet therapy in ACS

Clopidogrel demonstrated in the CURE study that it reduced a composite of CV death, MI, and stroke with an increase in major bleeding when compared to placebo in NSTEMI patients ([Yusuf et al 2001](#)). It became the current standard of care in combination with ASA for ACS patients. However, it has limitations. Even with the current standard of care, serious CV events recur in approximately 11% of ACS patients, most within several months of the index ACS event ([Yusuf et al 2001](#), [Wiviott et al 2007](#)). The need remains for antiplatelet therapy that provides greater efficacy over the current practice of dual therapy with clopidogrel and ASA, preferably without increased risk of serious bleeding. Several of clopidogrel's properties underscore the need for a better antiplatelet medicine:

- In recent years there has been consideration of higher loading doses for clopidogrel from 300 mg (4 tablets) to 600 mg (8 tablets). Despite this doubling of the loading dose it can still take 8 hours to reach maximal IPA with the 600 mg dose, which may be of relevance with respect to rapid inhibition of platelets in the acute setting, a period of particularly high risk in ACS.
- Clopidogrel's inhibition of platelets is incomplete. After a 600 mg loading dose, patients responsive to clopidogrel display a mean peak IPA of 50%. At steady state, with chronic administration of 75 mg, clopidogrel-responsive patients have a mean IPA of 60%. Higher IPA is associated with better efficacy ([Wiviott et al 2007](#)).

- Clopidogrel's platelet inhibition is not consistently observed in all patients. Many patients, up to 30%, have a minimal or poor IPA response to clopidogrel plus ASA, manifest as a high interpatient variability in IPA ([Gurbel et al 2003](#), [Jernberg et al 2006](#)). To be effective, the inactive prodrug clopidogrel requires transformation to its active metabolite. Inconsistent effect associates with recurrent major cardiac events ([Matetzky et al 2004](#), [Simon et al 2009](#)).

The newest approved thienopyridine, prasugrel, provides better (>80%) IPA and clinical efficacy than clopidogrel, but at the cost of a marked increase in major bleeding events (including fatal and life-threatening), especially in patients over 75 years old, those with body weight <60 kg, those with a history of transient ischemic attack (TIA) or stroke, and in those undergoing CABG surgery ([Effient Prescribing Information 2009](#)).

Based on the limitations described above, patients could benefit substantially from an antiplatelet agent with both quick onset and offset of action, one active upon absorption without requiring metabolic activation, with effects more consistent from patient to patient, and that achieves better IPA than clopidogrel without an increased risk of bleeding. This was the overall rationale for developing ticagrelor and the central goal of the development program.

3. OVERVIEW OF NON-CLINICAL DEVELOPMENT

The pharmacological properties of ticagrelor were investigated relative to its ability to block platelet aggregation both *in vitro* and *in vivo*. Ticagrelor was also examined for interaction with a comprehensive set of enzymes and receptors for potential for activity unrelated to its IPA through the P2Y₁₂ receptor. It was evaluated in a standard battery of safety pharmacology studies in rats and dogs, and in human receptor-expressing hamster cells, to test for unwanted effects on the gastrointestinal (GI), CV, respiratory, renal and central nervous organ systems. A comprehensive non-clinical package has been developed with ticagrelor, in order to understand its pharmacology, safety pharmacology, pharmacokinetics, toxicokinetics, metabolism, distribution, excretion, and safety.

Key findings from the non-clinical development program demonstrate:

- Ticagrelor is a potent, selective, orally active, direct P2Y₁₂ receptor antagonist which produces reversible, concentration (dose)-related inhibition of ADP-induced platelet aggregation.
- Ticagrelor exhibits a reversible mechanism of action distinguishing it from thienopyridine agents, which are prodrugs requiring metabolic activation to form active metabolites that covalently bind to the P2Y₁₂ receptor, inhibiting aggregation for the life-span of the platelet.

- Ticagrelor's major circulating metabolite, AR-C124910XX, shows pharmacological activity comparable to that of the parent molecule. No unique human metabolites have been identified.
- Ticagrelor itself has low activity at adenosine receptors, but inhibits adenosine uptake in red blood cells, inhibits adenosine-induced depolarization in isolated rat and guinea pig vagal nerve fibers through adenosine A₁, A_{2B} or A₃ receptors and enhances adenosine-mediated effects on blood flow in the canine heart.
- There is evidence for subclinical bleeding at high doses in all species tested, as evidenced by increased spleen weights and splenic hematopoiesis, clinical pathology changes including decreases in hemoglobin, red blood cell counts, and/or hematocrit, and increases in reticulocytes and platelets.
- Consistent observations of adverse effects across species in repeat dose toxicity studies occur primarily in the GI tract, but were inconsistent with respect to the location, severity, and type of the observations.
- Ticagrelor and the active metabolite AR-C124910XX do not exhibit any genotoxic potential.
- A 2-year carcinogenicity study with ticagrelor showed increased uterine epithelial tumors only in the high dose (180 mg/kg/day) in female rats, accompanied by a reduced incidence of pituitary hyperplasia/adenoma and mammary tumors. Ticagrelor was not carcinogenic in male rats or mice. This tumor pattern occurs in rats who have sustained reduction in circulating prolactin. Prolactin is leuteotrophic in rats; its suppression leads to extended reproductive viability and prolonged unopposed estrogen exposure. Estrogen stimulates the endometrium, promoting the development of uterine tumors. Suppression of prolactin secretion in rats could arise from reduced body weight gain after prolonged high-dose ticagrelor administration, inhibition of dopamine transporter activity, and/or increased testosterone during estrus. Prolactin has no leuteotrophic effect in humans, rendering this mechanism of action not relevant to women ([Alison et al 1994](#), [Neumann 1991](#), [Ben-Jonathan et al 2008](#), [Freeman et al 2000](#)). In the same non-clinical study in female rats, a mild increase in hepatocellular tumors was noted at this dose level. This non-clinical observation is considered due to a metabolic adaptive response evidenced by increased liver weight, induction of drug metabolizing enzymes and centrilobular hepatocellular hypertrophy, which is unique to rodents with no human correlate. It is accepted that such tumors are rodent specific ([Graham and Lake 2008](#), [Greaves 2007](#)).
- Reproductive toxicity studies show no indication of any reproductive risk to the fetus, neonate, or to adults of childbearing age.

Non-clinical data related to specific safety topics evaluated in the ticagrelor development program are described within Section [9](#).

4. TICAGRELOR CLINICAL DEVELOPMENT PROGRAM

Clinical pharmacology

The clinical pharmacology program, comprised of 41 studies with approximately 1000 volunteers, has characterized well the PK, PD, absorption, distribution, metabolism, excretion, and drug-drug interactions (DDIs) of ticagrelor (Table 1). PD studies included *ex vivo* assessments of platelet activation and aggregation, indices of bleeding risk, and adverse drug effects and their relationships to dose or exposure (see Section 5). Ticagrelor demonstrates a profile appropriate for administration to ACS patients.

Phase II

The Phase II program consisted of 4 studies (Table 1). DISPERSE assessed the PD effects of ticagrelor at doses of 50 mg bid, 100 mg bid, 200 mg bid, and 400 mg once daily (qd) in the presence of ASA compared to clopidogrel 75 mg with ASA in patients with stable coronary artery disease (CAD). DISPERSE2 studied the target dose for Phase III, 90 mg bid, and double that dose, 180 mg bid in patients with NSTEMI-ACS. The 2 Phase II PK/PD studies (ONSET/OFFSET, RESPOND), conducted in stable CAD patients, provide clinical insights into onset, offset, and consistency of response of IPA following ticagrelor administration, as well as the PK/PD response of switching between ticagrelor and clopidogrel (see Section 5). The more than 1400 patients with either atherosclerosis/stable CAD (DISPERSE, ONSET/OFFSET, RESPOND) or NSTEMI-ACS (DISPERSE2) participating in the Phase II program formed a substantial safety database. Therefore, the Phase II program achieved its goals of identifying several potential safety concerns associated with ticagrelor administration, among them dyspnea, ventricular pauses, and increased serum uric acid, so that the pivotal study could explore them in depth (see Section 5). The Phase II program provided evidence supporting the dosing regimen taken forward (see Section 5.3.2).

Phase III: the PLATO study

PLATO constitutes the single, pivotal efficacy and safety Phase III study of the ticagrelor development program (Table 1). The purpose was to confirm the findings obtained from non-clinical, tolerability, dose-finding, and other Phase II studies. This large outcome study (N=18624) compared the efficacy, safety, and tolerability of ticagrelor with the current standard, clopidogrel. Its design incorporated clinically relevant aspects of ACS and its current, guideline-recommended treatment.

Sections 6, 7, and 8 of this document provide additional features, strengths, and limitations of the PLATO study design, conduct, and results.

Table 1 Scope of the clinical development program for ticagrelor

<i>In vitro</i> clinical pharmacology study			1 study
Phase I studies:			
Bioavailability, bioequivalence and food interaction			9 studies
Pharmacokinetics and initial tolerability			5 studies
Pharmacokinetics - intrinsic factors			8 studies
Pharmacokinetics - extrinsic factors (drug/drug interactions)			15 studies
Pharmacodynamics			4 studies
Phase II clinical pharmacology PK/PD studies			
Study name (number)	No. and type of patients randomized	Dose of ticagrelor Comparator Duration of treatment	Condensed objective
ONSET/OFFSET	123 Patients with stable CAD	Ticagrelor: 180 mg loading dose then 90 mg bid + ASA 75 to 100 mg Clopidogrel: 600 mg loading dose then 75 mg qd + ASA 75 to 100 mg 6 weeks	Assessment of onset and offset profiles by IPA of ticagrelor and of clopidogrel.
RESPOND	98 Patients with stable CAD 41 non-responders and 57 responders to clopidogrel	Ticagrelor: 180 mg loading dose then 90 mg bid + ASA 75 to 100 mg Clopidogrel: 600 mg loading dose then 75 mg qd + ASA 75 to 100 mg 2 weeks	Assessment of IPA when switching from ticagrelor to clopidogrel; switching from clopidogrel to ticagrelor; and, giving ticagrelor to clopidogrel non-responders.
Phase II studies providing design information for Phase III			
DISPERSE	201 Patients with documented atherosclerotic disease	Ticagrelor: 50, 100, or 200 mg bid, or 400 mg qd + ASA 75 to 100 mg Clopidogrel: 75 mg qd + ASA 75 to 100 mg 28 days	Pharmacodynamic assessment by IPA after 14 and 28 days of various dosing regimens of ticagrelor plus ASA compared to clopidogrel plus ASA.
DISPERSE2	990 Patients with non-ST segment elevation ACS	Ticagrelor: 270 mg loading dose then 90 or 180 mg bid +ASA 75 to 100 mg Clopidogrel: 300 mg loading dose then 75 mg qd + ASA 75 to 100 mg 4, 8, or 12 weeks	Safety and tolerability assessment by adjudicated bleeding events after 4 weeks of 2 doses of ticagrelor plus ASA compared with clopidogrel plus ASA.

Table 1 Scope of the clinical development program for ticagrelor

Phase III study			
PLATO	18624 patients with ACS Ticagrelor: 9333 Clopidogrel: 9291	Ticagrelor: 180 mg loading dose then 90 mg bid + ASA 75 to 325 mg Clopidogrel: ≤600 mg loading dose then 75 mg qd + ASA 75 to 325 mg 6 to 12 months	To test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events in patients with ACS.

ACS Acute coronary syndromes; ASA acetylsalicylic acid; bid twice daily; CAD coronary artery disease; CV cardiovascular; IPA inhibition of platelet aggregation; MI Myocardial infarction; PK/PD pharmacokinetic/pharmacodynamic; qd once daily;.

Table 2 provides a list of the key publications and presentations resulting from studies conducted within the ticagrelor program to date; a copy of each is provided in Appendix A.

Table 2 List of key publications and presentations from the ticagrelor clinical program to date

Study	Reference
PLATO study design	James S, Akerblom A, Cannon C, Emanuelsson H, Husted S, Katus, H, et al. Comparison of ticagrelor, the first reversible oral P2Y ₁₂ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J 2009;157:599-605.
PLATO overall results	Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held, C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009a;361:1045-57.
PLATO STEMI results (slides)	Steg PG, Becker RC, Cannon CP, et al. Comparison of ticagrelor: the first reversible oral P2Y ₁₂ receptor antagonist with clopidogrel in patients with ST-elevation acute coronary syndromes: results from the PLATelet inhibition and patient Outcomes (PLATO) trial. Late-breaking clinical trial abstract. [Presented at the American Heart Association annual congress, November 14-18, Orlando, FL]
PLATO INVASIVE management results	Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al, for the PLATelet inhibition and patients Outcomes (PLATO) investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomized double-blind study. Lancet. 2010;375:283-93.
PLATO CABG results (slides)	Held C, Bassand J-P, Becker RC, et al. Ticagrelor Versus Clopidogrel In Patients With Acute Coronary Syndromes Undergoing Coronary Artery Bypass Surgery: Results From The PLATO Trial. 2009 [Abstract 3020-11 presented at the American College of Cardiology, March 14-16, Atlanta, GA].

Table 2 **List of key publications and presentations from the ticagrelor clinical program to date**

Study	Reference
ONSET/OFFSET results	Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. <i>Circulation</i> . 2009;120:2577-85
RESPOND results	Gurbel PA, Bliden KP, Butler K, Antonino MJ, Wei C, Teng R, et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. <i>Circulation</i> . 2010;121:1188-99.
DISPERSE2 results	Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, et al. DISPERSE-2 Investigators. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. <i>J Am Coll Cardiol</i> . 2007;50:1844-51.
DISPERSE results	Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y ₁₂ antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. <i>Eur Heart J</i> . 2006;27:1038-47.

5. OVERVIEW OF CLINICAL PHARMACOLOGY PROGRAM

Clinical pharmacology studies conducted in the ticagrelor development program investigated the safety, tolerability, PK, PD, bioavailability, bioequivalence, effect of food and DDIs of ticagrelor, as well as PK and PD characteristics in special patient populations. Some other studies were also performed to examine the time and dose dependency in exposure to ticagrelor in both healthy subjects and special patient populations.

A population PK analysis was also conducted in a subset of patients from the Phase III study PLATO and the Phase II study DISPERSE2. Exposure-response relationships were explored in the PLATO study. The dose ranges for oral administration of ticagrelor in the clinical pharmacology studies were 0.1 to 1260 mg for single doses, 50 to 600 mg for multiple once daily (qd) dosing, and 50 to 300 mg for multiple bid dosing. In the DDI studies, ticagrelor 180 mg or 270 mg was studied with the highest therapeutic doses of co-administered drugs. Generally, plasma concentrations of ticagrelor and AR-C124910XX and the final extent IPA (20 µM ADP) were used for the PK and PD analyses. The proposed therapeutic dose of ticagrelor is a 180 mg loading dose, followed by 90 mg bid maintenance dosing.

5.1 Pharmacokinetics

5.1.1 Absorption, distribution, metabolism, and excretion

- Ticagrelor undergoes rapid absorption with peak plasma concentrations (C_{\max}) attained at a median time (t_{\max}) of approximately 1.5 hours after oral administration. The formation of the major circulating active metabolite AR-C124910XX is rapid (median t_{\max} of approximately 2.5 hours) and is present at approximately 40% of parent concentrations. Ticagrelor can be given with or without food.
- Both ticagrelor and its active metabolite bind extensively (>98%) to plasma proteins; age, sex, severe renal impairment, and mild hepatic impairment do not affect the plasma protein binding.
- Both the area under the concentration-time curve (AUC) and C_{\max} of both ticagrelor and its active metabolite show approximately proportional increases with increasing oral doses, indicating linear pharmacokinetics.
- The mean terminal half-life ($t_{1/2}$) of ticagrelor is 7.2 hours and 8.5 hours for the active metabolite. Elimination of ticagrelor is mainly via hepatic metabolism, and the primary route of elimination of the active metabolite is likely through biliary excretion. Neither depends on renal elimination, with <1% recovery in urine for parent and active metabolite.

5.1.2 Drug interactions

In vitro studies indicate that ticagrelor and AR-C124910XX are substrates and/or weak inhibitors of CYP3A isoenzymes; are potential activators of CYP3A4 mediated metabolism; and are also substrates and inhibitors of the P-glycoprotein (P-gp) transporter (MDR1). *In vitro*, ticagrelor and/or AR-C124910XX were shown to moderately inhibit CYP2C9 activities. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. The *in vivo* DDI studies for ticagrelor were planned to assess the effect of CYP3A inhibition and induction on ticagrelor, as well as the effect of ticagrelor on CYP3A substrate drugs. The results of these studies are presented in [Table 3](#) and [Table 4](#).

Table 3 Effect of co-administration of inhibitors and inducer on ticagrelor exposure

Co-administered drug (dosing regimen)	Ticagrelor Dose (mg)	Ticagrelor		AR-C124910XX	
		Change in AUC	Change in C _{max}	Change in AUC	Change in C _{max}
Ketoconazole CYP3A inhibitor (200 mg bid for 10 days)	90 mg single dose	↑ 632%	↑ 135%	↓ 56%	↓ 89%
Diltiazem CYP3A inhibitor (240 mg qd for 14 days)	90 mg single dose	↑ 174%	↑ 69%	↓ 13%	↓ 38%
Rifampin CYP3A inducer (600 mg qd for 14 days)	180 mg single dose	↓ 86%	↓ 73%	↓ 46%	No change

AUC Area under the concentration-time curve; bid Twice daily; C_{max} Peak plasma concentration; CYP Cytochrome P₄₅₀; qd Once daily.

Table 4 Effect of ticagrelor on the exposure to other drugs

Ticagrelor dosing regimen	Name and dose of co- administered drug	Change in AUC	Change in C _{max}
270 mg loading dose and 180 mg bid	Simvastatin CYP3A substrate (80 mg single dose)	↑ 56%	↑ 81%
270 mg loading dose and 90 mg bid for 7 days	Atorvastatin CYP3A substrate (80 mg single dose)	↑ 36%	↑ 23%
90 mg bid for 28 days	Oral contraceptive CYP3A substrate (ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg)	↑ 20% for ethinyl estradiol No change for levonorgestrel	↑ 31% for ethinyl estradiol No change for levonorgestrel
400 mg qd for 16 days	Digoxin P-gp substrate (0.25 mg for 7 days)	↑ 28%	↑ 75%
180 mg bid for 9 days	Tolbutamide CYP2C9 substrate (500 mg single dose)	No change	No change
50 mg bid or 200 mg bid for 5 days	ASA (75 to 300 mg qd)	No change in ticagrelor AUC	No change in ticagrelor C _{max}

ASA Acetylsalicylic acid; AUC Area under the concentration-time curve; bid Twice daily; C_{max} Peak plasma concentration; CYP Cytochrome P₄₅₀; qd Once daily; P-gp glycoprotein.

Ticagrelor affects exposure to drugs that are CYP3A and P-glycoprotein substrates. Simvastatin exposure was modestly (60%) increased with ticagrelor co-administration, with some individual increases up to 2- to 3- fold. Therefore, co-administration of ticagrelor with simvastatin doses greater than 40 mg could potentially exceed exposures with 80 mg of simvastatin, which is the highest approved dose. Ticagrelor may have similar effects on lovastatin. This increase in exposure should be considered when making treatment decisions for patients requiring both ticagrelor and doses of simvastatin exceeding 40 mg or high doses of lovastatin. Ticagrelor increased atorvastatin exposure modestly (30%) however no dose adjustment is needed for atorvastatin. Modest increases (20%) in ethinyl estradiol exposure by ticagrelor are not expected to impact oral contraceptive efficacy.

Ticagrelor increases digoxin exposure by approximately 30%. As digoxin is a narrow therapeutic index drug, monitoring of digoxin levels should be considered with initiation or change in ticagrelor therapy.

The magnitude of changes in ticagrelor exposure observed when ticagrelor is administered with a strong CYP3A4 inhibitor, such as ketoconazole, warrant a warning that they not be co-administered. More modest changes are seen with a moderate CYP3A4 inhibitor, and a 90 mg bid ticagrelor dose with moderate CYP3A4 inhibitors was observed to be well tolerated in PLATO. Co-administration of ticagrelor with a potent CYP3A4 inducer such as rifampin results in significant reductions in exposure to ticagrelor; therefore, a caution is indicated as co-administration of ticagrelor with CYP3A inducers may result in reduced efficacy. However, an efficacy benefit appears to be present in patients who received CYP3A inducers with ticagrelor treatment in PLATO (13% of patients).

In Phase II and III clinical studies, ticagrelor was commonly administered with ASA, heparin, low molecular weight heparin (LMWH), intravenous glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, protein pump inhibitors, statins, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB) for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions.

5.2 Pharmacodynamics

The ticagrelor development program used final extent of IPA to 20 μ M ADP via light transmission aggregometry as a biomarker for antiplatelet activity, and a sigmoid maximum effect of inhibition (E_{\max}) model to describe the relationship of IPA to plasma concentrations of ticagrelor and/or its active metabolite. IPA increases with increasing ticagrelor plasma concentrations, and then decreases as ticagrelor plasma concentrations decrease, indicative of reversible P2Y₁₂ receptor binding. The concentration-response profile to achieve high levels of IPA is similar between different types of patients with atherosclerotic disease, as well as in healthy subjects. There is generally less inter-individual variability of IPA response with ticagrelor compared to clopidogrel.

Additional DDI studies were conducted with ticagrelor and drugs which may affect platelet aggregation where a PK interaction was not expected. These studies showed that co-administration of ticagrelor with heparin or enoxaparin did not have any effect on ticagrelor or the active metabolite plasma levels. Co-administration of ticagrelor and heparin had no effect on activated partial thromboplastin time and activated coagulation time assays. Co-administration of ticagrelor and enoxaparin had no effect on factor Xa assay. Co-administration of a 300 mg once daily dose of ASA with either 50 mg bid or 200 mg bid of ticagrelor did not alter the pharmacokinetics of ticagrelor or the platelet aggregation effect of ticagrelor compared to ticagrelor given alone.

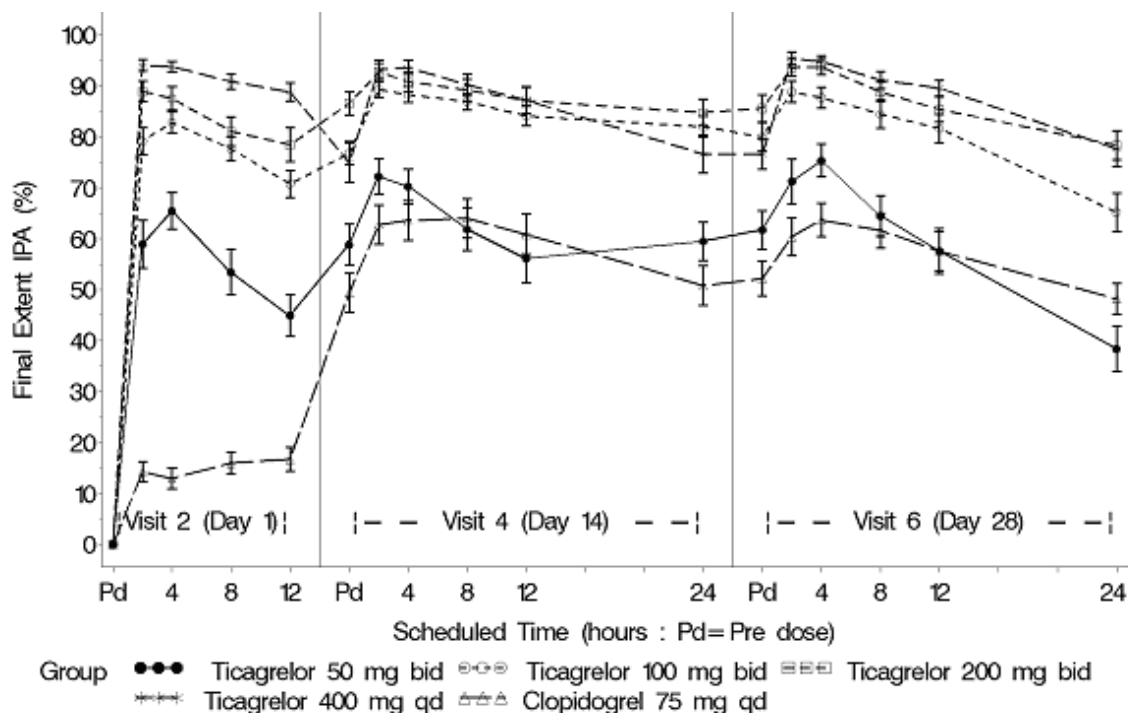
5.3 Phase II studies providing design information for Phase III

5.3.1 Inhibition of platelet aggregation: DISPERSE study

DISPERSE and DISPERSE2 confirmed that ticagrelor can achieve greater and more consistent IPA as compared to standard doses of clopidogrel in both stable CAD and ACS patients. DISPERSE was a study designed to assess the PD effects of ticagrelor at doses of 50 mg bid, 100 mg bid, 200 mg bid, and 400 mg qd in the presence of ASA compared to clopidogrel 75 mg with ASA in patients with stable CAD.

DISPERSE demonstrated that 100 mg bid or 200 mg bid of ticagrelor provided greater and more consistent IPA, compared to that of 75 mg daily clopidogrel. IPA with 50 mg bid ticagrelor appeared similar to that with 75 mg daily clopidogrel. Thus the lowest ticagrelor dose, 50 mg, seemed unlikely to provide an efficacy advantage to clopidogrel ([Figure 2](#)). BID dosing is necessary to achieve higher trough IPA levels of ticagrelor compared to clopidogrel with less peak to trough variation.

Figure 2 Mean inhibition of ADP-induced platelet aggregation (final extent) in CAD patients (DISPERSE)



Note: No loading dose was used in this study.

ADP Adenosine diphosphate; bid Twice daily; CAD Coronary artery disease; IPA Inhibition of platelet aggregation; qd Once daily; Pd Pre dose

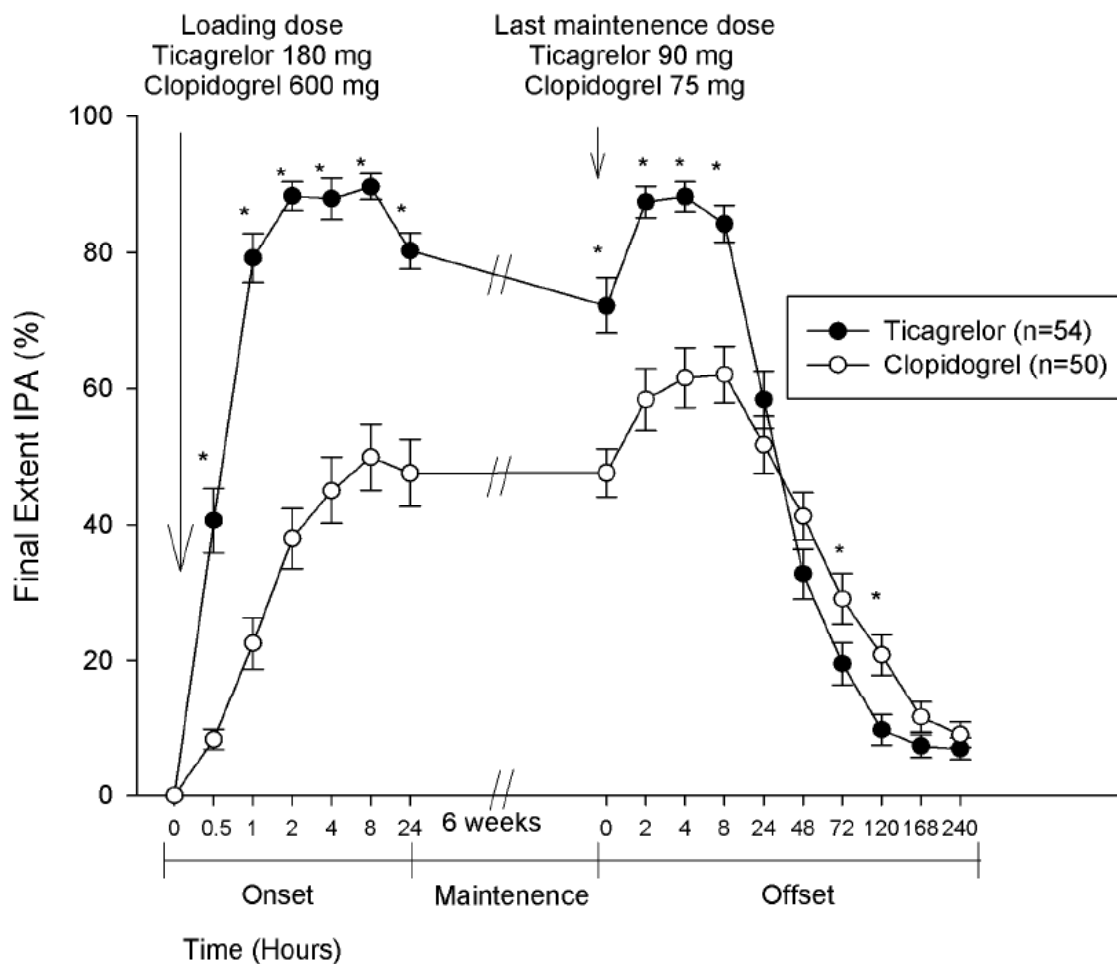
5.3.2 Safety and tolerability for dose selection: DISPERSE2 study

DISPERSE2 was designed to assess the safety and tolerability of 90 mg bid and 180 mg bid of ticagrelor and ASA compared to clopidogrel and ASA in patients with non-ST segment elevation ACS. Total bleeding was similar among 90 mg bid ticagrelor, 180 mg bid ticagrelor, and 75 mg daily clopidogrel groups and therefore a 180 mg bid ticagrelor dose for PLATO was initially chosen. However, a post-hoc analysis of Holter monitor data (3-lead digital continuous ECG [cECG] recording) for asymptomatic ventricular pauses, as well as dyspnea in ticagrelor-treated patients suggested a possible dose relationship for these observations. Additionally, results from clinical pharmacology studies indicated potential for greater drug exposure in patients receiving moderate inhibitors of CYP3A4. Despite the limited data regarding the mechanism of dyspnea and asymptomatic ventricular pauses and relationship to dosing, and with consideration of the potential for increased exposure in sensitive subpopulations and with concomitant moderate CYP3A inhibitors, the PLATO dose was amended to 90 mg bid to increase safety margins for these observations. Ticagrelor 90 mg bid and 180 mg bid demonstrated similar high levels of IPA, therefore, based on these considerations, the 90 mg bid maintenance dose appeared to provide the best balance of efficacy and safety.

5.3.3 Onset and offset of IPA effect: ONSET/OFFSET study

The ONSET/OFFSET study compared the time course of onset and offset of platelet inhibition of ticagrelor with that of clopidogrel or placebo in patients with stable CAD. In the ONSET phase of the study, platelet inhibition was more rapidly achieved with ticagrelor than with clopidogrel: the level of IPA measured 30 minutes following a 180 mg loading dose of ticagrelor was not reached with clopidogrel until 4 hours after a 600 mg loading dose was administered (Figure 3). Maximal IPA following the ticagrelor loading dose (~88%) was reached by 2 hours, as compared to 8 hours for clopidogrel (~48%). The rapid onset of IPA closely follows the rise in ticagrelor plasma concentrations, reflecting an active drug that is rapidly absorbed. Greater inhibition obtained with ticagrelor is maintained with chronic dosing as patients maintain an IPA that is 20% to 30% higher than clopidogrel at 6 weeks (Figure 3).

Figure 3 Mean (\pm SE) final extent %IPA induced by 20 μ M ADP after the first dose by protocol time (ONSET/OFFSET – ITT analysis set)



ADP Adenosine diphosphate; IPA Inhibition of platelet aggregation; ITT Intent to treat; SE Standard error.

The offset of IPA in stable CAD patients was characterized over a 10-day period following 6 weeks of ticagrelor 90 mg bid or clopidogrel 75 mg qd. Ticagrelor has a faster offset rate of IPA compared to clopidogrel. Final extent IPA during the maintenance dosing interval is approximately 20% to 30% (absolute difference) higher for ticagrelor compared to clopidogrel. However, by 24 hours following the last maintenance doses of both agents, the IPA is similar between ticagrelor and clopidogrel, indicating that the offset of IPA effect for ticagrelor is more rapid compared to clopidogrel and patients who miss a maintenance dose of ticagrelor can still maintain an IPA level comparable to those treated with qd clopidogrel of 75 mg. Mean IPA level for ticagrelor at 72 hours (Day 3) post last maintenance dose was comparable to that of clopidogrel at Day 5. Mean IPA for ticagrelor at Day 5 was similar to that of clopidogrel at Day 7, which is not statistically different from placebo.

5.3.4 Consistency of IPA effect: RESPOND study

Up to 30% of patients treated with standard clopidogrel doses have sub-optimal levels of platelet inhibition ([Gurbel et al 2003](#)). These non-responders may experience greater risk of ischemic events despite clopidogrel treatment ([Moblely et al 2004](#)).

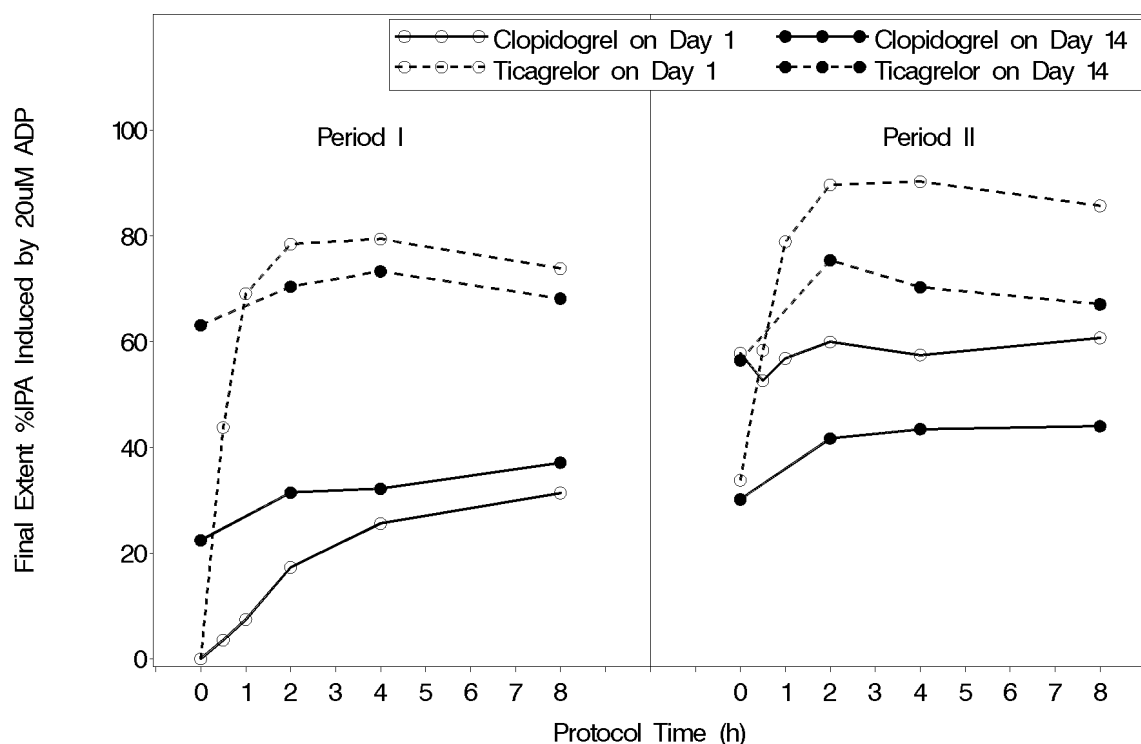
RESPOND was conducted to determine whether ticagrelor (180 mg loading dose followed by 90 mg bid for 2 weeks) could overcome suboptimal levels of platelet inhibition in stable CAD patients who were identified as non-responders to clopidogrel. Ticagrelor treatment resulted in consistently higher IPA compared with clopidogrel, and this was apparent post-dose for both responders and non-responders; mean IPA from 4 to 8 hours post ticagrelor loading dose was 80% to 96% in responders and 74% to 90% in non-responders with or without prior clopidogrel treatment. Residual clopidogrel has little effect on the ticagrelor IPA profile. High E_{max} values in both the non-responder and responder suggest that ticagrelor can completely inhibit platelet aggregation within this dosing range.

Trough plasma concentrations of ticagrelor were at least 2-fold higher than EC_{50} estimates (near the upper plateau of the response curve) for ticagrelor, indicating that the plasma concentrations of ticagrelor at the end of the 90 mg bid dosing interval were sufficient to maintain the high IPA during the dosing interval. These results indicate that clopidogrel non-responders and responders exhibit superior platelet inhibition during therapy with ticagrelor.

5.3.4.1 Switching between clopidogrel and ticagrelor

[Figure 4](#) provides a graphic display of mean IPA (%) induced by 20 μ M ADP after first dose, multiple dosing, and switching from clopidogrel to ticagrelor or ticagrelor to clopidogrel treatment in non-responders.

Figure 4 Mean %IPA induced by 20 μ M ADP - Non-responders (Final extent, ITT analysis set)



Note: Non-responders were assigned to 1 of 2 sequences (clopidogrel then ticagrelor or ticagrelor then clopidogrel) as follows: One group received clopidogrel for 14 \pm 2 days during Period I. These patients then received ticagrelor for an additional 14 \pm 2 days during Period II. A second group received ticagrelor for 14 \pm 2 days during Period I. These patients then received clopidogrel for an additional 14 \pm 2 days during Period II.

ADP Adenosine diphosphate; h Hours; IPA Inhibition of platelet aggregation.

Figure 4 shows that the IPA response to ticagrelor is higher than clopidogrel both at the initiation of treatment (Day 1, Period 1) and at steady state (Day 14 of both periods). There is an apparent additive effect on Day 1, Period 2 of ticagrelor treatment, if clopidogrel is given first, as the IPA on Day 1 of Period 2 is slightly higher compared with Day 1 of Period 1. For clopidogrel treatment in Period 2, there is an offset/residual effect of ticagrelor on Day 1, Period 2 if ticagrelor is given first, as the IPA of clopidogrel is substantially higher on Day 1 of Period 2 as compared to Day 1 of Period 1.

- In patients with stable CAD judged responsive to clopidogrel, switching from clopidogrel to ticagrelor resulted in an absolute IPA increase of 26.4% and switching from ticagrelor to clopidogrel resulted in an absolute IPA decrease of 24.5%. Increased IPA occurs after the first dose when switching to ticagrelor.

- Patients who are non-responders to clopidogrel are responsive to ticagrelor. Patients with stable CAD judged non-responsive to a single 600 mg dose of clopidogrel (ie, patients who exhibited <10% change from baseline in platelet aggregation when administered clopidogrel) showed a 40% absolute increase in mean IPA upon switching from stable dosing of clopidogrel to ticagrelor. Ticagrelor's IPA response occurs whether or not patients respond to clopidogrel.
- Patients can switch from clopidogrel to ticagrelor without interruption of antiplatelet effect. The first dose of ticagrelor should be given 24 hours following the last dose of clopidogrel.

5.4 Special populations

Patients with ACS can be expected to have impairment in critical organ function, including renal and hepatic impairment. Ticagrelor undergoes extensive hepatic metabolism with renal elimination playing a minor role. However, even in drugs that are extensively metabolized, severe renal impairment may affect elimination. Therefore, ticagrelor was studied in patients with severe renal impairment compared to volunteers with normal renal function. Ticagrelor C_{max} and AUC, and the AUC of its active metabolite, were modestly decreased (about 20%) in patients with severe renal impairment, compared to the normal renal function group. IPA was similar between the groups, although more variable in the renal impairment group. Based on these data, no dosing adjustment is required in patients with renal impairment. Patients undergoing renal dialysis have not been studied or treated with ticagrelor.

In patients with mild hepatic impairment, C_{max} and AUC for ticagrelor increased modestly (12% and 23%, respectively) in patients with mild hepatic impairment, compared to healthy volunteers. IPA remained similar between the 2 groups. Based on these data, no dose adjustment is necessary for patients with mild hepatic impairment. Ticagrelor has not been studied in moderate or severe hepatic impairment patients.

Higher exposure to ticagrelor (approximately 52% and 37% for C_{max} and AUC, respectively) and to the active metabolite (approximately 50% for both C_{max} and AUC) were observed in women compared to men. Higher exposures to ticagrelor, (approximately 60% for both C_{max} and AUC) and to the active metabolite (approximately 50% for both C_{max} and AUC) were observed in elderly (≥ 65 years) volunteers compared to younger volunteers (18 to 45 years). These differences are not considered clinically significant. High levels of IPA were achieved in all groups; IPA profile was similar between young and elderly adults and between men and women. No subjects under age 18 years have received ticagrelor.

C_{max} and AUC for ticagrelor in healthy Japanese subjects were 40% higher compared to those in Caucasians. When normalized by body weight, the exposure increased only about 20% in Japanese. IPA was similar between Japanese and Caucasians. This exposure difference is not clinically meaningful.

The population PK analysis results are generally in agreement with the observations regarding males vs females and Japanese in clinical pharmacology studies. Based on the modest

changes observed in these special populations, no recommendations are made for dose adjustment based on age, sex, or race.

6. PLATO – PIVOTAL STUDY

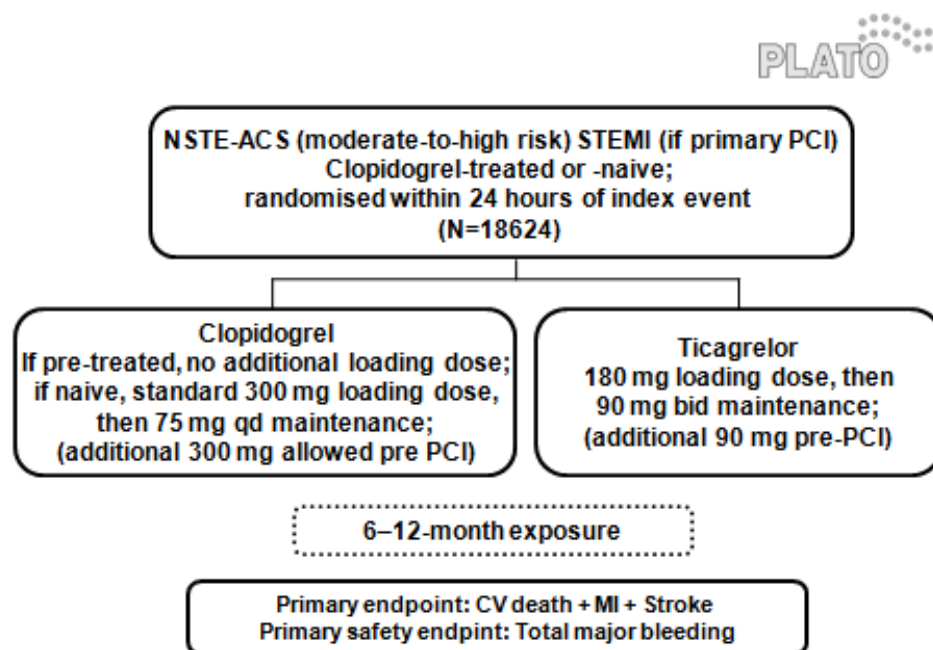
The PLATO study design encompassed clinically relevant aspects of ACS and its current, guideline-recommended treatment, ie:

- Enrollment included patients across the entire spectrum of ACS: UA, STEMI, and NSTEMI. PLATO provided for all ACS treatment strategies, including PCI, CABG surgery, and medical management.
- Dual antiplatelet treatment began within 24 hours of the index event to help protect patients early during this initial high-risk period. Investigators had discretion to provide an additional loading dose of the comparator, clopidogrel, as practiced in some regions depending on treatment strategy.
- Patients receiving chronic clopidogrel therapy could enroll, as could patients given open-label clopidogrel upon admission to hospital prior to randomization.
- Investigators were advised to use the currently recommended 75 mg to 100 mg ASA dose as maintenance treatment although they were allowed to provide up to 325 mg ASA for up to 6 months, as recommended by guidelines in the US after stent placement ([King et al 2008](#), [Antman et al 2008](#)).

6.1 PLATO study design

PLATO was a randomized, double-blind, parallel-group, Phase III, efficacy and safety comparison of ticagrelor to clopidogrel, each given in combination with ASA and other standard therapy. The study design, summarized in [Figure 5](#), took into account both USA and EU regulatory and medical guidelines ([Braunwald et al 2002](#), [Bertrand et al 2002](#), [CHMP 2005](#), FDA March 2006 - Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees).

Figure 5 PLATO study design



bid Twice daily; CV Cardiovascular; MI Myocardial infarction; NSTEMI-ACS Non ST segment elevation acute coronary syndromes; qd Once daily; PCI Percutaneous coronary intervention; STEMI ST-elevation myocardial infarction; UA Unstable angina.

Patient inclusion/exclusion criteria

Patients enrolled were hospitalized for ACS with the onset of symptoms occurring within 24 hours. Investigators could assess patient eligibility directly as they would in clinical practice. ACS inclusion criteria were as follows (for further details, refer to [James et al 2009](#), [Wallentin et al 2009a](#)):

If ST segment elevation, both apply:

- Persistent ST-segment elevation of ≥ 0.1 mV in 2 leads or new left bundle branch block, and
- Primary PCI intended

If no ST segment elevation, ≥ 2 of the following apply:

- Ischemic ST segment changes
- Biomarker showing myocyte necrosis
- Additional risk factor (eg, age, medical history).

Key exclusion criteria included contraindications for clopidogrel, use of fibrinolytic therapy within 24 hours before randomization, a need for oral anticoagulation therapy, an increased risk of bradycardia, prior medical history of intracranial hemorrhage, patients requiring dialysis and patients with moderate or severe hepatic impairment and concomitant therapy with a strong CYP3A inhibitor or inducer.

Treatment pathways in PLATO

Key features of the PLATO study were (1) the randomization and initiation of treatment within 24 hours after symptom onset, prior to the assessment of coronary anatomy by angiography, and thus prior to, and irrespective of, whether patients were medically managed or invasively managed (with PCI or CABG), as well as (2) long-term maintenance (up to 12 months) of antiplatelet therapy.

Investigators prospectively indicated planned invasive (PCI or CABG) or planned medical management at the time of randomization. However, patients who were subsequently assigned either medical or invasive management may have undergone cardiac catheterization. The study allowed treatment with all management paths regardless of initial intent.

Timing of ticagrelor dose (for PCI patients)

By specifying randomization within 24 hours of symptom onset, the PLATO protocol followed standard medical practice ([Anderson et al 2007](#), [Antman et al 2008](#)) and allowed for pre-procedural start of study drug for patients intended for PCI.

Regional variation in clinical practice

The GRACE ([Fox et al 2002](#)) and CRUSADE ([Peterson et al 2006](#)) international registries show that variation in medical practice among major geographic regions is smaller than the variation among hospitals within a single geographic region, so regional differences in disease progression or treatment were unlikely to occur ([Fox et al 2002](#), [Peterson et al 2006](#)). In the US, ASA maintenance doses following stent placement vary; guidelines recommend 325 mg qd for 6 months ([King et al 2008](#)). Outside the US, low ASA maintenance doses (75 to 100 mg qd) predominate, based on guidelines ([Bassand et al 2007](#), [Van de Werf et al 2008](#)).

Double-blind double-dummy dosing

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 initial loading dose at randomization. Patients then received 90 mg bid. Section 5.3 explains the rationale behind dose selection within the discussion of the Phase II studies.

Consistent with current standard of care, clopidogrel 300 mg loading dose and 75 mg qd was the comparator used in PLATO ([Anderson et al 2007](#), [Antman et al 2008](#), [Braunwald et al 2002](#), [Van de Werf et al 2008](#)). Current medical practice encompasses administration of a loading dose of 300 mg to 600 mg clopidogrel prior to PCI ([Anderson et al 2007](#), [Antman et al 2008](#), [Bassand et al 2007](#), [King et al 2008](#), [Van de Werf et al 2008](#)). The PLATO protocol

permitted loading doses of clopidogrel. [Table 5](#) shows how loading, maintenance, and additional PCI dosing in PLATO were conducted in a blinded manner.

Table 5 Dosing for patients randomized to ticagrelor and clopidogrel in PLATO

Treatment group Clopidogrel pre-study status	Ticagrelor		Clopidogrel	
	Naive	Pre-treatment	Naive	Pre-treatment
Loading doses				
Tablets	2 x 90 mg	2 x 90 mg	2 (placebo)	2 (placebo)
Capsules	4 (placebo)	1 (placebo)	4 x 75 mg	1 x 75 mg
Maintenance doses				
Tablets	90 mg bid	90 mg bid	1 placebo bid	1 placebo bid
Capsules	1 placebo qd	1 placebo qd	75 mg qd	75 mg qd
Additional dosing for PCI				
	<24 hours	>24 hours	<24 hours	>24 hours
Tablets	-	1 x 90 mg	-	1 (placebo)
Capsules	4 (placebo)	4 (placebo)	4 x 75 mg	4 x 75 mg

Placebo tablets were for ticagrelor. Placebo capsules were for clopidogrel.
For clopidogrel, PCI additional dosing optional and unrelated to pre-treatment status.
bid Twice daily dosing; qd Once daily dosing; PCI Percutaneous coronary intervention.

Duration of study drug treatment

The treatment duration planned in the PLATO study was a minimum of 6 months to a maximum of 12 months with an expected average study duration of approximately 10 months. The duration of therapy up to 12 months reflects guidelines for treatment of patients with ACS events ([Anderson et al 2007](#), [King et al 2008](#)) and results of the CHARISMA trial ([Bhatt et al 2006](#)).

Concomitant ASA doses

Consistent with current treatment guidelines, PLATO investigators administered both ticagrelor and clopidogrel against a background of ASA therapy, unless patients were allergic or intolerant to ASA ([Anderson et al 2007](#), [Antman et al 2008](#), [Bassand et al 2007](#), [Van de Werf et al 2008](#)). The clinical study protocol specified a once daily ASA dose of 75 to 100 mg. Previous clinical studies ([Peters et al 2003](#), [Patrono et al 2004](#)) indicate this daily dose range for ASA in combination therapy protects against CV events.

For patients not previously on ASA, a first loading dose of 160 mg to 500 mg ASA was allowed (maximum loading dose of 325 mg preferred; however, 500 mg ASA was allowed where this is standard practice). Following stenting, use of 325 mg of ASA for up to 6 months

was allowed following bare-metal stent or drug-eluting stent as per ACC/AHA Guidelines ([Anderson et al 2007](#), [King et al 2008](#)), at the investigator's discretion.

Other concomitant medicines

Treatments for concomitant conditions were limited only if they had substantial interactions with ticagrelor or clopidogrel (eg, strong CYP3A4 inhibitors and inducers). Oral anticoagulants, additional oral antiplatelet therapies, and fibrinolytic therapy were not allowed during the study due to increased risk of bleeding and confounding of study results. Parenteral anticoagulants and GPIIb/IIIa receptor antagonists for short-term use were allowed during the study.

Post-study medicines

After the patient completed or discontinued the study they were treated according to local medical practice. At the End of Treatment Visit, the investigator decided which antiplatelet medication the patient should receive as part of his/her ongoing post-study clinical care: if continued P2Y₁₂ inhibition, the patient received 75 mg open label clopidogrel qd starting 12 to 24 hours after the last dose of study medication. At their discretion, investigators could give a first loading dose of 300 mg clopidogrel.

6.2 Endpoint adjudication process

A central adjudication committee independent of the sponsor and investigators (Independent Central Adjudication Committee [ICAC]), adjudicated and evaluated all clinical primary and secondary efficacy events throughout the study and a 30 day post-study-drug observational period. The investigator initially collected these events. All cases adjudicated as CV death were evaluated to determine whether an MI was the cause of death.

The ICAC reviewed all reported bleeding events in PLATO, except for minimal bleeding not related to CABG surgery. The ICAC categorized every patient undergoing CABG for bleeding, using all available evidence, whether or not the investigator initially reported a bleeding event. This comprehensive approach differs from that taken in other antiplatelet trials, which report relatively low CABG-related bleeding rates. Treatment comparisons of both the CABG- and non-CABG bleeding events contribute important information.

6.3 Data and safety monitoring board

An independent, external Data and Safety Monitoring Board (DSMB) monitored patient safety and made recommendations to the Executive Committee (EC) for early safety or efficacy termination. The DSMB also monitored Holter data to make recommendations to the EC about whether to maintain an enrollment exclusion criterion for increased risk of bradycardic events. Upon recommendation from the DSMB, per the PLATO protocol, additional maintenance laboratory testing was curtailed on 30 March 2008. Patients randomized on or before 31 January 2008 continued to have safety laboratory testing (hematology and chemistry) during the course of the study. Patients randomized on or after 1 February 2008 had safety laboratory testing only at randomization.

6.4 Endpoints for efficacy and safety

See Sections 8 and 9, respectively, for definitions and protocol specifications of these endpoints. Refer to [Appendix B](#) for a detailed description of efficacy endpoint definitions.

6.5 PLATO substudies

Continuous ECG (Holter) monitoring in a subset of DISPERSE2 patients in Phase II disclosed an imbalance among treatment groups in the incidence of largely asymptomatic ventricular pauses. This led to an extensive Holter monitoring substudy in PLATO in over 2900 patients for an in-depth safety assessment of this observation.

Multiple studies measured pulmonary function to probe the safety implications of the sensation of breathlessness, reported as dyspnea, which sometimes accompanies ticagrelor administration. These include studies of patients with asthma or chronic obstructive pulmonary disease (COPD); patients with stable CAD; and a substudy in PLATO of approximately 200 ACS patients.

The PLATO Executive Committee conducted additional substudies. One of these, the genetics substudy, has results reported in Section 10.

6.6 Statistical methodology

The primary analysis used (1) the time from randomization to the earliest event occurring in the composite endpoint; (2) Cox regression analyses with treatment as a factor; (3) Kaplan-Meier (KM) estimates of event rates; and (4) the full analysis set ([Table 6](#)). The secondary efficacy endpoints (see Section 8.2), tested in hierarchical sequence to control the overall type I error rate, provided confirmation of the primary objective. Secondary endpoints listed after the first non-significant result in the sequence have their results presented descriptively.

Subgroup exploratory analyses of the primary efficacy composite evaluated its robustness and consistency, using 31 prespecified factors such as age, sex, race, weight, geographic region, type of index event (STEMI, NSTEMI, UA), and varying medical histories. Forest plots present these results with treatment by subgroup interaction significance levels not corrected for multiplicity. Additional exploratory analyses prespecified in the Statistical Analysis Plan prior to database lock, but not listed in the study protocol, include treatment effects for stent thrombosis, net clinical benefit, and primary composite events in the 30 days following permanent study drug termination.

Bleeding analyses used the time from randomization to the first bleeding event, Cox regression analysis with treatment as a factor, Kaplan-Meier estimates of event rates, and the safety analysis set ([Table 6](#)). Based on the predicted offset time of action of clopidogrel, safety analyses censored events occurring more than 7 days after permanent study drug termination. Cox proportional hazards regression with treatment as a factor and Kaplan-Meier estimates of event rates analyzed various bleeding category severities and clinical contexts to assess secondary bleeding objectives. Subgroup exploratory analysis of the primary bleeding

endpoint evaluated its robustness and consistency, using the same factors used for the primary efficacy subgroup analysis and also early PCI (or not) as a factor.

The analysis dataset definitions and any decisions regarding the inclusion or exclusion of patients from analyses occurred on blinded data prior to database lock.

Analysis sets in PLATO

Table 6 presents the definitions for PLATO analysis sets.

Table 6 Definitions of analysis sets in PLATO

Analysis set	Definition
Full analysis set	All patients randomized to study treatment regardless of protocol adherence or participation in the study, and according to study medication assigned at randomization regardless of medication actually taken. Event censoring occurred upon withdrawal of patient consent if that happened. Applies to all efficacy variables. For patients who did not withdraw consent, regardless of study drug status, study personnel made every effort to obtain full information on MI, stroke, and mortality up to the end of scheduled study duration.
Safety analysis set	All patients who received at least 1 dose of study medication according to the randomized study medication actually received. Analyses generally show events that occurred on-treatment, defined as ≤ 7 days after discontinuation of study treatment, unless specifically noted as including “off-treatment” events. “Off ticagrelor” and “off clopidogrel” event tallies refer to those events.
Laboratory analysis set	All patients in the safety analysis set randomized prior to 31 January 2008. Safety laboratory testing (hematology and chemistry) continued for these patients for their durations of study participation according to the study plan and regardless of calendar date. Patients randomized on or after 1 February 2008 had only baseline laboratory samples analyzed and are excluded from the Laboratory Analysis set.

Interim analysis

The DSMB conducted a single interim analysis, after 1200 identified primary events, at a critical significance level of 0.001, so that the final primary outcome hierarchical analyses utilized a critical significance level of 0.0497 to keep the overall type I error at 5%.

Duration in trial and censoring

PLATO was an event-driven trial. Based on event projections, study enrollment terminated on 18 July 2008. The protocol allowed shortening the duration of the treatment period when the target number of primary efficacy events had been reached. To ensure 6 months minimum treatment, per DSMB, and 12 months maximum treatment, per protocol, final visits were scheduled between 18 October 2008 and 18 January 2009. Depending on enrollment date, a

patient's final visit was their 6-, 9-, or 12 month visit. Patients continued to be followed for efficacy up to their scheduled final visit even if they prematurely discontinued study medication.

All efficacy events that occurred during the intended treatment period were included in the ITT analysis. Patients without an event who had their scheduled final visit were censored at their final visit in the ITT analysis. Patients without an event who missed their final scheduled visit were censored at the planned date of the final scheduled visit in the ITT analysis.

Study sample size

In PLATO it was estimated that 18000 patients would be randomized, and based on an expected event rate of 11% over 12 months, there would be 1780 events needed for at least 90% power to detect a relative risk reduction (RRR) of 15% with 4.97% type I error.

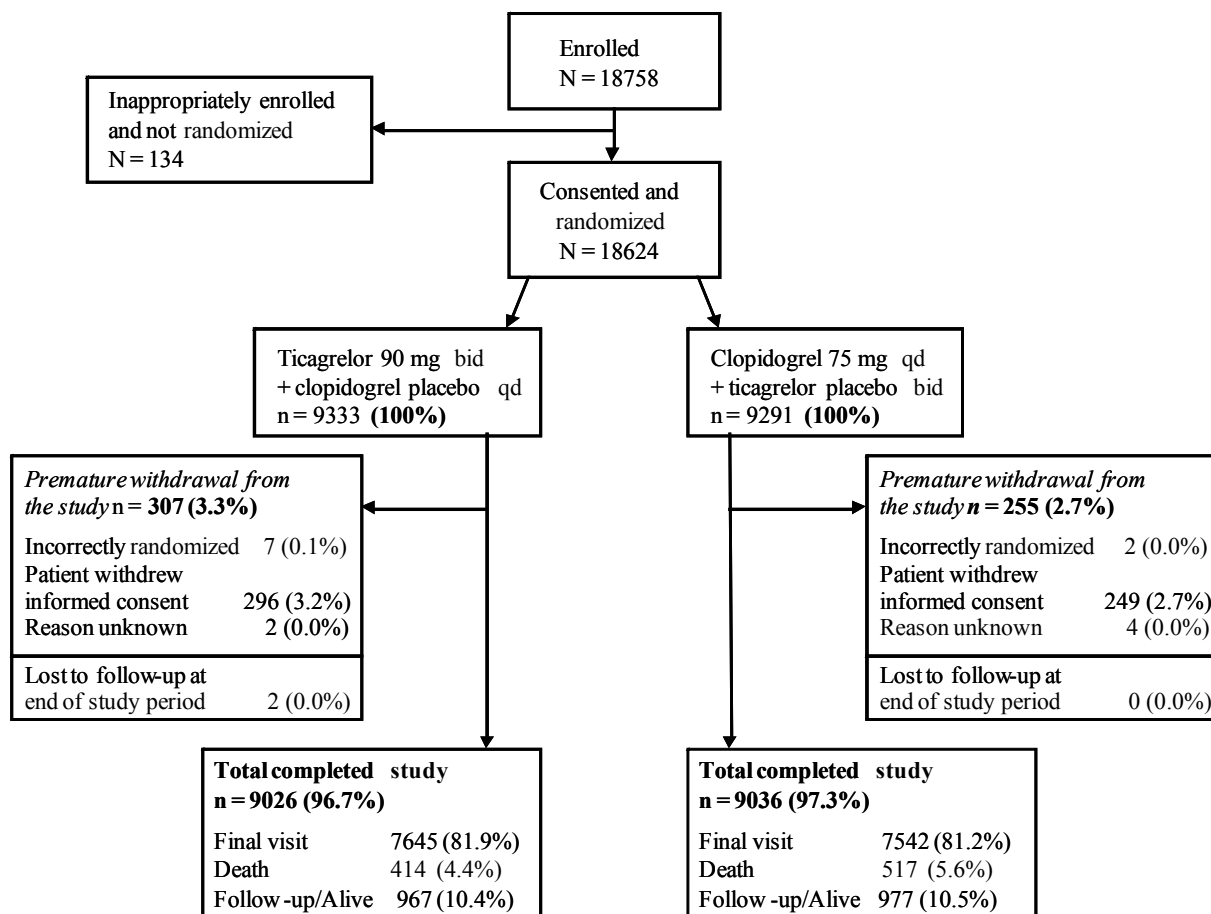
7. PATIENT POPULATION IN PLATO

7.1 Patient disposition

In total, 18758 patients enrolled into the study from 43 countries in North America (NA), South America and Central America, Asia and Australia, as well as Europe, the Middle East, and Africa. The first patient enrolled on 11 October 2006 and the last patient completed the study on 27 February 2009. The study randomized almost all enrolled patients (99.3%). Almost all patients (97%) remained in the study over the randomized treatment period or during the post-study drug observation period, permitting valid assessment of study endpoints. The majority of patients received randomized study drug to the end-of-treatment visit (77.3%), allowing for assessment of safety and tolerability.

Of 18624 randomized patients, 562 prematurely withdrew from the study and 18062 patients completed the study (defined as completing an End of Treatment visit and a 30-day follow-up visit or if they discontinued study drug continued to be followed until his/her last scheduled visit, and any events observed before that time were included in the main efficacy analysis). A total of 22.5% (23.4% and 21.5% for ticagrelor and clopidogrel, respectively) of all randomized patients prematurely and permanently discontinued from study drug during the randomized treatment period, but continued to be followed until his/her last scheduled visit. Any events observed before their last visit were included in the main efficacy analysis. The most common reason for premature permanent discontinuation of study drug was patient not willing to continue treatment (9.8% of those enrolled). [Figure 6](#) shows the disposition of patients in the study and reasons for premature withdrawal.

Figure 6 Patient disposition by study completion – PLATO full analysis set



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. Death is an endpoint in the study; patients who died completed the study. “Premature withdrawal” refers to permanent loss to follow-up and “completed study” refers to patients with follow-up data. “Final visit”, “Death” and “Follow-up/Alive” refer to “patients with primary endpoint event”, “patients who died” and “patients w/o primary event or death”, respectively. bid Twice daily dosing; qd Once daily dosing.

In the full analysis set, a total of 18421 (98.9%) patients (9235 ticagrelor patients and 9186 clopidogrel patients) received at least 1 dose of study drug. Mean exposure to study drug in PLATO was 248 days (246 days for ticagrelor and 250 days for clopidogrel), with a median exposure of 277 days. A total of 7470 (80.9%) patients in the ticagrelor group and 7547 (82.2%) of patients in the clopidogrel group had >90 days of exposure to study treatment, 6762 (73.2%) and 6915 (75.3%) patients in the respective groups were exposed for >180 days, 5082 (55.0%) and 5159 (56.2%) of patients in these groups had >270 days of exposure, and 3138 (34.0%) and 3184 (34.7%) had >360 days of exposure to the respective study treatments.

Section 6 describes the PLATO prespecified analysis sets. Table 7 summarizes the number of patients in each analysis set. All PLATO analysis sets are balanced across treatment groups. The full analysis and safety analysis sets excluded small percentages of patients (134 [0.7%] and then another 203 [1.1%], respectively).

Table 7 Patients included in analysis sets and substudies

Category	Ticagrelor 90 mg bid	Clopidogrel 75 mg qd	Total
Patients included in the full analysis set	9333	9291	18624
Patients included in the safety set	9235	9186	18421
Patients included in the safety laboratory analysis set ^a	5610	5582	11192
Patients included in the PK substudy ^b	6832	6836	13668
Patients included in the Holter monitoring substudy ^c	1472	1436	2908
Patients with paired readings in the Holter monitoring substudy	964	985	1949
Patients included in the pulmonary function substudy ^d	101	98	199
Patients included in the genetics substudy	5137	5148	10285

Note: Participation in the full analysis set is presented by randomized treatment. All other analysis sets are presented by actual treatment.

^a As planned in the protocol, upon recommendation from the DSMB, additional laboratory testing was curtailed on 30 March 2008.

^b Blood samples were obtained from the first 13668 patients, regardless of randomization, to maintain the study blind. The PK analysis set included only patients with evaluable plasma levels of ticagrelor and the active metabolite, AR-C124910XX; PK analyses did not include clopidogrel patients. Analysis took place after unblinding.

^c Patients with paired Holter readings had evaluable Holter data at Visit 1 and Visit 2.

^d Enrollment in the Pulmonary function substudy was limited to the last 7 months of the study.

bid Twice daily dosing; DSMB Data and Safety Monitoring Board; EC Executive Committee; qd Once daily dosing; PK Pharmacokinetics.

7.2 Baseline characteristics and index event data

PLATO enrolled a population generally representative of ACS patients (Mehta et al 2000, Wiviott et al 2007, Fox et al 2002, Peterson et al 2006), a predominantly Caucasian cohort (92%), with nearly one-third the population women (28%) and approximately 43% of the PLATO population ≥ 65 years of age, and 16% of the population ≥ 75 years of age. PLATO investigators indicated intent for invasive management in 72% of the 18624 patients randomized (see Table 10). Of those designated for invasive management at randomization, 97% had coronary angiography, 77% had early PCI, and 6% early CABG, consistent with both current practice patterns and treatment guidelines.

By final diagnosis at discharge from hospital for index event, 42.7% had NSTEMI, 37.7% STEMI, and 16.7% UA, similar to distributions reported in large ACS registries

(Fox et al 2002, Peterson et al 2006). Table 8 summarizes demographic and key baseline characteristics of study patients in the full analysis set.

Table 8 Demographic and baseline characteristics at enrollment – PLATO full analysis set

Characteristic	Statistic or category	Ticagrelor 90 mg bid N=9333	Clopidogrel 75 mg qd N=9291
Age (years)	N	9332 (100%)	9290 (100%)
	Mean (SD)	62.1 (11.21)	62.3 (11.21)
	Median (min, max)	62.0 (19, 97)	62.0 (21, 94)
Age group	Total	9332 (100%)	9290 (100%)
	<65 years	5310 (56.9%)	5333 (57.4%)
	≥65 years	4022 (43.1%)	3957 (42.6%)
	<75 years	7936 (85.0%)	7808 (84.0%)
	≥75 years	1396 (15.0%)	1482 (16.0%)
	Unknown	1 (0.0%)	1 (0.0%)
Sex	Total	9333 (100%)	9291 (100%)
	Male	6678 (71.6%)	6658 (71.7%)
	Female	2655 (28.4%)	2633 (28.3%)
Race	Total	9332 (100%)	9291 (100%)
	Caucasian	8566 (91.8%)	8511 (91.6%)
	Black	115 (1.2%)	114 (1.2%)
	Asian	542 (5.8%)	554 (6.0%)
	Other	109 (1.2%)	112 (1.2%)
	Unknown	1 (0.0%)	0
Ethnic Group	Total	9330 (100%)	9286 (99.9%)
	Hispanic	152 (1.6%)	133 (1.4%)
	Japanese	2 (0.0%)	4 (0.0%)
	Native American	31 (0.3%)	21 (0.2%)
	Native Alaskan/Inuit	0	1 (0.0%)
	Native Hawaiian/Pacific Islander	3 (0.0%)	4 (0.0%)
	African	8 (0.1%)	5 (0.1%)
	African-American	61 (0.7%)	76 (0.8%)
	African-Caribbean	3 (0.0%)	8 (0.1%)

Table 8 **Demographic and baseline characteristics at enrollment – PLATO full analysis set**

Characteristic	Statistic or category	Ticagrelor 90 mg bid N=9333	Clopidogrel 75 mg qd N=9291
	Asian (except Chinese/Japanese)	556 (6.0%)	554 (6.0%)
	Chinese	289 (3.1%)	296 (3.2%)
	Not Applicable	8186 (87.7%)	8151 (87.7%)
	Other	39 (0.4%)	33 (0.4%)
	Unknown	3 (0.0%)	5 (0.1%)
Weight (kg)	N	9305 (99.7%)	9263 (99.7%)
	Mean (SD)	80.6 (15.97)	80.3 (16.01)
	Median (min, max)	80.0 (28, 174)	80.0 (29, 180)
Weight group	Total	9305 (99.7%)	9263 (99.7%)
	<60 kg	652 (7.0%)	660 (7.1%)
	≥60 kg	8653 (92.7%)	8603 (92.6%)
	<80 kg	4517 (48.4%)	4538 (48.8%)
	≥80 kg	4788 (51.3%)	4725 (50.9%)
	male <82kg; female <71kg	4499 (48.2%)	4502 (48.5%)
	male ≥82kg; female ≥71kg	4806 (51.5%)	4761 (51.2%)
	Unknown	28 (0.3%)	28 (0.3%)
Waist circumference (cm)	N	8766 (93.9%)	8703 (93.7%)
	Mean (SD)	98.5 (14.22)	98.6 (14.32)
	Median (min, max)	98.0 (35, 386)	98.0 (34, 381)
Waist circumference group	Total	8829 (94.6%)	8776 (94.5%)
	<100 cm	4847 (51.9%)	4780 (51.4%)
	≥100 cm	3982 (42.7%)	3996 (43.0%)
	Unknown	504 (5.4%)	515 (5.5%)
BMI (kg/m ²)	N	9291 (99.5%)	9241 (99.5%)
	Mean (SD)	27.9 (4.68)	27.8 (4.73)
	Median (min, max)	27.4 (13, 68)	27.3 (13, 70)

Table 8 **Demographic and baseline characteristics at enrollment – PLATO full analysis set**

Characteristic	Statistic or category	Ticagrelor 90 mg bid N=9333	Clopidogrel 75 mg qd N=9291
BMI group	Total	9291 (99.5%)	9241 (99.5%)
	<30 kg/m ²	6641 (71.2%)	6713 (72.3%)
	≥30 kg/m ²	2650 (28.4%)	2528 (27.2%)
	Unknown	42 (0.5%)	50 (0.5%)
Troponin I ^a	Total	9050 (97.0%)	9007 (96.9%)
	Positive	7525 (80.6%)	7564 (81.4%)
	Negative	1525 (16.3%)	1443 (15.5%)
	Unknown	283 (3.0%)	284 (3.1%)
Smoking status	Total	9325 (99.9%)	9285 (99.9%)
	Non-smoker	3592 (38.5%)	3664 (39.5%)
	Ex-smoker	2373 (25.4%)	2303 (24.8%)
	Habitual smoker	3360 (36.0%)	3318 (35.7%)
Proton pump inhibitor at randomization	Total	9333 (100%)	9291 (100%)
	No	6133 (65.7%)	6116 (65.8%)
	Yes	3200 (34.3%)	3175 (34.2%)

^a Troponin I at baseline as analyzed by the central laboratory. The cut-off value for the central Troponin I analyses was 0.05 µg/L.

bid Twice daily dosing; BMI Body mass index; max Maximum; min Minimum; qd Once daily dosing; SD Standard deviation.

The GRACE and CRUSADE registries were observational analyses to determine the association between hospital process performance and clinical outcomes in ACS patients. The GRACE registry included 11543 patients enrolled at 95 hospitals in 14 countries and the CRUSADE registry included 64775 patients enrolled at 350 academic and non-academic US centers. Information was recorded about patient management and outcome during hospitalization and after discharge. Data on treatments administered were analyzed by baseline condition, by hospital type, by the presence or absence of a catheterization laboratory, and by geographical region. [Table 9](#) presents a comparison of selected demographic and baseline characteristics in the PLATO, TRITON ([Wiviott et al 2007](#)) and CURE studies ([Mehta et al 2000](#)), the GRACE ([Fox et al 2002](#)) and CRUSADE ([Peterson et al 2006](#)) ACS registries.

Table 9 Comparison of selected demographic and baseline characteristics for ACS patients in PLATO, TRITON and CURE studies, GRACE and CRUSADE registries

	PLATO	CURE	TRITON	GRACE	CRUSADE
Male	72%	62%	75%	66%	59%
Age (median years)	62	64	61	65 ^a	68
Caucasian race	92%	Not available	93%	Not available	81%
Diabetes mellitus	25%	23%	23%	Not available	33%
Hypertension	65%	60%	64%	Not available	69%
Previous MI	21%	32%	18%	31%	31%
UA/NSTEMI	59%	99%	74%	63%	88% (all NSTEMI)
STEMI	38%	Not included	26% ^b	30%	Not available
Percutaneous coronary intervention					
As index procedure	61% ^c	21%	99%	Not available	
Study drug prior to PCI	94.7%	74%	25%, 26% ^d	Not available	
Coronary artery bypass graft					
As index procedure	5.5%	Not available	Not available	Not available	
CABG during study	10%	Not available	1%	Not available	
Medications taken post-randomization					
ASA	97.4%	99.1%	99%	Not available	
ACE inhibitors	79%	48.9%	75%, 76% ^d	Not available	
Beta blockers	86%	77.5%	88%	Not available	
Calcium channel blockers	25%	35.0%	17%, 18% ^d	Not available	
Lipid-lowering agents	93%	45.6%	92%	Not available	

Source: TRITON-TIMI 38 (Wiviott et al 2007); CURE (Mehta et al 2000); PCI-CURE (Mehta et al 2001); GRACE (multinational) (Fox et al 2002); CRUSADE (United States) (Peterson et al 2006).

^a Reported as mean in GRACE registry.

^b TRITON limited the number of STEMI patients enrolled to 3534 (Wiviott et al 2007).

^c Includes patients at randomization with intent for invasive and with intent for medical management.

^d ACE inhibitor or ARB; data reported for clopidogrel and prasugrel treatment arms, respectively.

ACE Angiotensin converting enzyme; ACS Acute coronary syndrome; ASA Acetylsalicylic acid; MI Myocardial infarction; NSTEMI Non-ST-elevation MI; PCI Percutaneous coronary intervention; STEMI ST-elevation MI; UA Unstable angina.

The PLATO study population demographically resembles those of other large ACS studies (CURE [Mehta et al 2000]; TRITON [Wiviott et al 2007]) although PLATO contained

slightly more males than CURE owing to inclusion of STEMI patients (GUSTO II trial; [Hochman et al 1999](#))

PLATO enrolled patients intended for either invasive (72%) or medical (28%) management. TRITON limited enrollment to patients scheduled for PCI so that those without ECG ST elevations had to have coronary anatomy known prior to randomization. The vast majority (94%) of PLATO PCI patients received study drug prior to PCI, reflecting current ACS guidelines, compared to only one-quarter of TRITON PCI patients ([Wiviott et al 2007](#)), and to three-quarters of CURE patients ([Mehta et al 2001](#)).

The distribution of final diagnoses of index event in PLATO strongly resembles that in the GRACE registry. Inclusion of both NSTEMI and STEMI patients ensured that PLATO enrolled a representative ACS population.

7.3 Prior, concomitant and post-study medications

Prior medications

Prior to index event, 8.2% of ticagrelor and 8.3% of clopidogrel patients were treated with thienopyridines (7.9% and 7.8% taking clopidogrel, respectively); 32.7% of ticagrelor and 32.3% of clopidogrel patients were treated with ASA and derivatives. Approximately 46% of patients in each treatment group received clopidogrel between the index event and randomization (<24 hours prior to randomization), despite the fact that, as per protocol, patients were randomized promptly after onset of symptoms (<24 hours). Treatment arms were well-balanced for both open-label clopidogrel as loading doses and for subsequent administration of blinded study drug as loading doses prior to PCI. In the ticagrelor and clopidogrel groups, 59.8% and 60.3% received placebo or actual clopidogrel loading doses of 300 to 375 mg, respectively, and 29.3% and 29.1% received placebo or actual clopidogrel loading doses >375 mg, respectively. Similar percentages of patients in each treatment group received prior parenteral and oral anticoagulants and fibrinolytic medications.

Concomitant medications

The majority of patients (97%) received concomitant ASA while taking study drug; the percentages were similar by treatment group. The protocol recommended ASA 75 to 100 mg/day during the treatment period. High dose ASA, 325 mg, was used variably and was not necessarily driven by stent usage, as recommended by the guidelines ([King et al 2008](#)). Additional exploratory information related to ASA doses used in the PLATO study in different geographic regions is discussed in Section [8.8.1](#).

During the randomized treatment period, similar percentages of patients in both treatment groups were treated with thienopyridines (clopidogrel and ticlopidine). Parenteral and oral anticoagulants as well as fibrinolytic medications were also taken by similar percentages of ticagrelor and clopidogrel patients, respectively.

Post-study medications

At the beginning of the post-study drug observation period, investigators specified their intent to replace study treatments mainly with ASA: 84.6% and 84.2% of patients in the ticagrelor and clopidogrel groups respectively. Similar percentages of patients in both treatment groups were treated with open-label clopidogrel in the post-study drug observation period (32.2% in the ticagrelor group and 32.8% in the clopidogrel group).

Summary of other medications

Prior, concomitant, and post-study medications, including prior and concomitant anticoagulant therapy, in the PLATO study were as expected for an ACS population and balanced between the treatment groups; no important bias was apparent that would be attributable to these factors. The pattern of other medications taken during the randomized treatment period is typical of an ACS population (Wiviott et al 2007, GRACE/Fox et al 2002, CRUSADE/Peterson et al 2006) confirming that the study population matches the target population for the ACS indication.

7.4 Coronary procedures conducted during the study

A summary of the invasive procedures that were conducted during the index hospitalization, split by intended treatment strategy, is provided in [Table 10](#). A summary of patients with all procedures conducted during the entire study including the index hospitalization is presented in [Table 11](#).

- Because investigators prospectively indicated the intended treatment path at randomization, these strata of patients (intended invasive and intended medical management) could be analyzed as randomized subsets.
- A total of 97% of patients with planned invasive management and 42% of patients with planned medical management underwent coronary angiography during their index hospitalization.
- During the entire study, of the total study population, approximately 64% had PCI and 10% had CABG.

Table 10 **Planned treatment approach for patients with invasive procedures during index event hospitalization – PLATO full analysis set**

Procedure	Planned invasive treatment		Planned medical management	
	Ticagrelor 90 mg bid N=6732	Clopidogrel 75 mg qd N=6676	Ticagrelor 90 mg bid N=2601	Clopidogrel 75 mg qd N=2615
Coronary angiography	6527 (97.0%)	6484 (97.1%)	1098 (42.2%)	1115 (42.6%)
Any therapeutic procedure	5513 (81.9%)	2257 (82.8%)	650 (25.0%)	658 (25.2%)
Percutaneous coronary revascularization	5169 (76.8%)	5153 (77.2%)	538 (20.7%)	548 (21.0%)
Cardiac surgery	385 (5.7%)	421 (6.3%)	116 (4.5%)	113 (4.3%)
CABG	376 (5.6%)	414 (6.2%)	115 (4.4%)	111 (4.2%)
Other ^a	22 (0.3%)	23 (0.3%)	10 (0.4%)	11 (0.4%)
Other cardiovascular procedure	4027 (59.8%)	4068 (60.9%)	1403 (53.9%)	1424 (54.5%)

Note: Patients with planned invasive strategy may not have had a procedure and some patients with a medical management strategy at randomization had invasive procedures; patients may have had >1 procedure.

^a Other cardiac surgery includes valve replacement without CABG, other cardiac surgery, re-operation due to bleeding, and other re-operation per the eCRF.

bid Twice daily dosing; CABG Coronary artery bypass graft; eCRF Electronic case report form; qd Once daily dosing.

Table 11 **Summary of patients with coronary procedures during study – PLATO full analysis set**

Procedure	Ticagrelor 90 mg bid N=9333 n (%)	Clopidogrel 75 mg qd N=9291 n (%)
Coronary angiography	8005 (85.8%)	7972 (85.8%)
PCI	5978 (64.1%)	5999 (64.6%)
CABG	931 (10.0%)	968 (10.4%)
Other cardiac surgery	60 (0.6%)	74 (0.8%)

bid Twice daily dosing; CABG Coronary artery bypass graft; qd Once daily dosing; PCI Percutaneous coronary intervention.

Refer to [Appendix B](#) for the figure depicting the actual treatment pathways and percentages of patients in each treatment pathway for the PLATO study.

8. PLATO EFFICACY RESULTS

8.1 Primary efficacy endpoint

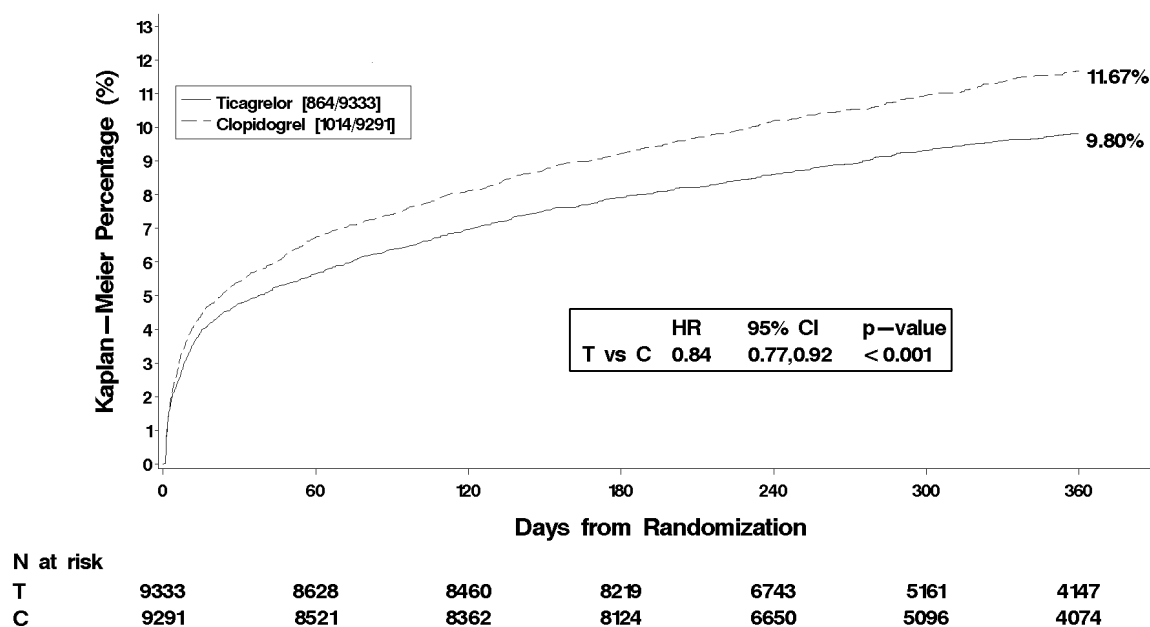
The primary efficacy endpoint is the time to first occurrence of any event from the composite of death from vascular causes, MI, or stroke. Death from vascular causes includes CV deaths, cerebrovascular deaths, and any other death for which there was no clearly documented nonvascular cause.

The primary composite efficacy endpoint consisted of objective components that were all individually clinically meaningful and had been previously accepted by worldwide regulatory authorities. All 3 components of the primary composite efficacy endpoint (CV death, MI, or stroke) represent irreversible loss of organ function that can be objectively assessed and are consistent with other ACS studies. Both ischemic and hemorrhagic strokes were included to avoid any potential issues of event misclassification.

Refer to [Appendix B](#) for a detailed description of efficacy endpoint definitions.

In PLATO, ticagrelor was shown to be superior to clopidogrel in reducing the rate of the primary efficacy endpoint of CV death, MI, or stroke after ACS events (RRR 16%, absolute risk reduction [ARR] 1.9%, hazard ratio [HR] 0.84 [95% confidence interval (CI) 0.77, 0.92]; $p=0.0003$) ([Figure 7](#)). Based on this ARR, treating 54 ACS patients with ticagrelor instead of clopidogrel for 12 months will prevent 1 patient from having a CV death, MI, or stroke event.

Figure 7 Kaplan-Meier plot of primary clinical endpoint events - estimate of the risk to the first occurrence of any event in the composite efficacy endpoint – PLATO full analysis set



C Clopidogrel; CI Confidence interval; HR Hazard ratio; T Ticagrelor.

8.2 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 death from vascular causes, MI, or 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).
- (ii) Time to first occurrence of any event from the composite of all-cause mortality, MI, or stroke
- (iii) 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
- (iv) 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
- (v) Time to occurrence of all-cause mortality.

Secondary efficacy endpoints of the primary objective provided the ability to demonstrate the effect of ticagrelor in different subsets of disease severity. The investigators' declaration of selected treatment strategy at the time of randomization allowed for a reliable analysis of patients intended for invasive management which comprises a medically important subgroup of patients. All-cause mortality provides a more inclusive endpoint than CV death. The hierarchical testing procedure preserves the Type I error rate ([Table 12](#)).

Table 12 Secondary efficacy endpoints – PLATO full analysis set

Secondary Endpoint	Ticagrelor 90 mg bid N=9333		Clopidogrel 75 mg qd N=9291		HR (95% CI)	p-value
	Patients with events	KM%/ year	Patients with events	KM%/ year		
Composite of all-cause mortality/ MI (excl. silent MI)/stroke	901 (9.7%)	10.2%	1065 (11.5%)	12.3%	0.84 (0.77, 0.92)	0.0001
Composite of CV death/total MI/Stroke/Severe recurrent cardiac ischemia/Recurrent cardiac ischemia/TIA/Other arterial thrombotic events	1290 (13.8%)	14.6%	1456 (15.7%)	16.7%	0.88 (0.81, 0.95)	0.0006
CV death	353 (3.8%)	4.0%	442 (4.8%)	5.1%	0.79 (0.69, 0.91)	0.0013
MI (excluding silent MI)	504 (5.4%)	5.8%	593 (6.4%)	6.9%	0.84 (0.75, 0.95)	0.0045
Stroke	125 (1.3%)	1.5%	106 (1.1%)	1.3%	1.17 (0.91, 1.52)	0.2249
<i>All-cause mortality</i>	<i>399 (4.3%)</i>	<i>4.5%</i>	<i>506 (5.4%)</i>	<i>5.9%</i>	<i>0.78 (0.69, 0.89)</i>	<i>0.0003</i>

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. A single event may be counted in more than 1 row.

Note: The number of first events for the components CV death, MI, or stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

bid Twice daily dosing; CI Confidence interval; CV Cardiovascular (CV death is death from vascular causes); excl. Excluding; HR Hazard ratio; KM Kaplan Meier; MI Myocardial infarction; qd Once daily dosing; TIA Transient ischemic attack.

Secondary efficacy endpoint results, which appear in [Table 12](#), indicate that the effect of ticagrelor is robust with regard to modifications in the efficacy endpoint:

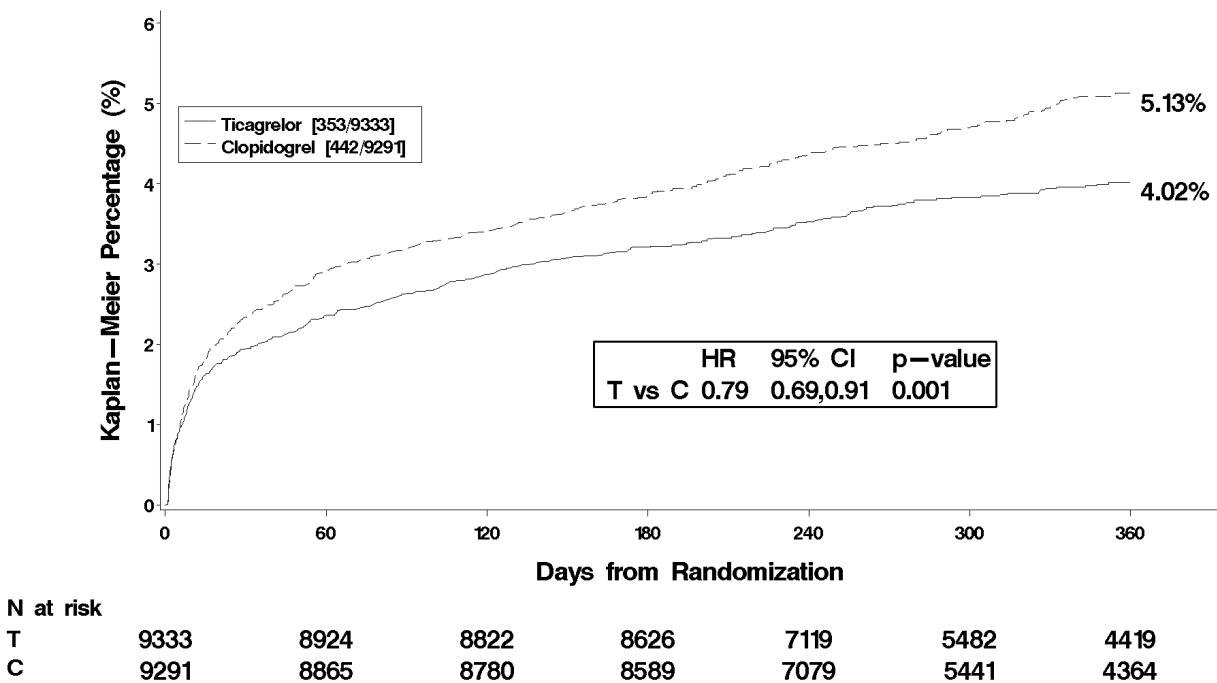
- Substitution of Total death for CV death in the composite endpoint resulted in maintenance of the RRR (HR=0.84 [0.77-0.92]; p=0.0001).
- Addition of less severe components to the composite endpoint resulted in maintenance of the benefit of ticagrelor over clopidogrel (HR=0.88 [0.81-0.95]; p=0.0006).
- Individual components of the composite endpoint—MI and CV death—retained the benefit of ticagrelor over clopidogrel (MI: HR=0.84 [0.75-0.95]; p=0.0045; CV death: HR=0.79 [0.69-0.91]; p=0.0013; stroke (HR=1.17 [0.91, 1.52]; p=0.2249), showed no significant difference between the treatment groups.
- Total mortality was the last endpoint to be analyzed in the predefined hierarchy and while nominally positive for ticagrelor, formal statistical testing ceased when significance was not reached for stroke.

Although the primary endpoint in patients intended for invasive management was included in the hierarchical testing procedure, the results for this subgroup are presented separately below.

CV death and MI

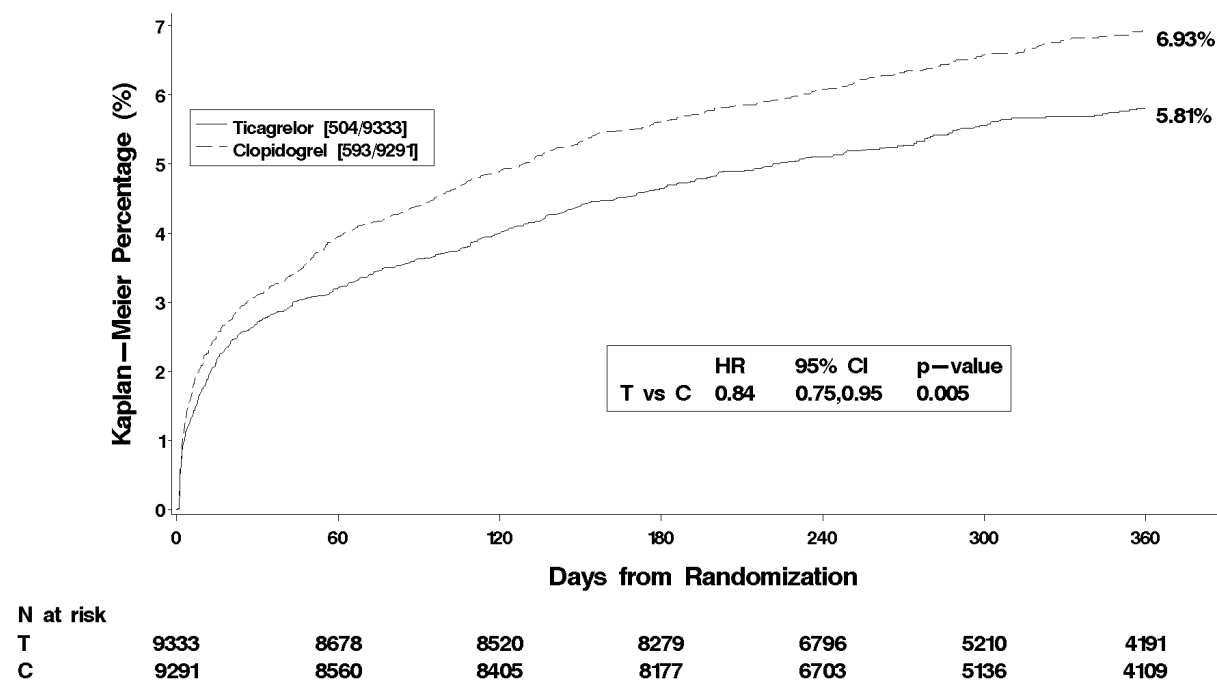
Figure 8 and Figure 9 illustrate the Kaplan-Meier estimates of the risk of the first occurrence of the secondary endpoints of CV death and of non-silent MI, respectively. A 1.1% ARR with ticagrelor was observed for both endpoints.

Figure 8 Kaplan-Meier plot of secondary clinical endpoint events CV death - estimate of the risk to the first occurrence of an event – PLATO full analysis set



C Clopidogrel; CI Confidence interval; CV Cardiovascular; HR Hazard ratio; excl. Excluding; MI Myocardial infarction; T ticagrelor,

Figure 9 **Kaplan-Meier plot of secondary clinical endpoint events MI (excl. silent) - estimate of the risk to the first occurrence of an event – PLATO full analysis set**



C Clopidogrel; CI Confidence interval; HR Hazard ratio. excl. Excluding; MI Myocardial infarction;
T Ticagrelor.

Further information is provided for the clinical contexts of myocardial infarction in Section 8.5.

Table 13 presents a summary of deaths that occurred in the PLATO study. The full ITT analysis set is used for this overview of deaths because it captures all deaths that occurred in the study, in contrast to the safety analysis set, which excludes patients who did not take at least 1 dose of study treatment.

Fewer patients died in the ticagrelor treatment arm compared to the clopidogrel treatment arm, whether counting them as 1) all deaths in the trial (443 vs 540); 2) all adjudicated deaths (418 vs 520); 3) adjudicated deaths occurring from randomization to last scheduled visit (399 vs 506); or 4) number of safety on-treatment deaths (283 vs 339) and the number of safety off-treatment deaths (125 vs 166).

Table 13 **Summary of deaths – PLATO all patients**

Deaths	Ticagrelor 90 mg bid N=9333	Clopidogrel 75 mg qd N=9291	Total N=18624
Total deaths ^a	443	540	983
Discovered after withdrawal of consent, not adjudicated	25	20	45
All adjudicated deaths	418	520	938
Adjudicated deaths within efficacy period (randomization to last scheduled visit date)	399	506	905
Adjudicated deaths 1 to 30 days after efficacy period (post-study drug observation period ^b)	15	12	27
Adjudicated deaths after post-study drug observation period ^b	4	2	6
Adjudicated deaths counted in safety analyses ^a	408	505	913
Deaths in safety on-treatment analysis (randomization to 7 days after the last dose of study drug)	283	339	622
Within efficacy period	281	339	620
After efficacy period	2	0	2
Deaths in safety off-treatment analysis (>7 days after the last dose of study drug)	125	166	291
Adjudicated deaths not counted in safety analyses – patient never took study drug	10	15	25

^a One patient (E2607003) in the ticagrelor group with a Fatal bleed who was adjudicated by ICAC as Fatal was alive and completed the study.

^b Post-study observation period (30-day period after the last scheduled visit of the efficacy follow-up study period - includes all deaths in the period following last scheduled visit date).

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 (0.0%) patients could not be contacted, 3 in the ticagrelor group (E1019005, E1704019 and E2714012) and 2 in the clopidogrel group (E1002004 and E2410013).

bid Twice daily; ICAC Independent Central Adjudication Committee; qd Once daily.

Stroke

The estimated proportion of patients with stroke at 12 months post-randomization was similar between ticagrelor (1.5%, n=125 patients) and clopidogrel (1.3%, n=106 patients) (HR 1.17; p=0.2249, [Table 12](#)).

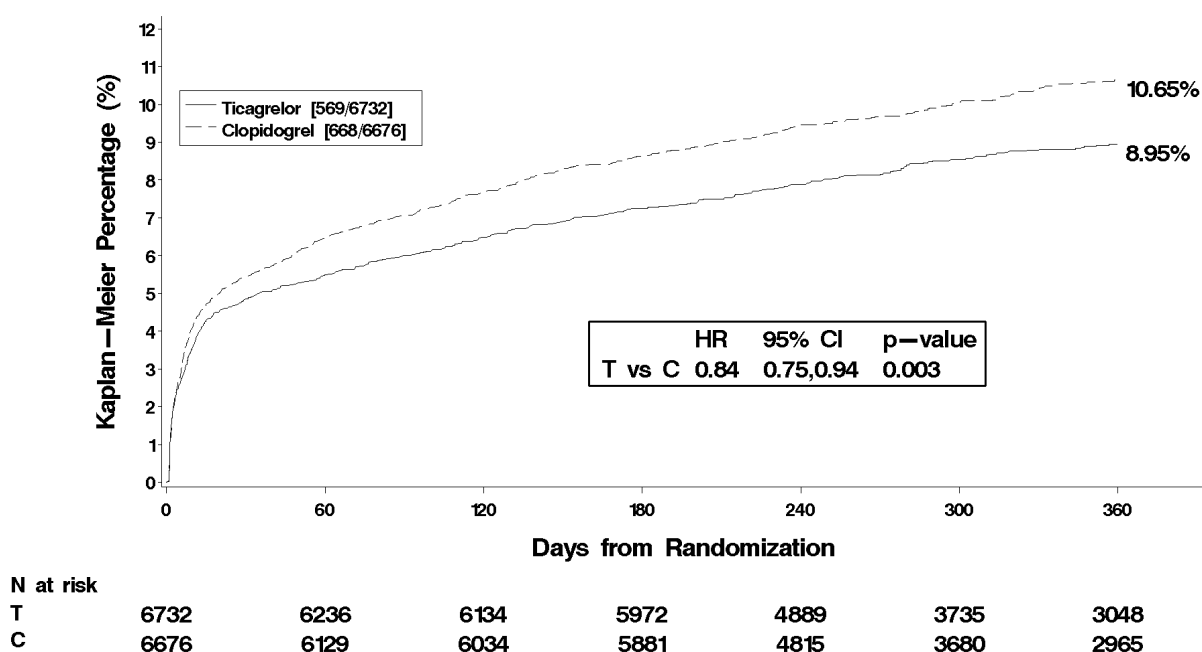
One-hundred non-hemorrhagic strokes occurred in 96 patients in the ticagrelor group compared to 95 non-hemorrhagic strokes in 91 clopidogrel patients. Twenty-three

hemorrhagic strokes occurred in the ticagrelor group compared to 13 in the clopidogrel group. For detailed safety information on intracranial bleeding events, refer to Section 9.1.2.1.

Primary composite endpoint in patients with planned invasive treatment or medical management

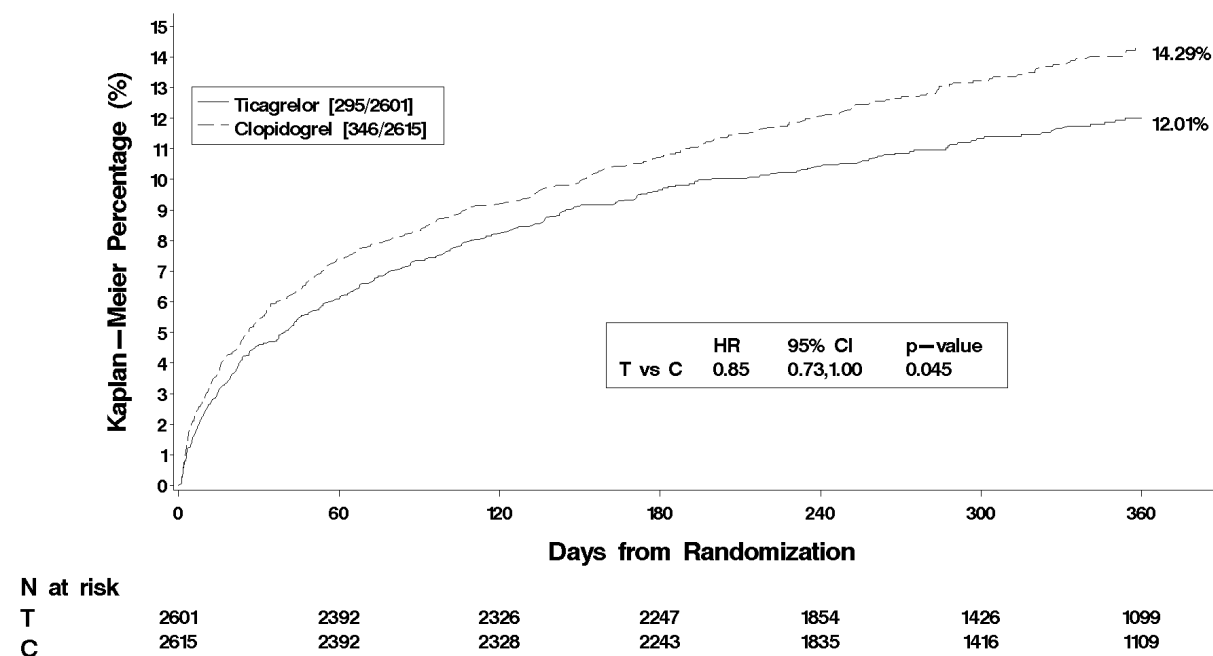
Figure 10 and Figure 11 show the primary composite endpoint in the subset of patients intended for invasive (prespecified analysis) or medical management (descriptive analysis), respectively. These analyses demonstrated a benefit of ticagrelor over clopidogrel in both subgroups.

Figure 10 Kaplan-Meier plot of primary endpoint in patients intended for invasive management – PLATO full analysis set



C Clopidogrel; CI Confidence interval; HR Hazard ratio; T Ticagrelor.

Figure 11 **Kaplan-Meier plot of primary endpoint in patients intended for medical management – PLATO full analysis set**

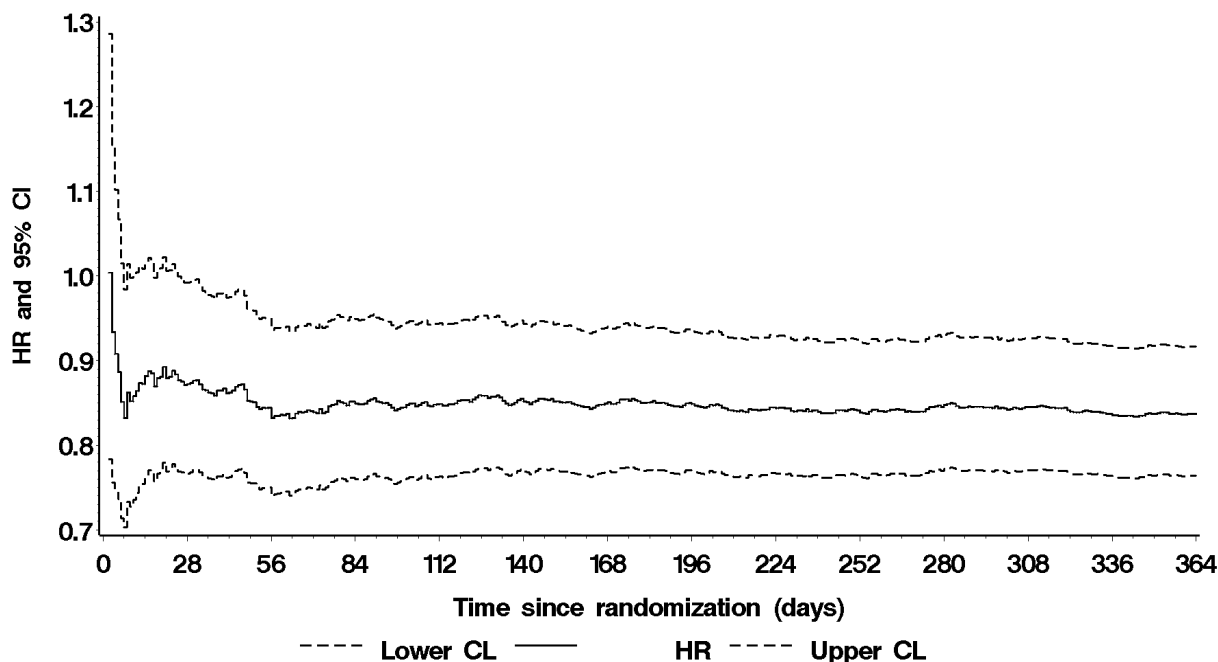


C Clopidogrel; CI Confidence interval; HR Hazard ratio; T Ticagrelor.

8.3 Consistency of effect over time

Figure 12 displays the cumulative hazard ratio (solid line) and its 95% CI (broken lines) for the primary efficacy composite endpoint as a function of time in trial, day by day. Within a month or 2, the HR demonstrates stability around 0.84, without progressive movement towards 1.0 with increasing time. This indicates persistence and constancy of ticagrelor effect over the duration of the 12 months studied.

Figure 12 Primary efficacy endpoint - cumulative hazard ratios - PLATO



Cumulative hazard ratio is computed at daily intervals as $R0(t)/R1(t)$, where t is the timepoint, $R0(t)$ is the number of ticagrelor patients who had events by time t divided by their total follow-up time by time t , $R1(t)$ is the number of clopidogrel patients who had events by time t divided by their total follow up time by time t .

95% confidence interval at time t is computed using $(1/E0[t] + 1/E1[t])$ as the approximation for the log hazard ratio variance, where $E0(t)$ is the number of events on ticagrelor by time t , and $E1(t)$ is the number of events on clopidogrel by time t .

CI Confidence interval; CL Confidence limit; HR Hazard ratio.

8.4 Results in patients with stents

A prespecified exploratory analysis of time to stent thrombosis (timing of stent thrombosis could differ among patients), as confirmed by ICAC, prospectively examined whether ticagrelor results in a decreased risk of stent thrombosis compared to clopidogrel for several categories of stent and several categories of likelihood by the Academic Research Consortium (Cutlip et al 2007) (Table 14). This analysis indicated that the benefit of ticagrelor in preventing stent thrombosis was maintained across various classifications of stent thrombosis.

For patients receiving intracoronary stenting during the study, ticagrelor demonstrated a 33% RRR compared to clopidogrel for definite stent thrombosis, with ARR=0.6%, KM% 1.3% vs 1.9%, HR 0.67 (95% CI 0.50, 0.91), and nominal p-value=0.0091 (Table 14). A similar result for ticagrelor was observed for all subcategories of stent thrombosis type or likelihood (Cutlip et al 2007) and for patients with a history of PCI receiving any stent during the study.

Table 14 Analysis of time to first ICAC-adjudicated stent thrombosis in patients with any stent during the study - PLATO

Category of stent thrombosis	Ticagrelor 90 mg bid N=5640		Clopidogrel 75 mg qd N=5649		Hazard ratio (95% CI)	p-value
	n (%)	KM%	n (%)	KM%		
Definite	71 (1.3%)	1.3%	106 (1.9%)	1.9%	0.67 (0.50, 0.91)	0.0091
Definite or probable	118 (2.1%)	2.2%	158 (2.8%)	2.9%	0.75 (0.59, 0.95)	0.0167
Definite, probable, or possible	155 (2.8%)	2.9%	202 (3.6%)	3.8%	0.77 (0.62, 0.95)	0.0131

CI Confidence interval; ICAC Independent central adjudication committee; KM Kaplan Meier.

Ticagrelor demonstrated a consistent benefit over clopidogrel in both the 7335 (39%) patient subgroup not receiving any stent (HR=0.81 [0.71, 0.93]) and the 11289 (61%) patient subgroup who received any stent (HR=0.87 [0.77, 0.98]).

8.5 Myocardial infarction clinical contexts

Treatment groups did not show clear differences in the clinical settings of adjudicated MIs according to the predefined criteria. The distribution reflects that of a typical ACS population, in which most MIs (60% for ticagrelor, 58% for clopidogrel) occurred not in association with PCI, CABG, stent thrombosis, or death. However, patients in PLATO with peri-PCI MIs constituted a relatively small proportion of patients, (17% ticagrelor; 18% clopidogrel) compared with another recent report ([Wiviott et al 2007](#)). MI associated with stent thrombosis accounted for 13% of ticagrelor and 17% of clopidogrel MIs. Furthermore, only about 1 out of 5 first MIs in PLATO became known because of systematic scrutiny of laboratory enzymes without clinical symptoms. Investigators reported 4 of 5 first MIs in each group. Early randomization of patients caused some peri-procedural MIs in the early period to be obscured by high index event enzyme levels that had not yet decreased, a second increase being poorly differentiated from the index one. The investigator reported new permanent Q-waves on scheduled ECGs as “silent” MIs. The primary efficacy clinical endpoint analysis in PLATO did not include silent MIs; they appear as part of a secondary efficacy analysis. Only 0.1% of patients in each treatment group had a silent MI.

8.6 CABG surgery and mortality

In the subgroup of patients undergoing CABG within 7 days of stopping study drug in PLATO, an exploratory analysis demonstrates a 5.0% ARR and 51% RRR for all-cause mortality with ticagrelor vs clopidogrel. Similar numbers of patients in both treatment groups had bleeding after CABG, measured by several different scales and levels of severity. This suggests that the reduction in mortality is not due to less CABG-related bleeding with ticagrelor.

8.7 Consistency of efficacy results

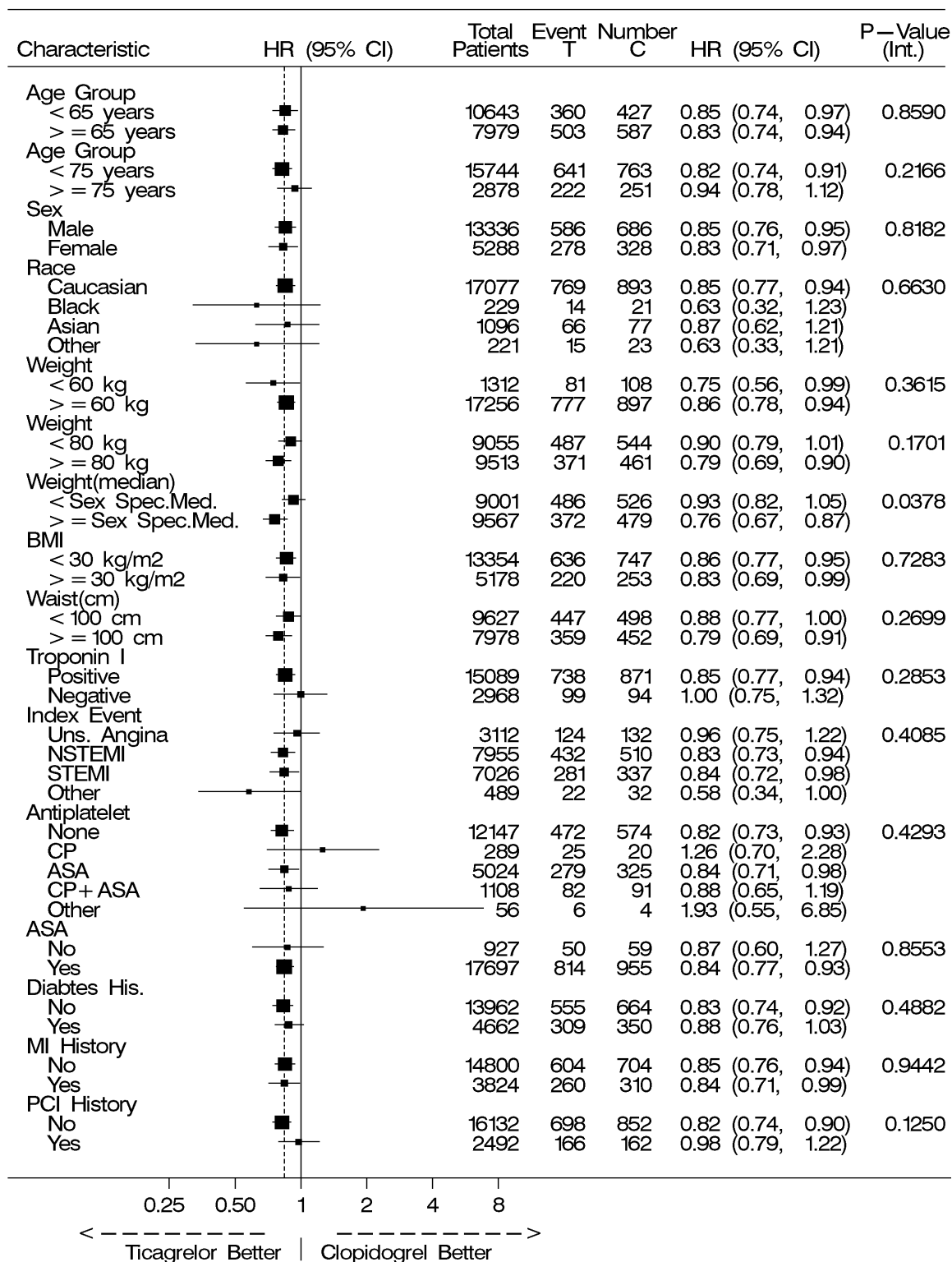
The Statistical Analysis Plan for PLATO included prespecified, descriptive subgroup analyses of 31 baseline factors, representing important patient and disease characteristics, to explore the consistency of the overall result across important patient subgroups ([Figure 13](#)).

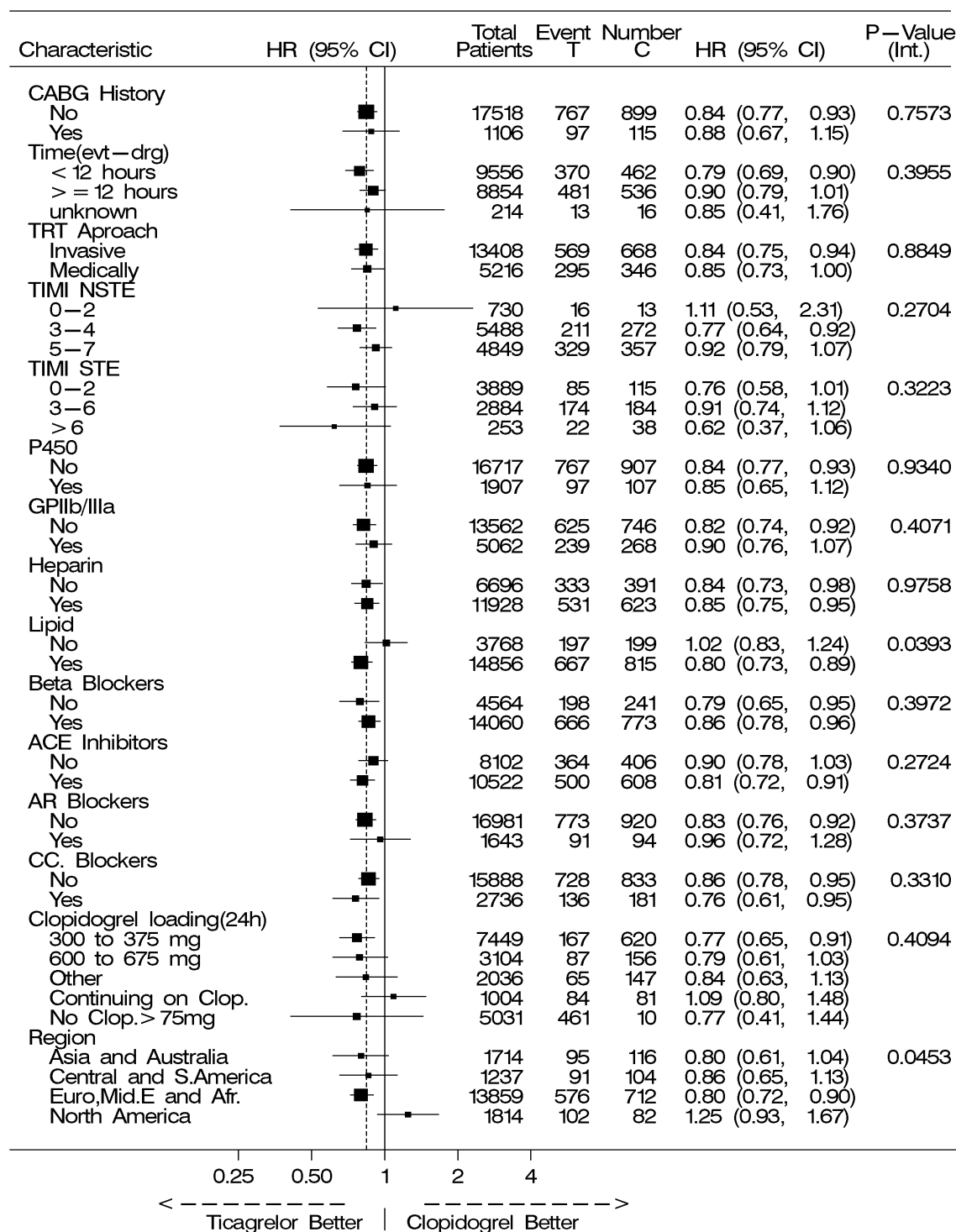
Overall, examination of these factors showed the treatment effect of ticagrelor relative to clopidogrel is largely consistent across subgroups, with little evidence of variation between randomized treatment and baseline factors for the primary endpoint.

Despite consistency of the treatment effect observed across nearly all factors evaluated, statistically marginal interactions were observed for 3 factors: region ($p=0.0453$), weight by sex-specific median ($p=0.0378$), and use of lipid-lowering agents at randomization ($p=0.0393$). Although each of these was further investigated, as described in [Section 8.8.1](#), region was considered to be of greatest interest because it was numerically qualitative in nature; that is, because the treatment effect in some regions (EU, Asia/Australia, Central/South America) appeared to favor ticagrelor and in others (NA) favor clopidogrel.

The observation of an interaction with region led to a thorough examination of the data. These analyses are described in the following section ([Section 8.8.1](#)).

Figure 13 Hazard ratios and rates of the primary clinical endpoint by patient subgroups (PLATO - full analysis set)





The dashed line represents the HR (ticagrelor:clopidogrel) for the primary endpoint for the overall study, 0.84.
 ACE Angiotensin-converting enzyme; AR Angiotensin II receptor; ASA Acetylsalicylic acid; BMI Body mass index; CP Clopidogrel; HR Hazard ratio; KM Kaplan-Meier; MI Myocardial infarction; NSTEMI Non-ST elevation myocardial infarction; PCI Percutaneous coronary intervention; STEMI ST elevation myocardial infarction; TIMI Thrombolysis in Myocardial Infarction.

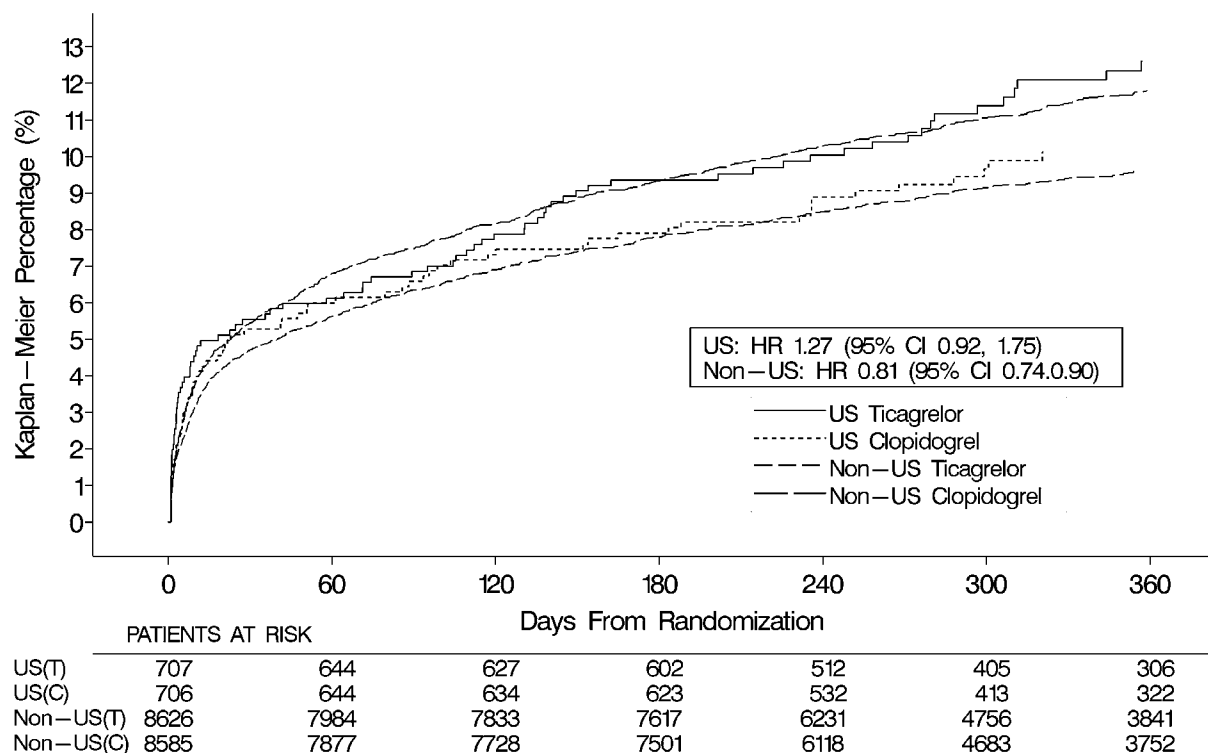
8.8 Exploratory analyses of treatment interactions in PLATO

8.8.1 Treatment-by-region interaction observed in PLATO

In PLATO, region was prospectively defined as (i) Europe, Middle East and Africa (74.4%, of which 94% were within Europe alone); (ii) Asia and Australia (9.2%); (iii) Central and South America (6.7%); and (iv) NA (9.7%).

As shown at the bottom of Figure 13, 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 post-hoc evaluation indicated that the observation regarding NA 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 (all non-US countries combined) (Figure 14).

Figure 14 Kaplan-Meier plot of ICAC-adjudicated primary endpoint by treatment in the US versus non-US (PLATO – Full analysis set)



C Clopidogrel; CI Confidence interval; ICAC Independent Central Adjudication Committee; HR Hazard ratio; T Ticagrelor.

For the individual components of the primary composite endpoint—CV death, MI, or stroke—as well as for all-cause mortality, ticagrelor event rates exceeded those for clopidogrel in the US cohort, so that no single component drove the qualitatively different efficacy result in the US (Table 15).

Table 15 ICAC-adjudicated primary endpoint and additional endpoints by US and non-US – PLATO full analysis set

Endpoint	Region	Ticagrelor 90 mg bid N=9333			Clopidogrel 75 mg qd N=9291			HR (95% CI)	p-value
		n	Patients with events	KM%	n	Patients with events	KM%		
CV death/MI (excl. silent)/Stroke	US	707	84 (11.9%)	12.6	706	67 (9.5%)	10.1	1.27 (0.92, 1.75)	0.1459
	Non-US	8626	780 (9.0%)	9.6	8585	947 (11.0%)	11.8	0.81 (0.74, 0.90)	<0.0001
All-cause mortality	US	707	28 (4.0%)	4.2	706	24 (3.4%)	3.6	1.17 (0.68, 2.01)	0.5812
	Non-US	8626	371 (4.3%)	4.6	8585	482 (5.6%)	6.1	0.77 (0.67, 0.88)	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
	Non-US	8626	329 (3.8%)	4.0	8585	423 (4.9%)	5.3	0.77 (0.67, 0.89)	0.0005
MI (excl. silent)	US	707	64 (9.1%)	9.6	706	47 (6.7%)	7.2	1.38 (0.95, 2.01)	0.0956
	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
	Non-US	8626	118 (1.4%)	1.5	8585	102 (1.2%)	1.3	1.15 (0.88, 1.50)	0.2964

bid Twice daily; CI Confidence interval; CV Cardiovascular; excl. Excluding; HR Hazard ratio; ICAC Independent Central Adjudication Committee; KM Kaplan-Meier; MI Myocardial infarction; qd Once daily.

8.8.2 Potential hypotheses to explain the apparent difference in outcome between the US and non-US regions

Possible explanations for the US observation are:

- Play of chance
- Systematic errors in study conduct
- Imbalances between US and non-US populations in patient characteristics, prognosis, or clinical management resulting in differential outcomes.

8.8.2.1 Role of play of chance

Evaluation of the data suggests that the apparent treatment-by-region interaction could be attributed to chance alone:

- The observed treatment-by-region interaction is of marginal statistical significance ($p=0.045$) and lacks robustness. If just 1 event were to switch from ticagrelor to clopidogrel in the NA region, then the regional interaction would be rendered $p=NS$ (Table 16). Further, if multiplicity adjustments were made for the 31 preplanned interaction tests, the regional interaction would fail to reach significance (see Appendix C, Section 1).
- Given the distribution of patients and events across the 4 prespecified regions and assuming a common overall HR across regions of 0.84 as observed in PLATO, the probability of observing a result that numerically favors clopidogrel in at least 1 region is 28% and the probability of observing a result numerically favoring clopidogrel in the NA region while numerically favoring ticagrelor in the other 3 regions is 10%.
- When data are examined by country, 12 of the 43 countries included in the trial are found to have an HR >1 and 3 to have a HR >1.25 . Given the distribution of events across countries and given an overall HR of 0.84, it would be expected to observe HRs >1 and 1.25 in 13 and 6 countries, respectively. A Forest plot of HRs by country shows treatment effects distributed symmetrically around the overall HR, suggesting no evidence of bias or any particular country to be an unusual outlier (Figure 15). A post-hoc global interaction test for differences in treatment effect across all countries was not significant ($\chi^2=27$ on 41 degrees of freedom, $p=0.95$).
- On the other hand, given the number of events in the NA region, the probability of observing a HR >1.25 if the true HR across all regions was 0.84 is estimated to be low, 1%. However, this calculation is likely to underestimate the true probability of achieving a HR >1.25 in the NA region, since it is post-hoc and ignores multiplicity.

Table 16 **Lack of robustness of the treatment-by-region interaction in PLATO**

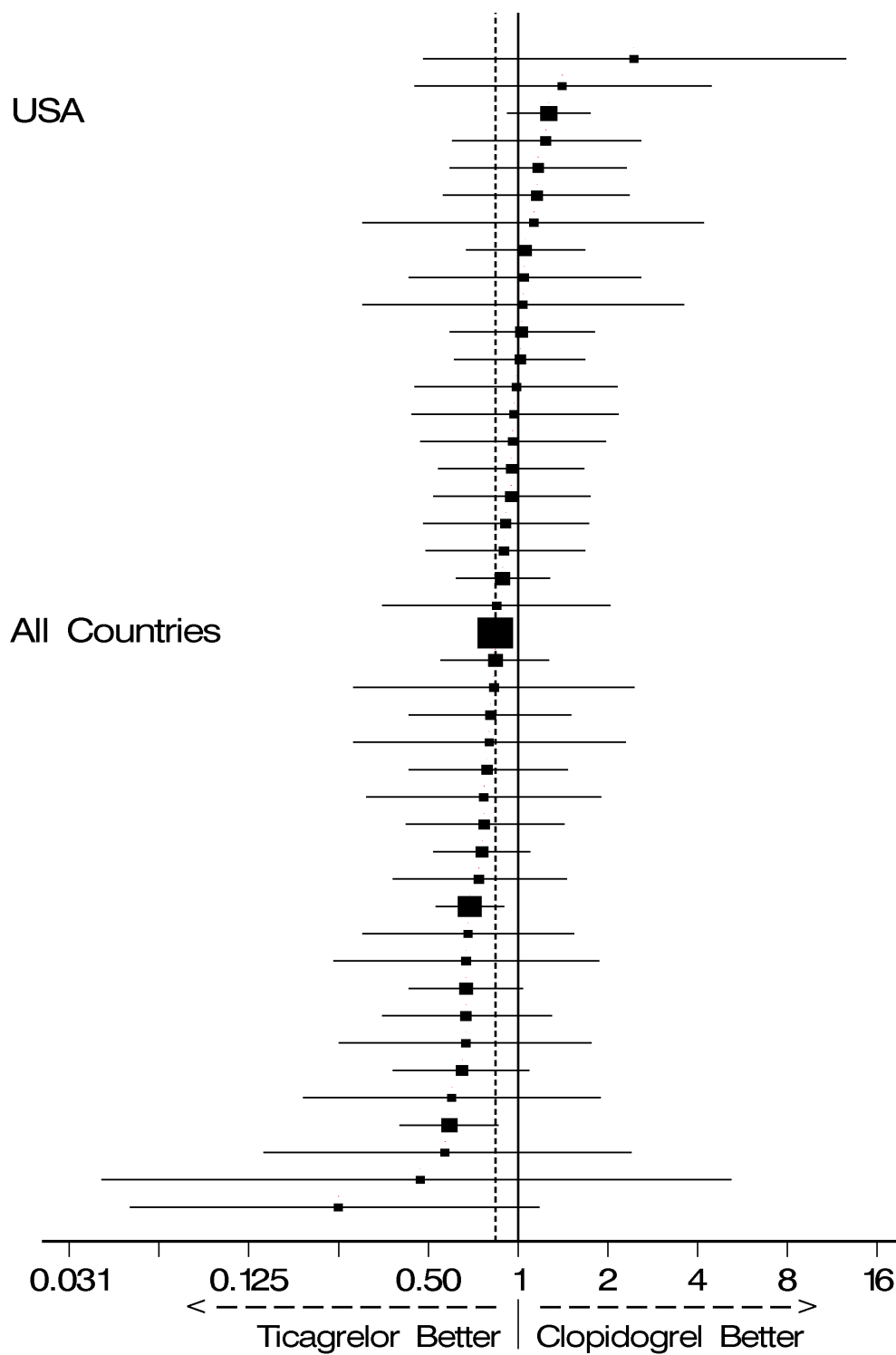
Events on Ticagrelor in NA region	Treatment-by-region interaction	HR & 95% CI in NA	Overall HR & 95% CI
Original data (102 for T vs 82 for C)	0.046	1.25 (0.93, 1.67)	0.84 (0.77, 0.92)
1 event switching (101 for T vs 83 for C)	0.065	1.22 (0.91, 1.63)	0.84 (0.77, 0.92)
2 events switching (100 for T vs 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.

These evaluations collectively suggest that the NA observation could be due to the play of chance alone.

However, because of the extent of the apparent effect (HR point estimate of 1.25 in NA and 1.27 in the US alone compared to 0.84 in the full analysis set) and the important ramifications of this observation, should it be a true finding, AstraZeneca extensively analyzed the data to determine the possible influence of all potentially relevant contributing factors.

Figure 15 Log hazard ratios by country (Forest plot)



Note: Countries are ordered according to hazard ratio. The overall hazard ratio (0.84) is shown essentially in the middle of the plot as “All countries” and is represented by the vertical dashed line.

8.8.2.2 Role of study conduct

AstraZeneca considered the possibility that the US finding was due to some systematic error in study conduct, which was carefully examined and ruled out.

Based on audits, it was concluded that there were no errors regarding batch numbers, randomization codes, or data from the interactive voice response system used for randomizing patients at US sites. Moreover, PK analyses indicated that patients randomized to the ticagrelor group contained ticagrelor in their sera. Site interviews revealed no management issues at specific US sites (including evaluation of large versus small sites), and regional differences in permanent discontinuation rates did not contribute to the observed treatment-by-region interaction.

8.8.2.3 Analysis of potential explanatory factors

Demographic and management characteristics across regions

Evaluation of the 31 prespecified baseline factors shown in [Figure 13](#), together with an exploratory analysis of a number of post-hoc factors related to both baseline and post-baseline characteristics, was undertaken to identify whether any were imbalanced across regions and, therefore, might account, at least in part, for the US observation.

The factors evaluated are listed in [Table 17](#).

It should be noted that many of the factors listed are prognostic for CV events (eg, weight, age, and history of diabetes) and some are imbalanced across the US and non-US (eg, weight). Neither of these necessarily means the factor is predictive of a differential treatment effect, although a factor must be meaningfully imbalanced across regions to play a role in a differential treatment effect. The aim of the following analyses was to identify whether any factors that were imbalanced across regions were associated with a differential effect of ticagrelor compared to clopidogrel, and therefore, could potentially explain the US observation.

Table 17 Baseline and clinical management factors evaluated as potential contributors to the observed treatment-by-region interaction

• Race	• NSAID at randomization	• PPI at randomization
• Index event	• Sex	• GPIIb/IIIa at randomization
• Weight ^a	• ASA at randomization	• Pre index antiplatelet
• Troponin	• CCB at randomization	• Diabetes history
• BMI ^a	• CYP3A at randomization	• Prior MI
• Age ^a	• Heparin use	• Prior CABG
• Compliance	• Having PCI	• Prior PCI
• Time index to 1st dose ^a	• Lipid-lowering agent at randomization	• Catheter lab access
• Invasive or med management	• Stent use	• Clopidogrel loading dose
• Smoking status	• ARB at randomization	• TIMI risk score
• Waist circumference	• BB at randomization	• ASA dose at randomization
• ACE at randomization		• Median ASA dose maintenance therapy ^a

^a Factors that were defined in multiple ways (eg, using different categorical cut-offs).

ACE Angiotensin converting enzyme; ASA Acetylsalicylic acid; ARB Angiotensin receptor blocker; BB Beta blocker; BMI Body mass index; CABG Coronary artery bypass grafting; CCB Calcium channel blocker; CYP Cytochrome P; GPIIb/IIIa Glycoprotein IIb/IIIa inhibitor; MI Myocardial infarction; NSAID Nonsteroidal anti-inflammatory drugs; PCI Percutaneous coronary intervention; PPI Proton pump inhibitor; TIMI Thrombolysis in Myocardial Infarction.

It should also be noted that some of the factors in [Table 17](#) could reasonably be defined in different ways. For example, age and weight were defined using different categorical cut-offs (eg, age was categorized < or ≥65 years as well as < and ≥75 years; weight was categorized as < or ≥60 kg as well as < and ≥80 kg).

In evaluating the impact of ASA therapy, the intent was to evaluate maintenance dose of ASA taken concurrently with the study drug separately from the initial loading dose of ASA at randomization, which would tend to be uniformly high and vary little between patients. This is also consistent with clinical guidelines, which discuss the initial dose during ACS and the subsequent maintenance dose separately. Since ASA maintenance dose could reasonably be defined in different ways, 3 variations of maintenance ASA dose are included in the analyses shown in [Figure 16](#) and [Figure 18](#). These are (i) maintenance ASA dose based on all ASA given between start of study drug and primary event (including loading dose) in all patients with at least 5 days of ASA dosing; (ii) maintenance ASA dose based on all ASA given between start of study drug and primary event (including the loading dose) in all patients with at least 2 days of ASA dosing; and (iii) maintenance ASA dose based on maintenance ASA dose, ie, excluding their loading dose (ie, Day 1 of ASA) from the calculations. This last definition therefore included all patients with at least 1 day of ASA maintenance dosing with study drug.

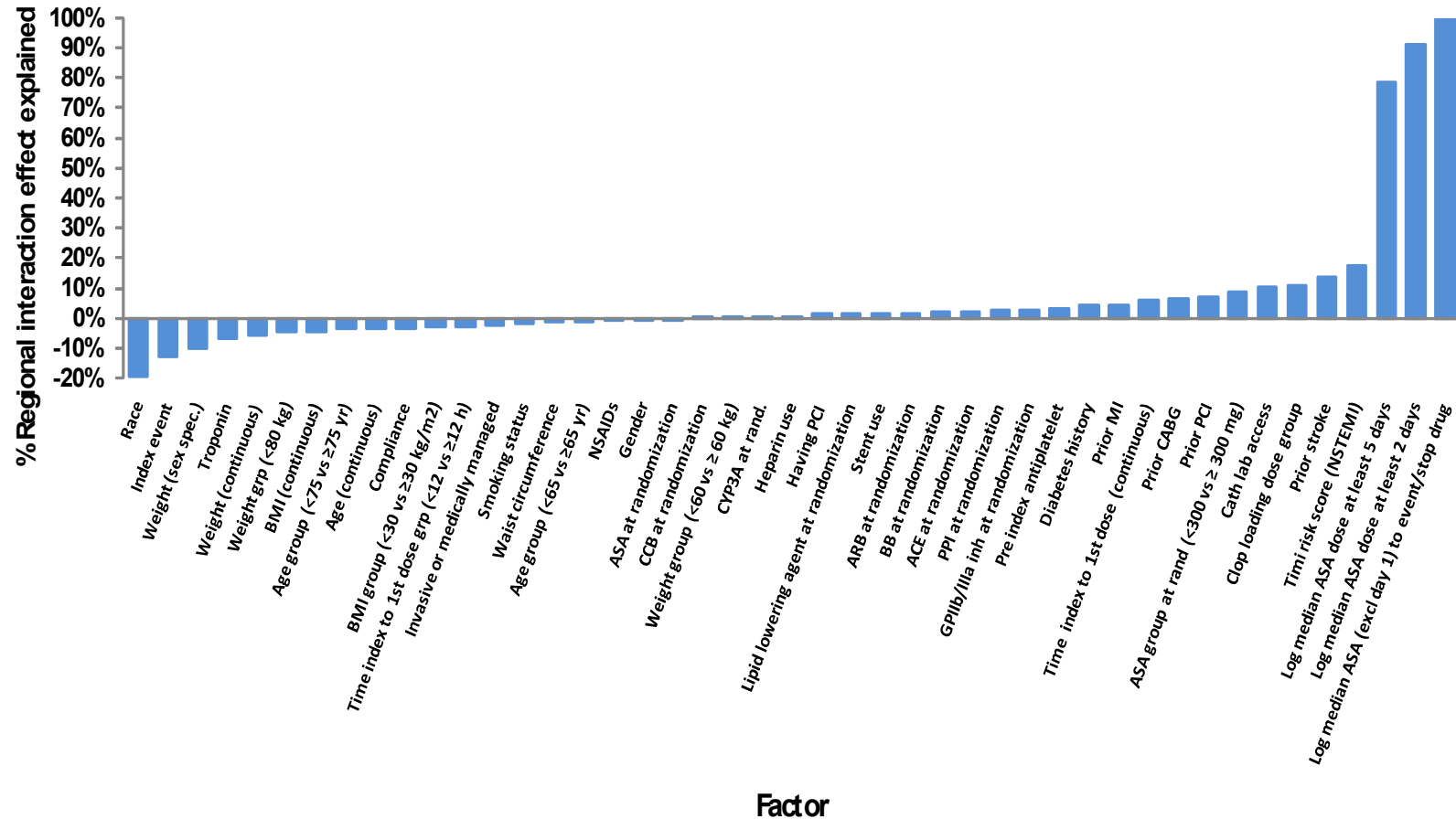
Statistical assessment of the contribution of individual factors to the observed regional interaction

Analyses were conducted to assess the degree of the treatment-by-region interaction that could be explained by a given characteristic or factor (of those listed in the preceding section).

In this analysis, a base Cox regression model was used containing terms for randomized treatment, region (US vs non-US) and treatment-by-region interaction. For each factor, the model is expanded to include terms for the factor and treatment-by-factor interaction. The change in the magnitude and significance of the treatment-by-region interaction term with the factor added to the model indicates the extent to which the observed regional interaction is attributable to the factor. For example, if age is added to the model and the treatment-region interaction term reduces from a value of 0.8, $p=0.01$ to a value of 0.2, $p=0.50$, then age will have accounted for $[0.8-0.2/0.8] = 75\%$ of the observed treatment by region interaction and adjusting for age renders the treatment-by-region interaction non-significant, $p=0.50$.

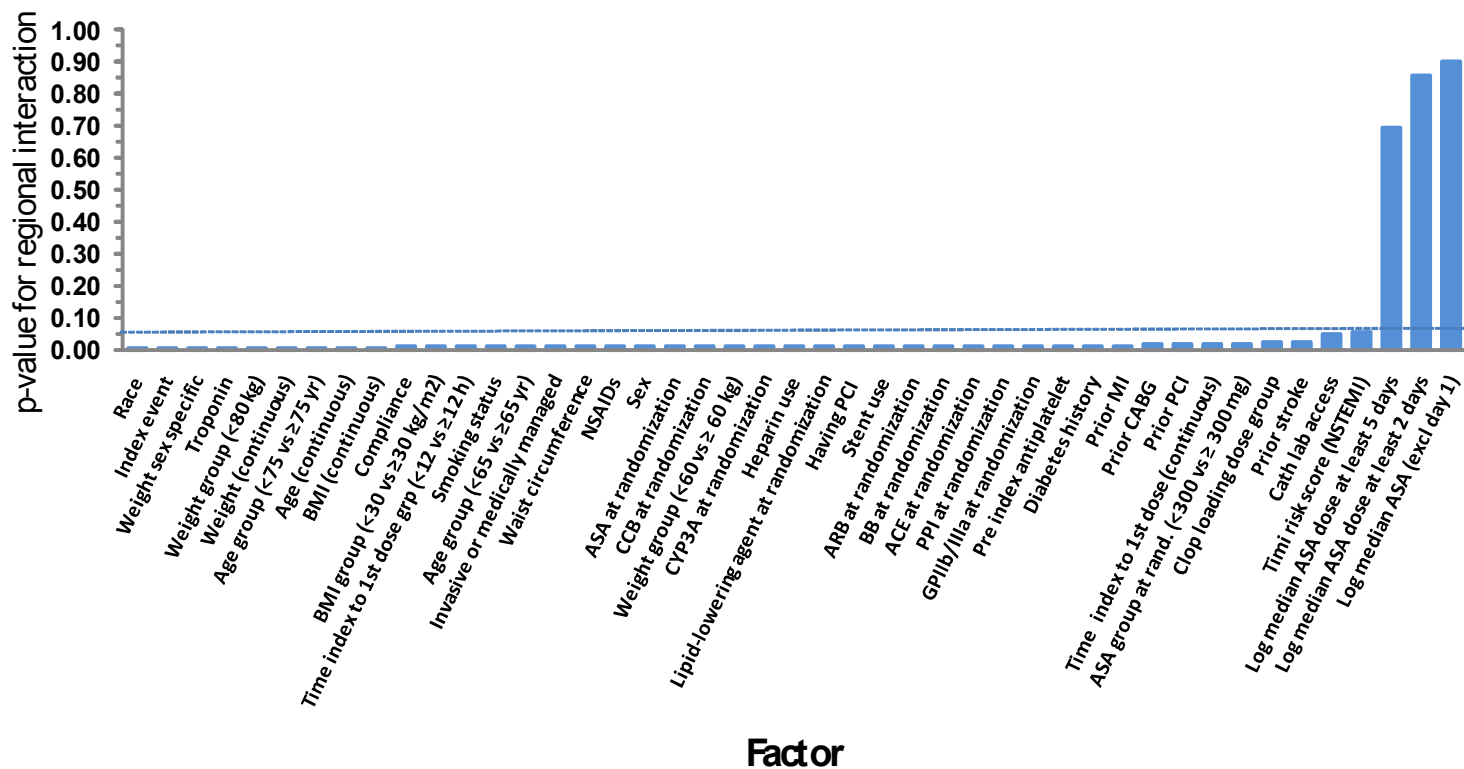
The results of this analysis are shown in [Figure 16](#) and [Figure 17](#). These figures show the extent to which a given factor explains the regional interaction and the extent to which a given factor alters the significance of the interaction, respectively.

Figure 16 **Extent to which individual factors explain the treatment-by-region interaction**



ACE Angiotensin converting enzyme; ASA Acetylsalicylic acid; ARB Angiotensin receptor blocker; BB Beta blocker; BMI Body mass index; CABG Coronary artery bypass grafting; CCB Calcium channel blocker; Clop Clopidogrel; CYP Cytochrome P; GPIIb/IIIa Glycoprotein IIb/IIIa inhibitor; NSAID Nonsteroidal anti-inflammatory drugs; NSTEMI Non-ST segment elevation myocardial infarction; PCI Percutaneous coronary intervention; PPI Proton pump inhibitor; TIMI Thrombolysis in Myocardial Infarction.

Figure 17 **Extent to which individual factors alter the significance of the treatment-by-region interaction**



ACE Angiotensin converting enzyme; ASA Acetylsalicylic acid; ARB Angiotensin receptor blocker; BB Beta blocker; BMI Body mass index; CABG Coronary artery bypass grafting; CCB Calcium channel blocker; Clop Clopidogrel; CYP Cytochrome P; GPIIb/IIIa Glycoprotein IIb/IIIa inhibitor; MI Myocardial infarction; NS Not significant; NSAID Nonsteroidal anti-inflammatory drugs; NSTEMI Non-ST segment elevation myocardial infarction; PCI Percutaneous coronary intervention; PPI Proton pump inhibitor; TIMI Thrombolysis in Myocardial Infarction.

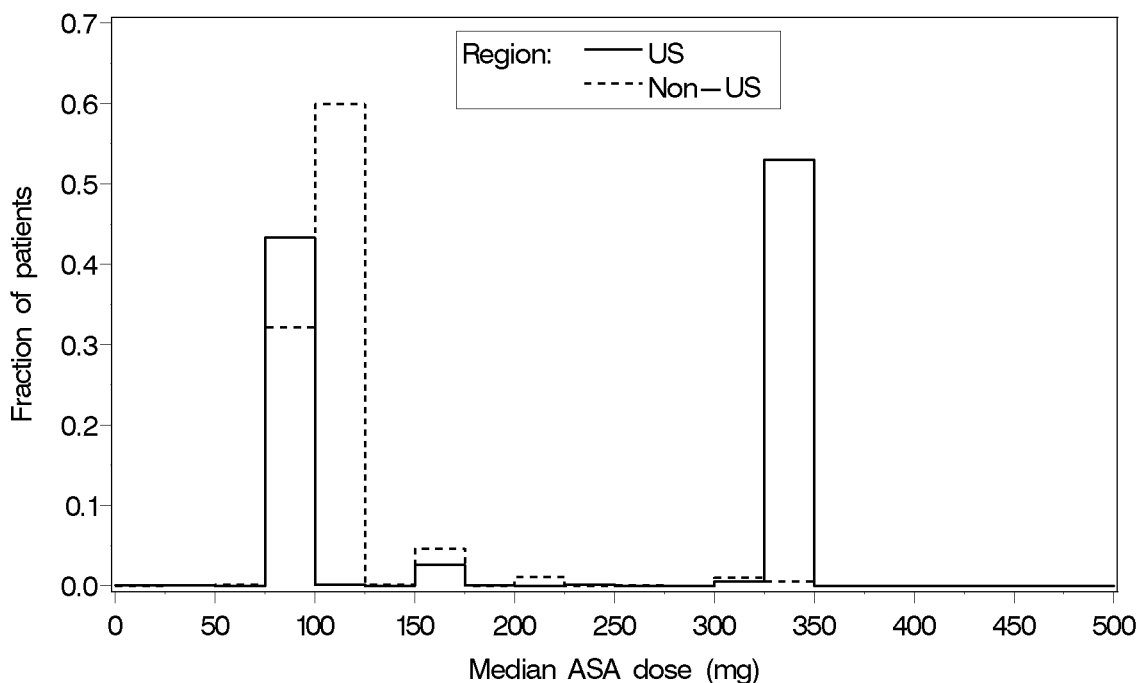
This analysis reveals that the observed treatment-by-region interaction effect was little changed, in terms of magnitude or significance, by the addition of any factor with the notable exception of median ASA maintenance dose. When added into the analysis, median ASA dose during therapy was found to account for between 80% to 100% of the observed interaction effect, depending on which definition of ASA dose was used; the observed interaction was therefore rendered non-significant when adjusted for the factor of ASA dose during therapy. These data suggest that median ASA dose may be responsible, at least in part, for the observed interaction between treatment and region (US vs non-US). In contrast, ASA dose on the day of randomization (ie, loading dose) accounted for only 9% of the observed regional interaction and, for example, stent use accounted for only 1% of the observed regional interaction.

Since qualitatively similar conclusions were supported using slightly different definitions for median ASA dose during therapy (shown by the 3 bars on the right side of each graph), further analyses presented in the following sections focus on the third definition, ie, ASA given from Day 2 of study drug and first primary event or cessation of randomized treatment for any reason. The rationale for this is that, this definition includes the maximum number of patients possible and because only the Day 1 (loading) dose is excluded, this may represent the most clinically relevant definition of maintenance ASA dosing.

Distribution of ASA dose across the US and non-US

A key question is why ASA dose during therapy emerges as the sole factor associated with the regional interaction. As can be seen in [Figure 18](#), evaluation of the distribution of maintenance ASA dose use shows a clear difference between the US and non-US regions. This provides some insight into why this factor, and no other, is so markedly associated with the observed regional interaction. The majority of non-US patients received median ASA doses of 75 mg or 100 mg, with the remainder (approximately 1250 patients) receiving ASA doses >100 mg. In contrast, just over half of US patients received a median ASA dose of 325 mg with the remainder receiving a median ASA dose of 81 mg.

Figure 18 ASA use in US and non-US regions by median dose category



ASA Acetylsalicylic acid; mg Milligrams; US United States.

Is ASA dose responsible for the treatment interaction seen in the US, or is it a marker for some other characteristic or aspect of clinical management?

The preceding analyses identified maintenance ASA dose as the only 1 of many characteristics evaluated that may provide an explanation for the treatment interaction observed in the US. An important question to consider is whether the association between ASA dose and the regional interaction is direct, or whether maintenance ASA dose is a marker for some other measured patient characteristic that is actually causing the treatment interaction.

Although it is of interest to look clinically and descriptively at demographic characteristics across the high and low-dose maintenance ASA groups, this process is made difficult by small subgroups and low numbers of events that can lead to inappropriate conclusions. To accurately determine if ASA maintenance dose or some other characteristic associated with ASA maintenance dose is independently associated with the treatment interaction, appropriate statistical analysis of the data is required. The preceding analyses that looked at the contribution of individual patient characteristics to the regional interaction confirmed that none, apart from ASA, played a role. As presented in the following section, this was confirmed via more complex multivariate analysis, which evaluated all factors simultaneously. The analysis also confirmed that no other factor evaluated was confounded with ASA dosing; otherwise it too would have been revealed in the analysis as explaining a large fraction of the regional interaction effect.

Multivariate and univariate analyses

Multivariate analysis in the full PLATO population: A multivariate analysis of the full PLATO patient population was conducted in order to investigate whether ASA dosing was independently associated with the observed regional interaction, or if it was associated with some other factor that could be driving the interaction. For a summary of these data, see [Appendix C, Section 2](#). While many factors were found to be prognostic for the primary endpoint, only ASA dose during therapy was found to be predictive of a qualitative differential treatment effect between ticagrelor and clopidogrel ($\chi^2=15.2127$, $p=0.0001$ for the median ASA dose by randomized treatment interaction).

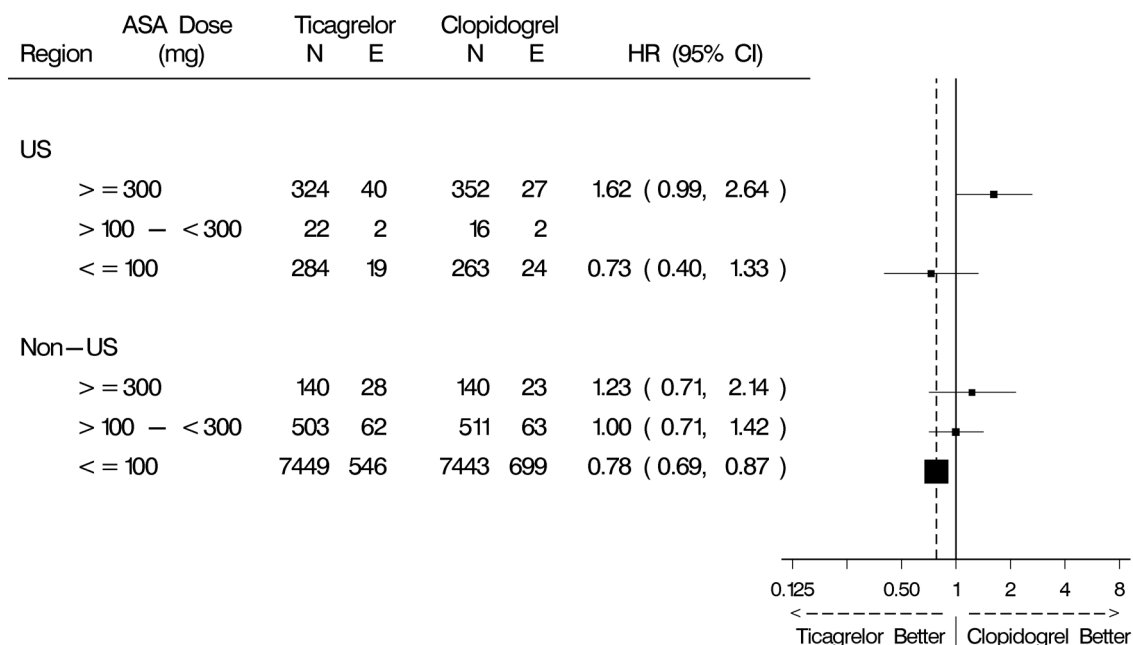
Univariate analysis in the non-US population: A univariate analysis was also conducted in the non-US patient group as an ‘independent’ dataset and reached the same conclusion—that ASA dose was associated with qualitatively differential efficacy of ticagrelor compared to clopidogrel. See [Appendix C, Section 3](#), for full results.

The possibility remains that the US observation is explainable by some factor associated with maintenance ASA dose that has not been considered and included in the analyses. However, based on extensive analyses of many demographic and clinical management factors that were captured in the study, maintenance ASA dose emerged as the 1 factor that appears to be playing a role in the observation.

Data by specific ASA dose categories in US and non-US patients

[Figure 19](#) shows data from the univariate analysis conducted in the US and non-US by ASA dose group. Both the US and non-US patient cohorts show a numerical trend toward an improving HR for ticagrelor compared with clopidogrel as ASA dose reduces. While CIs are wide, the HR in the low-dose US group (HR 0.73, 95% CI 0.44, 1.33) reflects that seen in the low-dose non-US group (HR 0.78, 95% CI 0.69, 0.87).

Figure 19 ICAC-adjudicated primary endpoint by ASA dose category and treatment for US and non-US



In this analysis, ASA dose was calculated based on ASA given from Day 2 of study drug and first of a primary event or cessation of randomized treatment for any reason (therefore excluding the ASA loading dose on Day 1 of randomization).

ASA Acetylsalicylic acid; CI Confidence interval; E Events; HR Hazard ratio; N Number of patients.

8.8.2.4 Quantification of the relationship between relative efficacy of ticagrelor:clopidogrel and ASA dosing on a continuum

In [Figure 19](#), ASA dose is evaluated based on a simple categorization of ASA dose as ≤100 mg, >100 to <300 mg and ≥300 mg. While the majority of patients in the non-US group received ASA doses of 100 mg or less, there were still approximately 1250 patients who received ASA doses >100 mg in the non-US dataset and thus, combined with data from the US group, information can be extracted across the entire ASA dose range for the full patient population to make for a more efficient and informative analysis of these data.

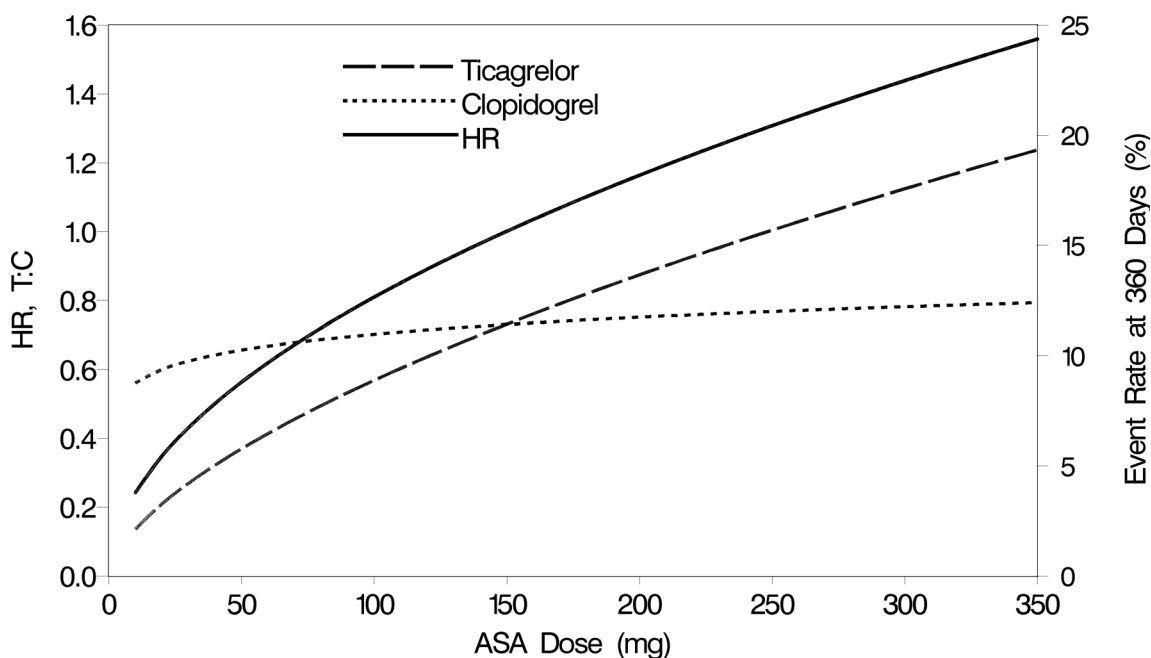
A further analysis of the primary endpoint was therefore conducted based on the actual ASA dose patients took as a continuous (as opposed to categorized) variable, along the full ASA dose continuum. The aim of these analyses was to quantify the relationship between median ASA dose and (i) the HR, ticagrelor:clopidogrel, and (ii) the yearly event rates on ticagrelor and clopidogrel, separately.

This analysis showed that the HR was associated with ASA dose such that, as ASA dose increases, the HR also increases, being progressively less in favor of ticagrelor ([Figure 20](#)). The estimated primary endpoint event rates by treatment arm suggest that the increased HR

with increasing ASA dose is due to a more rapidly increasing event rate in ticagrelor patients as compared to clopidogrel patients.

These data indicate that clopidogrel may also be associated with an increased event rate at higher doses of ASA, but the increase is to a sufficiently greater extent with ticagrelor as to cause a transition from <1 to >1 in the HR at approximately 150 mg ASA (Figure 20).

Figure 20 Analysis of the primary endpoint by ASA dose as a continuous variable – PLATO full analysis set

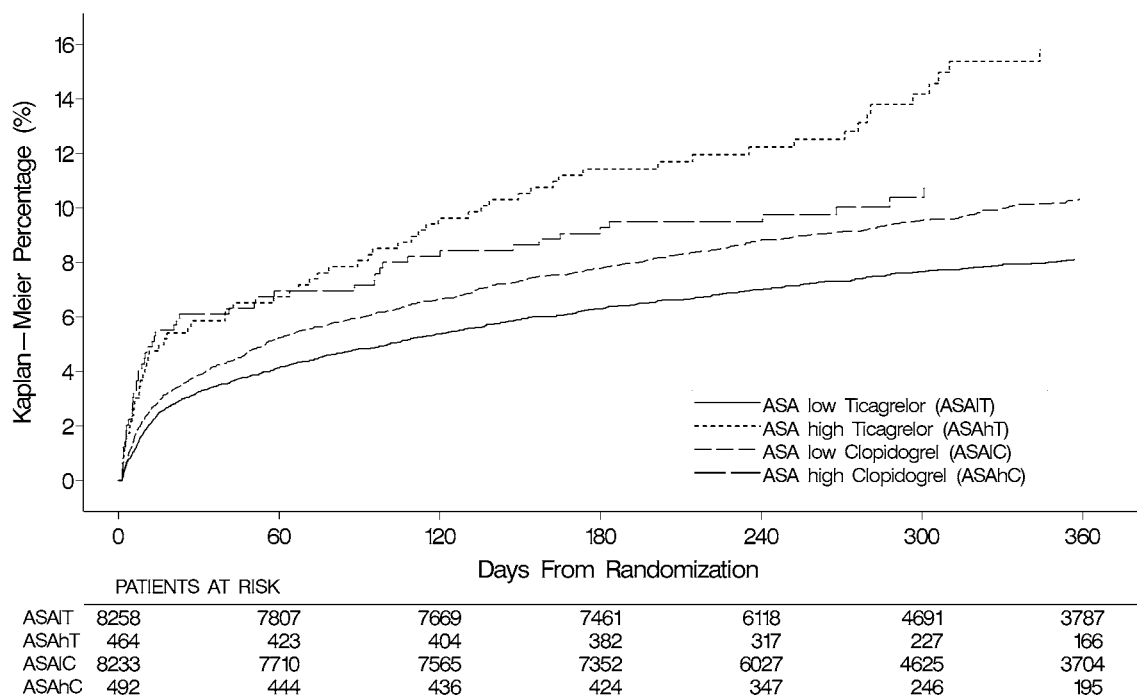


In this analysis, ASA dose was calculated based on ASA given from Day 2 of study drug and first of a primary event or cessation of randomized treatment for any reason (therefore excluding the ASA loading dose on Day 1 of randomization).

ASA Acetylsalicylic acid; C Clopidogrel; HR Hazard ratio; T Ticagrelor.

A Kaplan-Meier plot of the primary endpoint by ASA dose category (with high dose defined as median daily dose of ≥ 300 mg and low-dose defined as median daily dose of <300 mg) reflects the analysis in Figure 20, illustrating that clopidogrel has an increased event rate at higher ASA doses, although, as in the analyses above, the increase is numerically less than the corresponding increase seen with ticagrelor (Figure 21).

Figure 21 **Kaplan-Meier plot of ICAC-adjudicated primary endpoint by treatment group and ASA dose category – PLATO full analysis set**



High-dose ASA defined as median daily dose of ≥ 300 mg.

Low-dose ASA defined as median daily dose of < 300 mg.

In this analysis, ASA dose was calculated based on ASA given from Day 2 of study drug and first of a primary event or cessation of randomized treatment for any reason (therefore excluding the ASA loading dose on Day 1 of randomization).

ASA Acetylsalicylic acid; ICAC Independent Central Adjudication Committee.

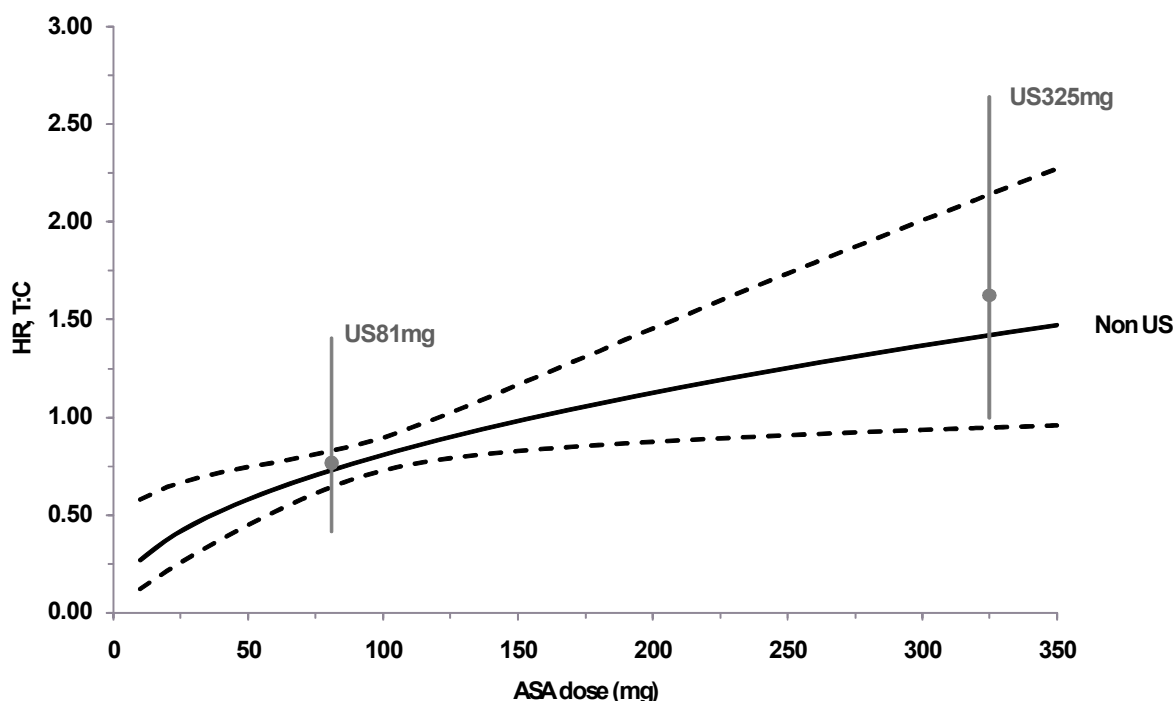
8.8.2.5 Predicting US outcome from ‘independent’ non-US data

It is interesting to consider the relationship between the HR and ASA dose in the non-US cohort and, thinking of this as ‘independent’ dataset (ie, the population in which the treatment interaction was not observed), to examine to what extent the outcome in the US subgroup might have been predicted by these independent data.

Figure 22 shows the HR as a function of ASA dose in non-US patients. Recalling that the predominant ASA doses in the US subgroup were 81 and 325 mg, when the results in these 2 US dose groups are superimposed, the HRs actually observed in the US subgroup lie within the range of what might be predicted from the ‘independent’ non-US data.

This observation—that there is a relationship between ASA dose and efficacy in a population of patients outside of the US, and, in this population, the expected HR at higher and lower ASA doses is in line with that actually seen in the US cohort—lends further credibility to ASA dose being a possible contributor to the US observation.

Figure 22 Analysis of the primary endpoint by ASA dose as a continuous variable: extent to which US outcomes are predictable by non-US data



In this analysis, ASA dose was calculated based on ASA given from Day 2 of study drug and first of a primary event or cessation of randomized treatment for any reason (therefore excluding the ASA loading dose on Day 1 of randomization).

ASA Acetylsalicylic acid; C Clopidogrel; HR Hazard ratio; T Ticagrelor.

8.8.2.6 Conclusions on evaluation of treatment-by-region interaction

Although the US observation may be due to play of chance, the implications of this observation may be important. Further analysis of the data suggest that the observation may be due to differences in the level of ASA maintenance dose between regions, where the efficacy of ticagrelor is highest when co-administered with low maintenance doses of ASA. The majority of PLATO patients received such low maintenance doses of ASA as recommended in the protocol. The overall trial result is the best estimate of the true treatment effect, providing clear evidence of a reduction in the combined endpoint of CV death, MI or stroke for ticagrelor over clopidogrel. The analyses by region and ASA dose provide guidance for the appropriate usage of ticagrelor in combination with ASA. Acknowledging that these insights come from post-hoc analyses, these data show a lower event rate for ticagrelor compared to clopidogrel for all patients, both in the US and non-US, when taken with low ASA maintenance doses. This forms the basis for the recommendation for routine usage of ticagrelor with low dose ASA in ACS.

8.8.3 Impact of ASA dose on ticagrelor safety

A post-hoc analysis of the impact of region and ASA dose on ticagrelor safety was conducted and is presented in Section 9.5 so that the data can be evaluated in the context of the overall safety profile.

8.8.4 Potential interaction between ASA dose and P2Y₁₂ inhibitors

The finding of an increased event rate with increasing ASA dose was observed with ticagrelor and—to a lesser extent—with clopidogrel treatment. This observation raises a question regarding an impact of ASA treatment on the efficacy of concomitant P2Y₁₂ inhibitors. This hypothesis is undergoing investigation in a series of non-clinical mechanistic studies. Additional possibilities, including potential DDIs and off-target (P2Y₁₂-independent effects) have also been investigated.

8.8.4.1 Mechanistic investigations of a potential interaction between ASA dose and P2Y₁₂ inhibitors

Because of the results of the exploratory analysis of treatment interactions reported here, external global experts in the area of ASA-related research were consulted to help explore possible mechanisms for the observations. With the aid of their recommendations, a series of studies was designed and implemented to explore the mechanism(s) involved in a potential interaction between P2Y₁₂ inhibitors and ASA. These studies can be grouped into those that are related to: (1) potential direct effects (effects mediated by P2Y₁₂ receptor blockade in the presence of high- and low-dose ASA), (2) potential off-target effects (effects mediated by processes independent of P2Y₁₂ receptor blockade by ticagrelor or clopidogrel, or effect modification by ASA), and (3) effects that are related to PK (potential DDIs between ASA and ticagrelor or clopidogrel).

Off-target or drug-drug interactions

Studies have been conducted to investigate a role for DDIs or off-target (P2Y₁₂-independent) effects playing a role in the apparent relationship between ASA dose and P2Y₁₂ inhibitor efficacy. The results of these studies failed to support a role for off-target effects or DDIs in the observed impact of ASA.

- There were no previous data from preclinical pharmacology studies that could explain why specifically ticagrelor could be less effective with concomitant administration of high-dose ASA. Drug interaction studies have been conducted with ticagrelor and ASA, and no effects were observed on ticagrelor PK or PD, measured as IPA. In addition, an *in vivo* study in dogs was conducted to investigate the effects of ticagrelor and clopidogrel on aspirin PK. Both ticagrelor and clopidogrel induced a small increase in aspirin exposure. However, the increase was similar for both compounds; therefore, a drug-drug interaction with aspirin is unlikely to be a contributor to any differential effects of the 2 agents.

- Tests of the activity of ticagrelor, ticagrelor active metabolite, prasugrel active metabolite, and clopidogrel inactive metabolite against a panel of receptors and enzymes indicate that potential off-target interactions do not play a role in the potential interaction between clopidogrel or ticagrelor and ASA.

Hypothesis regarding potential mechanism for interaction between ASA and P2Y₁₂ inhibitor efficacy

Data suggest that when a high degree of P2Y₁₂ inhibition is achieved (ie, by ticagrelor, prasugrel, or high clopidogrel response), thromboxane (TXA₂)-dependent pathways of platelet activation are potently and consistently inhibited even in the absence of ASA. This gives rise to a hypothesis that ASA, especially at high doses, would not further improve platelet inhibition, but the additional dose-dependent reduction in prostacyclin (PGI₂) levels could leave unopposed the thrombogenic and vasoconstrictive effect of ASA therapy. When a lower degree of P2Y₁₂ inhibition exists (ie, low-to-medium clopidogrel response), TXA₂ pathways are not potently inhibited. Thus, ASA can further improve platelet inhibition and thus to some extent counterbalance the detrimental effect on PGI₂ levels (ie, the net effect would be a decrease in the relative risk of thrombus formation). However since the antiplatelet effect of ASA will reach maximum at relatively low doses, the reduction in PGI₂ levels by higher ASA doses cannot be counterbalanced and this negative effect should be equal regardless of P2Y₁₂ antagonist used.

***In vitro* platelet study**

An *in vitro* study using human platelets has been conducted to test the hypothesis described in the preceding paragraph. The objective was to evaluate the overall antiplatelet effect of different levels of P2Y₁₂ inhibition by either the ticagrelor active metabolite or prasugrel active metabolite, the pharmacological properties of which are considered to be identical to those of clopidogrel active metabolite, or by concentrations of ASA alone and in combinations. ASA concentrations were chosen to mimic exposures after high- and low-“dose” ASA clinically. The results are consistent with the previously stated hypothesis: it was observed in platelet rich plasma that (1) high-level P2Y₁₂ inhibition, besides inhibition of ADP-induced aggregation, also provides inhibition of TXA₂-dependent pathways of platelet activation in the absence of ASA; (2) ASA was unable to compensate for suboptimal inhibition of ADP-induced aggregation; (3) ASA added much greater antiplatelet effect when combined with suboptimal P2Y₁₂ inhibition; (4) in these *in vitro* assays, ticagrelor and prasugrel active metabolite behaved similarly. Thus, the effects seen appear to be a class effect related to the level of P2Y₁₂ inhibition and not to the P2Y₁₂ antagonist used; and (5) high-“dose” ASA did not add additional antiplatelet effect compared with low-“dose” ASA.

***In vivo/ex vivo* Folts dog model**

To further evaluate the hypothesis in an animal model, the Folts dog model of arterial thrombosis was used. Using this model, platelet-dependent thrombus formation was visualized as cyclic blood flow reductions in the stenosed/damaged femoral artery. In parallel, the blood flow was also monitored in the control leg and the local peripheral resistance in both legs were calculated (arterial blood pressure/femoral artery blood flow). In addition *ex vivo*

platelet function was evaluated by a panel of agonists. The results are consistent with the proposed hypothesis. It was observed in this *in vivo* model that (1) high-level P2Y₁₂ inhibition, besides inhibition of *ex vivo* ADP-induced aggregation, also provided inhibition of *ex vivo* TXA₂-dependent pathways of platelet activation in the absence of ASA; (2) high-dose ASA added additional antithrombotic and antiplatelet effect when combined with sub-maximal levels of P2Y₁₂ inhibition; (3) high-dose ASA induced an increase (10%) in peripheral vascular resistance, an effect potentially due to reduced PGI₂ levels. This potential reduction in PGI₂ levels did not translate to a pro-thrombotic effect in this model, as visualized by a restoration of thrombus formation when high-dose ASA was combined with high level P2Y₁₂ inhibition; (4) in this *in vivo* study, equipotent P2Y₁₂ inhibitory concentrations of ticagrelor and clopidogrel behaved similarly. Thus, the effects seen appear to be a class effect related to the level of P2Y₁₂ inhibition and not to the P2Y₁₂ antagonist used.

Conclusions on mechanistic explorations

The results of mechanistic studies conducted have failed to support a role for off-target effects or DDIs in the observed impact of ASA.

The *in vitro* and *in vivo* experiments summarized above support the following potential mechanism:

- High-level P2Y₁₂ antagonism can inhibit both ADP-dependent and platelet TXA₂-dependent pathways of platelet activation independently of ASA.
- ASA dose-dependently inhibits TXA₂ synthesis, which reaches maximum effect at relatively low doses.
- However, ASA does not contribute to inhibition of ADP-dependent pathways of platelet activation.
- Therefore, ASA will add antiplatelet benefit predominantly when combined with suboptimal P2Y₁₂ inhibition, but will have only minor positive impact when combined with optimal P2Y₁₂ inhibition.
- ASA reduces PGI₂ levels dose-dependently which could, particularly at high doses, negatively affect endothelial function, potentially facilitate platelet activation, and ultimately contribute to increased thrombotic risk.

These mechanistic data are limited by the use of an animal model and human platelets *in vitro*, rather than evaluating an *in vivo* ACS environment. While these mechanistic results cannot explain the PLATO regional interaction, they do support a differential effect of ASA in the presence of partial versus near-complete P2Y₁₂ blockade, and are consistent with (1) high-dose ASA associating with higher event rates and (2) the reduced relative benefit of ticagrelor vs clopidogrel with increasing ASA dose.

8.9 Overall efficacy conclusions

In PLATO, ticagrelor was shown to be superior to clopidogrel in reducing the rate of the primary efficacy endpoint of CV death, MI, or stroke after ACS events (relative risk reduction [RRR] 16%, absolute risk reduction [ARR] 1.9%, hazard ratio [HR] 0.84 [95% CI 0.77, 0.92]; $p=0.0003$). Based on this ARR, treating 54 patients with ticagrelor instead of clopidogrel for 12 months will prevent 1 patient from having a major adverse cardiovascular event. The secondary efficacy analyses indicate that the effect of ticagrelor is robust with regard to modifications in the efficacy endpoint and in the individual components of CV death and MI, but not stroke. The reduction in CV death favoring ticagrelor over clopidogrel in PLATO, an active-control trial, is notable both for its clinical importance and its rarity as a trial result. Ticagrelor prevented 1 CV death for every 91 patients treated with ticagrelor instead of clopidogrel for 12 months. Although only nominally significant based on the prespecified testing order, ticagrelor reduced all-cause mortality compared to clopidogrel. Ticagrelor reduced the rate of the primary composite endpoint events, compared to clopidogrel, in patients intended to be managed medically or with an invasive strategy and reduced the rate of stent thrombosis. An analysis of the primary endpoint over time demonstrates that the treatment effect of ticagrelor is established to 12 months. The benefit of ticagrelor vs clopidogrel was maintained across the majority of subgroups, indicating consistency of effect. The PLATO results are broadly applicable to the ACS population and a range of treatment pathways.

One possible exception to the consistency of effect across subgroups relates to geographic region where there was statistical evidence of a treatment-by-region interaction (interaction p value=0.045). For patients in 3 regions (Europe, Middle East and Africa; Asia and Australia; Central and South America) ticagrelor performed better than clopidogrel, whereas, in the North America region, accounting for 10% of patients in the trial, patients did numerically better on clopidogrel than on ticagrelor. Given the number of interaction tests performed in PLATO, the play of chance alone could account for this apparent regional difference. Nevertheless, the data were extensively examined to ascertain if there were any issues in trial conduct or patient management or any imbalances in prognostic characteristics that could potentially account for the apparent difference in outcomes between regions. Further analyses of the data suggest that the regional interaction may be due to differences in the pattern of ASA used as maintenance dose between regions. The data suggest the efficacy of ticagrelor is highest when co-administered with low maintenance doses of ASA. The majority of patients in PLATO received low maintenance doses of ASA, as recommended in the protocol. These analyses provide guidance for the appropriate usage of ticagrelor in combination with ASA. Although these insights come from post-hoc analyses, these data show a lower event rate for ticagrelor compared to clopidogrel for all patients, both in the US and non-US, when taken with low ASA maintenance doses. This forms the basis for the recommending usage of ticagrelor with low dose ASA in ACS patients. The overall PLATO trial result is the best estimate of the true treatment effect, providing clear evidence of a reduction in the combined endpoint of CV death, MI or stroke with ticagrelor compared to clopidogrel.

9. CLINICAL SAFETY

The size and scope of the ticagrelor development program allowed for a thorough characterization of ticagrelor's adverse effect profile. In PLATO, 9235 patients received ticagrelor, with over 6300 patient-years of exposure. The majority of patients (55.6%) in the safety analysis set had a duration of exposure >9 months (270 days). The mean exposure for ticagrelor-treated patients was 246 days (median 276 days) and 250 days (median 278 days) for clopidogrel. The duration of treatment generally ranged from 6 to 12 months with planned study completion at 6, 9 and 12 months depending on the accrual of study endpoints and on the date patients entered the study, ie, patients that entered towards the end of the enrollment period had shorter durations of treatment.

The 4 Phase II studies, which ranged from 4 to 12 weeks in duration, included 960 ticagrelor-treated patients (in all dose groups) and 498 clopidogrel-treated patients in the safety population. In the Phase II studies, the mean exposure for patients taking the ticagrelor 90 mg bid dose was 44.4 days (median 39 days), compared to a mean exposure of 45.2 days (median 37 days) for patients taking clopidogrel 75 mg qd.

The PLATO study focused on patients with ACS (UA, NSTEMI or STEMI), including patients managed medically, as well as those managed with PCI or CABG; Phase II studies included patients with CAD or ACS. The population studied included patients ≥ 75 years of age and patients with a diverse range of medical conditions at study entry (including heart failure, diabetes, and renal impairment). Thus, the safety evaluation of ticagrelor is both broadly inclusive of a diverse patient population and representative of the target disease population.

9.1 Bleeding

Bleeding constitutes the most common, clinically significant safety concern during effective antiplatelet treatment. Inherent to their PD effects, antiplatelet agents increase the risk of bleeding. Thus the goal with any new antiplatelet regimen is to balance antithrombotic efficacy benefit against the inherent risk of bleeding.

The primary safety endpoint measured the time to first occurrence of any total major bleeding event using PLATO definitions. PLATO bleeding severity definitions evolved from those used in the CURE study (Mehta et al 2000, Yusuf et al 2001). These definitions were chosen as an inclusive and clinically relevant measure suitable for assessing bleeding events whether or not associated with surgery or another medical procedure. PLATO definitions characterize bleeding in both the acute and chronic settings in both invasive and medical management contexts. Compared with either the Thrombolysis in Myocardial Infarction – a cardiology clinical trials study group (TIMI) (Wiviott et al 2006) or GUSTO definitions (GUSTO 1993), PLATO definitions feature lower thresholds to capture bleeding events during both acute and chronic phases of ACS. For example, the hemoglobin decrease threshold for PLATO 'Major' bleeding, 3 g/dL, is lower than that for TIMI 'Major' bleeding, 5 g/dL, and matches that for TIMI 'Minor' bleeding (Table 18). Also, note that TIMI Major criteria resemble PLATO

‘Major Fatal or Life-threatening’ criteria; TIMI Minor criteria resemble PLATO ‘Major Other’ criteria; and TIMI Major + Minor resembles PLATO ‘Major’.

The PLATO-defined bleeding scale addresses an important element of the TIMI bleeding scale in which bleeding events cannot be assessed if hematology laboratory testing was not performed. For completeness of evaluation, bleeding events reported in PLATO were also mapped onto the TIMI scale by applying an algorithm to the bleeding events. Thus PLATO expresses bleeding results as PLATO-defined adjudicated events. [Table 18](#) provides a full comparison of TIMI and PLATO definitions. Providing key bleeding data according to both definitions allows a clinically meaningful comparison of ticagrelor and clopidogrel within the study.

Table 18 Comparison of definitions between the PLATO and TIMI bleeding severity scales

PLATO scale ^a		TIMI scale ^b
PLATO-defined Major Fatal/Life threatening Any 1 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 hemoglobin of more than 5 g/dL * Transfusion of 4 or more units (whole blood or packed red blood cells) for bleeding		TIMI-defined Major Intracranial, or Clinically significant overt signs of hemorrhage associated with a drop in hemoglobin of > 5 g/dL (or, when hemoglobin is not available, an absolute drop in hematocrit of > 15%) ^c NOTE: TRITON used ≥ 5 g/dL NOTE: Not all fatal or life-threatening etc bleeds are included in the TIMI-Major category.
		TIMI-Life threatening A subset of TIMI-Major that meets any of the following: is fatal; leads to hypotension requiring treatment with intravenous inotropic agents; requires surgical intervention for ongoing bleeding; necessitates the transfusion of 4 or more units of blood (whole blood or packed red blood cells) over a 48-hour period; is a symptomatic intracranial hemorrhage
PLATO-defined Major Other Any 1 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 packed red blood cells) for bleeding.		TIMI-defined Minor Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin of 3 to ≤ 5 g/dL (or, when hemoglobin is not available, a fall in hematocrit of 9 to $\leq 15\%$) ^c NOTE: TRITON used 3 to <5 g/dL
PLATO-defined Minor Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).		TIMI-defined Minimal Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin <3 g/dL (or, when hemoglobin is not available, a fall in hematocrit of <9%) ^c
PLATO-defined Minimal All others not requiring intervention or treatment		-

^a Based on Yusuf et al 2001 for PLATO bleeding scale.

^b TIMI-scale : from "TIMI definitions" at <http://www.timi.org/> (Wiviott et al 2006)

^c Hemoglobin change adjusted for units of blood transfused.

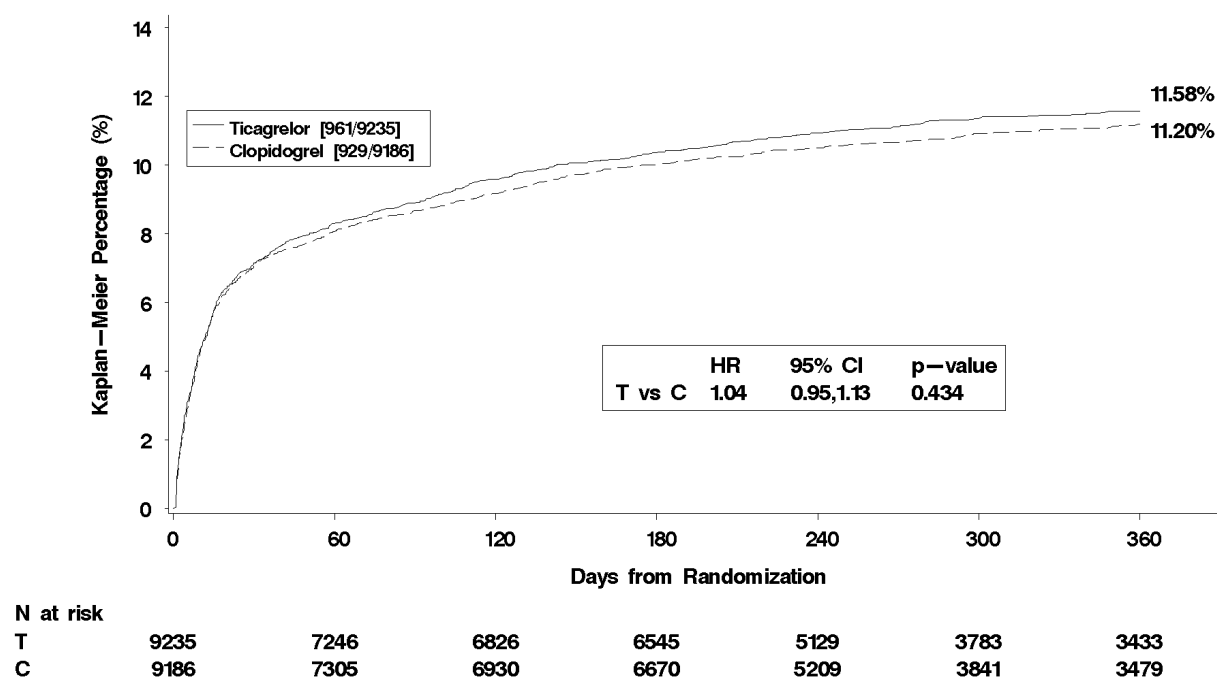
Note: Any PLATO Major Fatal/Life-threatening bleed was considered to be a TIMI Major Fatal/Life-threatening bleed unless 1) it did not qualify as a TIMI Major bleed, which is to say that the largest drop in hemoglobin, after adjustment for prior transfusion, was ≥ 5 g/dL; or 2) The sole criterion for PLATO Major Fatal/Life-threatening was "Intrapericardial bleed with cardiac tamponade".

Bleeding is presented in the 2 dimensions of context and severity. The context dimension has categories such as procedural - including CABG, PCI, angiography and other procedure - and non-procedural, a “spontaneous” bleeding event. The severity dimension classifies bleeding events as fatal, life-threatening, other major, minor or minimal. In addition, bleeding events are presented by anatomic location.

9.1.1 PLATO primary safety endpoint (‘Total Major’ bleeding)

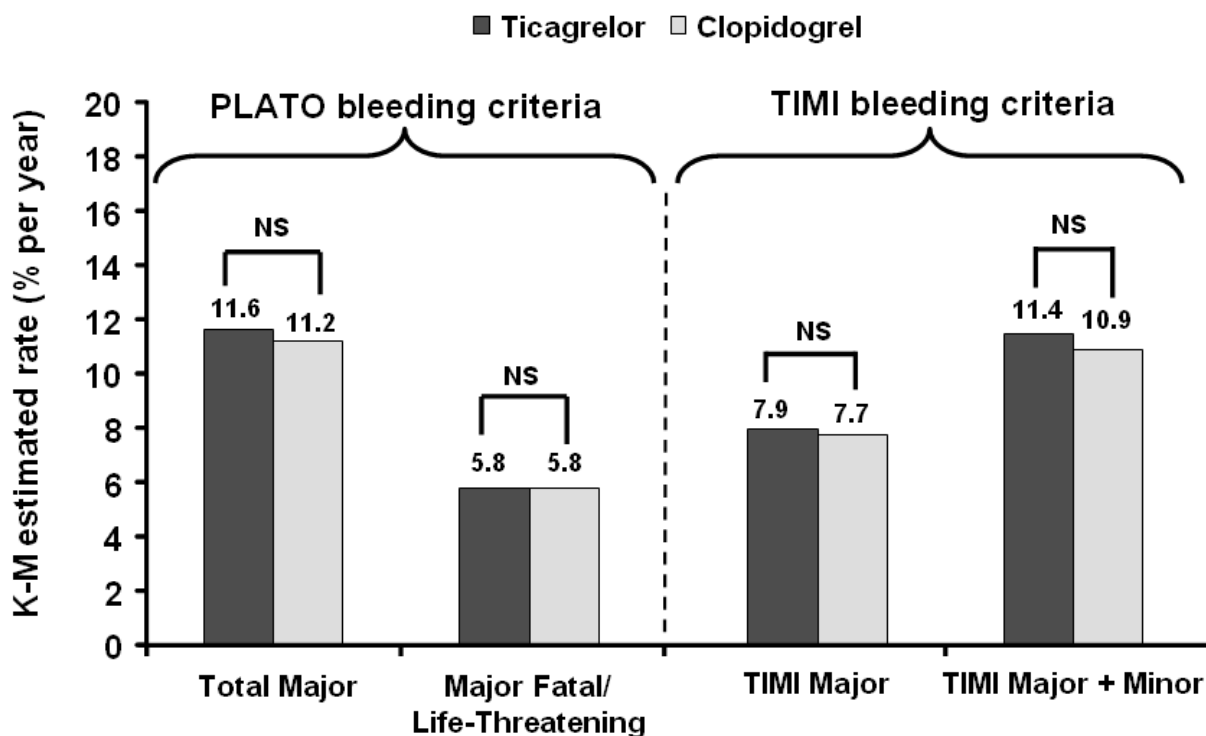
For the primary safety endpoint in PLATO, there was no significant difference in ‘Total Major’ bleeding, including fatal and life-threatening bleeding (Figure 23). When bleeding was assessed using 2 different bleeding scales (PLATO-defined ‘Total Major’ and TIMI-defined similar bleeding events), the results were consistent (Figure 24).

Figure 23 Kaplan-Meier estimate of time to first PLATO-defined ‘Total Major’ bleeding event



C Clopidogrel; CI Confidence interval; HR Hazard ratio; IP Investigational product; KM% Kaplan-Meier estimate of % of patients with an event at 12 months; T Ticagrelor.

Figure 24 Major bleeding in the PLATO study: PLATO and TIMI criteria



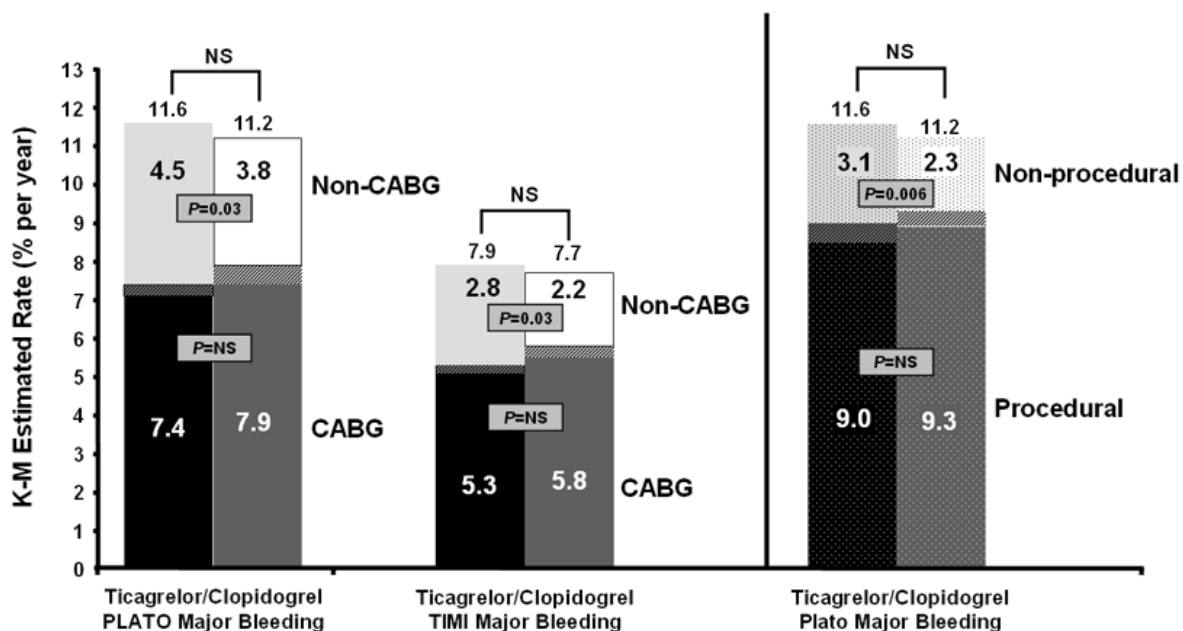
K-M Kaplan-Meier estimate of % of patients with an event at 12 months; NS Not significant; TIMI Thrombolysis in Myocardial Infarction – a cardiology clinical trials study group.

9.1.1.1 ‘Total Major’ bleeding by context

PLATO showed that ‘Total Major’ bleeding during ticagrelor treatment did not differ significantly from that with clopidogrel treatment, although statistically significant differences emerge when examined by clinical context, such as in non-CABG and non-procedural bleeding (Figure 25).

Approximately 80% of ‘Major’ bleeding was procedure-related bleeding, and 67% of ‘Major’ bleeding was CABG-related bleeding. The increased non-CABG and non-procedural bleeding reported with ticagrelor compared to clopidogrel appears in the less severe bleeding categories (Section 9.1.3). Removal of CABG-related bleeding from the analysis may bias the results by ignoring the multifactorial clinical impact of bleeding, transfusions and loss of red cell mass on ACS patients, including hypovolemia and its ensuing potential hemodynamic instability, increased incidence of wound infection, prolonged hospitalizations, and post-operative morbidity. It also ignores a potential treatment impact on CABG incidences during the trial, biasing against a treatment associated with fewer subsequent CABG procedures. A full assessment of the impact of bleeding associated with antiplatelet agents best includes both CABG and non-CABG bleeding.

Figure 25 Major bleeding: CABG and non-CABG; procedural and non-procedural



Patients may be counted in more than 1 bleeding event category. The hatched areas in the middle of the columns represent patients with both a CABG bleed and a non-CABG bleed, or both a procedural bleed and a non-procedural bleed.

CABG Coronary artery bypass graft; K-M Kaplan-Meier estimate of % of patients with an event at 12 months; NS Not significant.

9.1.1.2 Subgroup analysis for 'Total Major' bleeding

In a prespecified subgroup analysis of the bleeding events, there was consistency of the results across a range of subgroups including age, weight, gender, and other subgroup baseline and clinical characteristics – prior TIA/stroke does not appear in figures. No specific subgroups have been identified as having an increased risk of bleeding with ticagrelor. Few treatment by factor interactions, indicating differential treatment effect between subgroups, reached significance at the $p < 0.05$ level. For 'Total Major' bleeding, body mass index (BMI) had a nominally significant interaction ($p = 0.0465$) (refer to [Figure 1 in Appendix D](#)), with BMI < 30 kg/m² favoring ticagrelor.

A similar result – no particular subgroup at greater risk than any other – exists for non-CABG or non-procedural Major bleeding (refer to [Figure 2 in Appendix D](#)). Among patient subgroups of interest, the elderly, women, and those of lower body weight, there were no more increase in risk of non-CABG or non-procedural Major bleeding with ticagrelor relative to clopidogrel compared to their complementary subgroups, ie, the younger, men and those of higher body weight. History of PCI at randomization, beta blocker use, or any of the other categories explored, did not demonstrate any characteristic that could predict treatment differential non-CABG or non-procedural bleeding. Therefore these data do not identify any

subgroup of patients that is at greater relative risk compared to other subgroups for treatment differential non-CABG or non-procedural bleeding.

9.1.2 Fatal and ‘Fatal/Life-threatening’ bleeding

The PLATO study also demonstrated that Fatal and ‘Fatal/Life-threatening’ bleeding events were generally similar for ticagrelor and clopidogrel overall and within each clinical context (Table 19).

Table 19 Fatal and Fatal/Life-threatening bleeding events by clinical context - PLATO

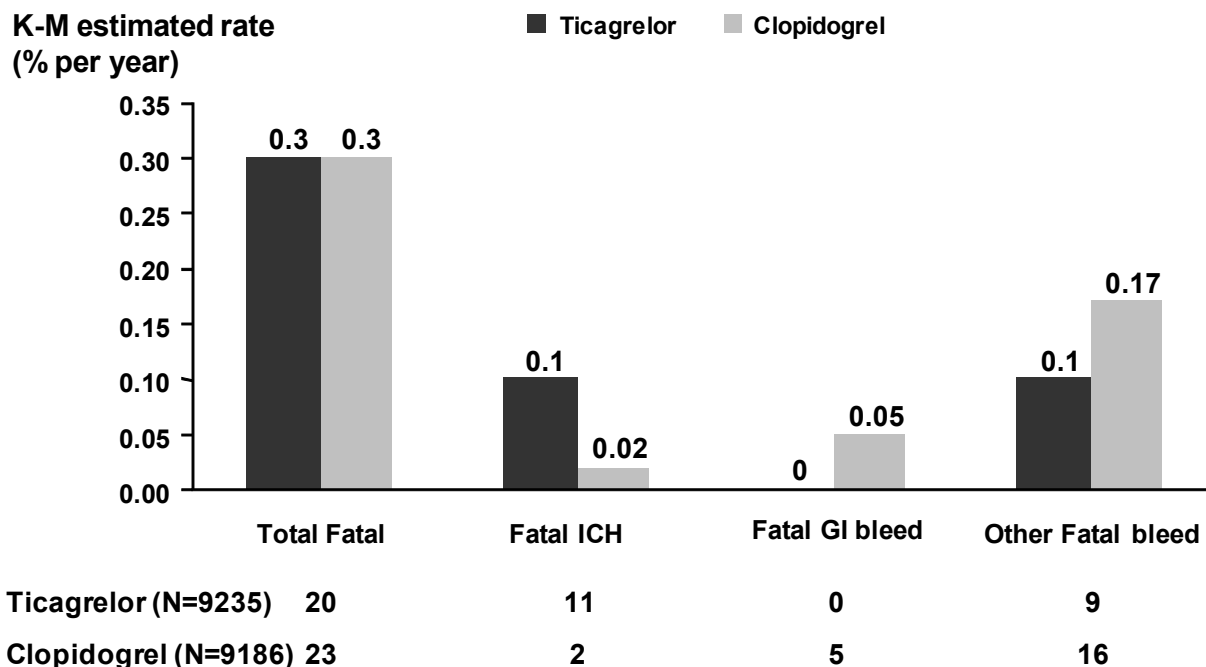
Characteristic	Ticagrelor 90 mg bid N=9235	KM%	Clopidogrel 75 mg qd N=9186	KM%	Hazard ratio (95% CIs)	p-value
Fatal	20 (0.2%)	0.3%	23 (0.3%)	0.3%	0.87 (0.48, 1.59)	0.6553
CABG	6/770 (0.8%)	0.9%	6/814 (0.7%)	0.9%	1.06 (0.34, 3.30)	0.9155
Non-CABG	15 (0.2%)	0.2%	16 (0.2%)	0.2%	0.94 (0.47, 1.90)	0.8663
Non-procedural	13 (0.1%)	0.2%	12 (0.1%)	0.2%	1.09 (0.50, 2.38)	0.8331
Fatal/Life-threatening	491 (5.3%)	5.8%	480 (5.2%)	5.8%	1.03 (0.90, 1.16)	0.6988
CABG	329/770 (42.7%)	46.9%	341/814 (41.9%)	46.9%	1.04 (0.90, 1.21)	0.5956
Non-CABG	171 (1.9%)	2.1%	151 (1.6%)	1.9%	1.14 (0.91, 1.41)	0.2516
Non-procedural	103 (1.1%)	1.3%	95 (1.0%)	1.2%	1.09 (0.82, 1.44)	0.5456

Patients may be counted in more than 1 bleeding event category (eg, some patients had both CABG and non-CABG events).

bid Twice daily dosing; CABG Coronary artery bypass grafting; KM% Kaplan-Meier estimate of % of patients with an event at 12 months; qd Once daily dosing.

Fatal bleeding events represent a small proportion of the total deaths that occurred during the PLATO study (20/408 for ticagrelor and 23/505 for clopidogrel). In the ticagrelor group, more than half of the Fatal bleeding events were associated with intracranial hemorrhage (ICH), whereas in the clopidogrel group those Fatal bleeding events occurred over a broader range of locations and clinical contexts (Figure 26).

Figure 26 Total fatal bleeding events in PLATO



For the 2 clopidogrel fatal ICH cases, 1 was a fatal non-procedural ICH (D5130C05262/E4102025) and 1 was a fatal procedural ICH (D5130C05262/E3801001).

GI Gastrointestinal; ICH Intracranial hemorrhage; K-M Kaplan-Meier estimate of % of patients with an event at 12 months.

9.1.2.1 Intracranial hemorrhage and stroke

Within the most severe bleeding category, Fatal bleeding, there was no difference in bleeding events between ticagrelor and clopidogrel. However, with ticagrelor more patients had non-procedural ICH (26 vs 14) and fatal ICH (11 vs 2), but fewer had fatal extracranial hemorrhage (9 vs 21) (Figure 26). Similar numbers of patients sustained non-fatal ICH: 15 ticagrelor vs 13 clopidogrel. All but 1 of the ICH events (on the clopidogrel arm) were non-procedural bleeding events. All hemorrhagic strokes counted not only as bleeding events, but also in the primary efficacy endpoint, for which ticagrelor demonstrated an overall significant benefit. The rates (KM%/year) of ‘Major Fatal/Life-threatening’ ICH were low in both treatment groups (0.3% and 0.2%) relative to rates of CV death (4.0% and 5.1%) and of MI (5.8% and 6.9%).

Further analyses and extensive evaluation of the cases of ICH failed to identify any subgroup at increased risk for ICH, except that a previous history of ICH was associated with an increased risk of ICH in both treatment groups. Although prior history of ICH was an exclusion criterion in PLATO, some patients with prior history of ICH or with probable ICH component in the medical history were randomized and received treatment. Of 15 ticagrelor patients with medical history of ICH or probable ICH component in medical history, 1 patient had a subsequent fatal ICH. Of 13 clopidogrel patients with such history, 2 had subsequent

non-fatal ICH. Of the 564 and 588 patient with a past medical history of prior TIA or non-hemorrhagic stroke in the ticagrelor and clopidogrel treated patients, respectively, only 4 patients in each treatment group had a treatment emergent non-fatal ICH. The increased incidence of subsequent ICH in such patients is sufficient to recommend a contraindication of ticagrelor in patients with prior ICH (Table 20).

Table 20 PLATO: Intracranial hemorrhage in patients with history of TIA or stroke

Event	Patients without prior TIA/non-hemorrhagic stroke		Patients with prior TIA/non-hemorrhagic stroke	
	Ticagrelor patients (%) with events N=8762	Clopidogrel patients (%) with events N=8700	Ticagrelor patients (%) with events N=564	Clopidogrel patients (%) with events N=588
ICH	22 (0.3%)	11 (0.1%)	4 (0.7%)	4 (0.7%) ^a
Non-fatal ICH	11 (0.1%)	9 (0.1%)	4 (0.7%)	4 (0.7%)
Fatal ICH	11 (0.1%)	2 (0.0%)	0	0

^a One patient in the clopidogrel group had a procedural ICH.
ICH Intracranial hemorrhage; TIA Transient ischemic attack.

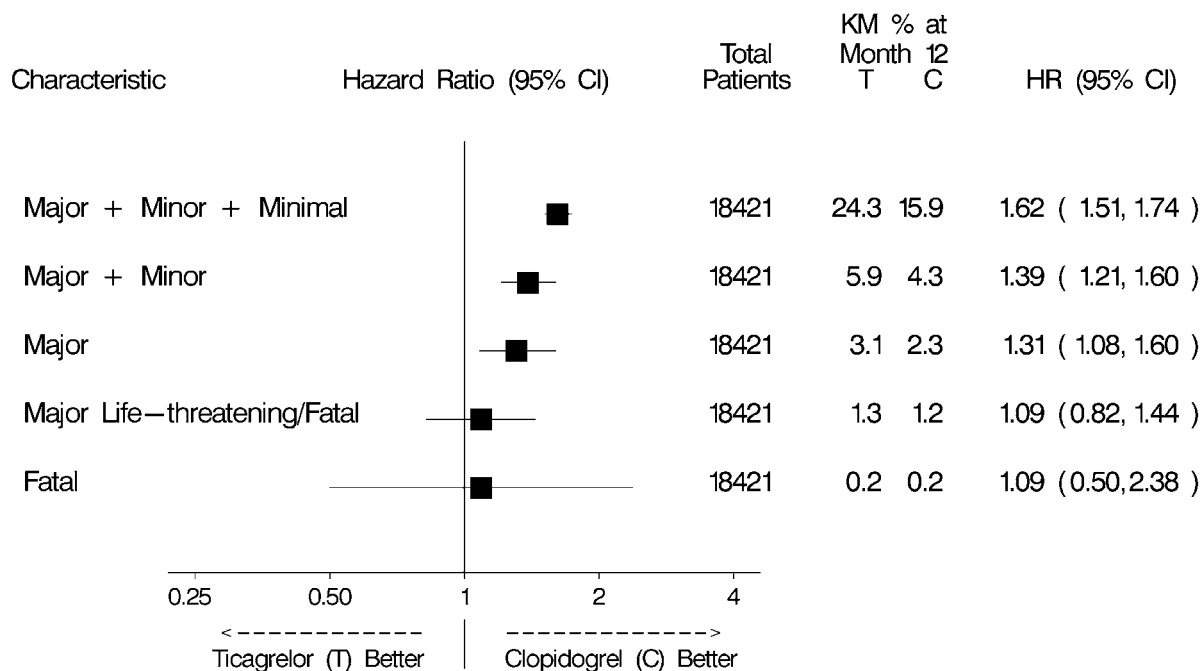
For a listing of patients with ICH by demographic factors refer to Table 1 in Appendix D.

9.1.3 Non-procedural bleeding (includes non-CABG bleeding)

The ticagrelor and clopidogrel treatment groups show similar numbers of non-procedural fatal bleeds and non-procedural fatal or life-threatening bleeds. When less severe events are included more non-procedural bleeding was reported in the ticagrelor treatment group compared to the clopidogrel treatment group (Figure 27).

Non-procedural PLATO-defined 'Total Major' bleeding rates were significantly greater with ticagrelor compared to clopidogrel (3.1% vs 2.3%, HR 1.31 [95% CI 1.08, 1.60]; p=0.0058). The imbalance arises mainly from GI bleeding events (124 vs 94, ticagrelor vs clopidogrel, respectively). Non-procedural PLATO-defined 'Major + Minor' bleeding rates were also significantly greater with ticagrelor compared to clopidogrel (5.9% vs 4.3%, HR 1.39 [95% CI 1.21, 1.60]; p<0.0001).

Figure 27 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.

Overall, there were more non-procedure related bleeding events on ticagrelor versus clopidogrel ([Table 21](#)). There were more (n=124) GI ‘Total Major’ bleeding events with ticagrelor than with clopidogrel (n=94). There were also more (n=27 events in 26 patients) intracranial non-procedural ‘Total Major’ bleeding events with ticagrelor than with clopidogrel (n=14). Section [9.1.2.1](#) presents further details regarding Fatal ICH.

Table 21 **Non-procedure-related ‘Total Major’ bleeding events by anatomic location - PLATO**

Primary location	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Total bleeds	251	190
Gastrointestinal	124	94
Intracranial	27	14
Urinary	13	14
Pericardial	11	11
Epistaxis	11	8
Subcutaneous/dermal	11	4
Hemoptysis	6	3
Retroperitoneal	2	3
Intraocular	0	2
Other	46	37

Patients may be counted in >1 bleeding event category.

In the ticagrelor group, Patient E3907032 had 2 adjudicated ‘Major Fatal/Life-threatening’ intracranial bleeding events.

bid Twice daily dosing; qd Once daily dosing.

9.1.4 Major + Minor bleeding

Kaplan-Meier analysis showed that Major + Minor bleeding was comparatively greater in ticagrelor-treated patients (16.1%) than in clopidogrel-treated patients (14.6%); HR 1.11 87(95% CI 1.03, 1.20, p=0.0084); similarly non-procedural Major + Minor bleeding rates were 5.9% vs 4.3%; HR 1.39 (95% CI 1.21, 1.60, p<0.0001). This imbalance arose mostly from more Minor bleeding events with ticagrelor (4.8% vs 3.8%). The majority of these minor bleeding events occurred from epistaxis (106 ticagrelor vs 54 clopidogrel) or at angiography/PCI access sites (103 vs 73).

9.1.5 CABG bleeding

As the need for urgent CABG surgery cannot always be anticipated, and patients may be taking antiplatelet therapy when CABG is needed, it is important to characterize bleeding risk associated with antiplatelet treatment in the CABG setting.

The PLATO study demonstrated that ‘Total Major’ CABG bleeding events, including Fatal and ‘Life-threatening’ CABG bleeding events, were generally similar for ticagrelor and clopidogrel (Table 22). Fatal CABG bleeding was uncommon: 6 patients (0.8% ticagrelor vs 0.7% clopidogrel) in each treatment group.

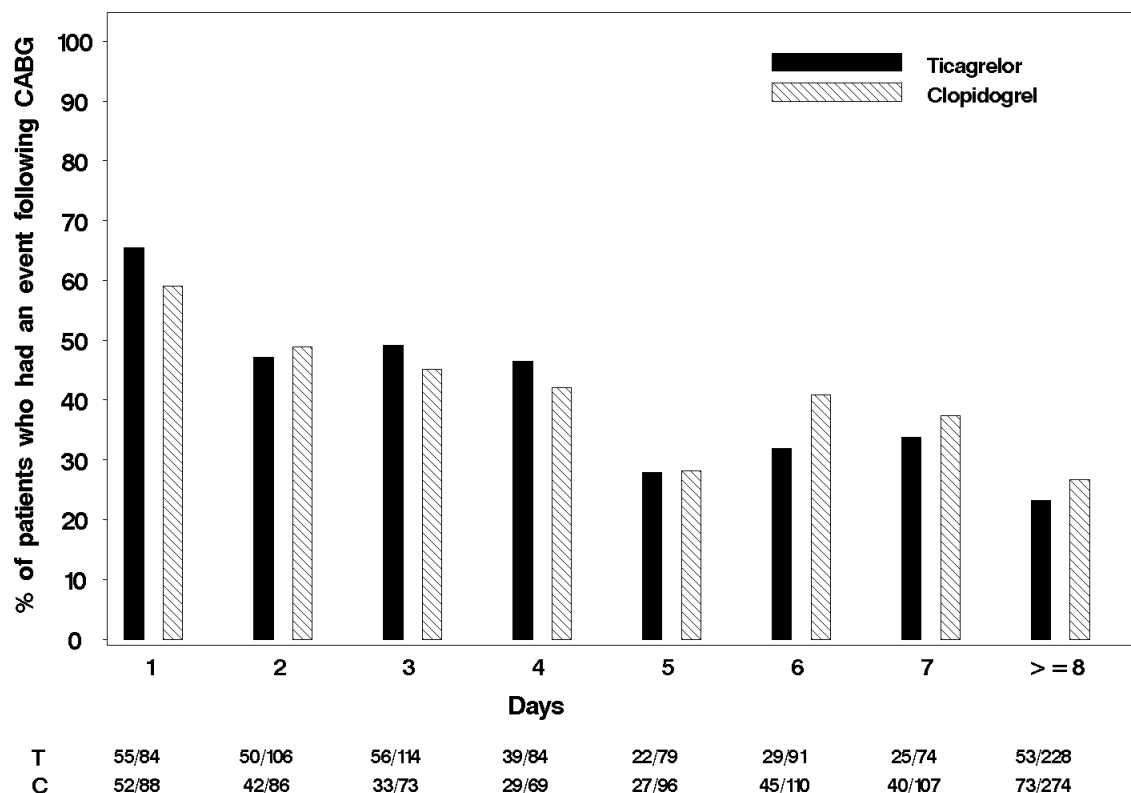
Table 22 **First occurrence bleeding events in patients who had CABG procedure - PLATO**

Bleeding severity	Ticagrelor 90 mg bid N=770	Clopidogrel 75 mg qd N=814
Any bleed	737 (95.7%)	783 (96.2%)
Total Major CABG bleeding	619 (80.4%)	654 (80.3%)
Fatal/Life-threatening	329 (42.7%)	341 (41.9%)
Fatal	6 (0.8%)	6 (0.7%)
Minor	47 (6.1%)	58 (7.1%)
Minimal	71 (9.2%)	71 (8.7%)

bid Twice daily dosing; CABG Coronary artery bypass grafting; qd Once daily dosing.

There was no apparent difference between ticagrelor and clopidogrel in ‘Major/Fatal/Life-threatening’ CABG-related bleeding with respect to time from last dose of study drug between ticagrelor and clopidogrel, even when drug was stopped within 1 day prior to CABG surgery ([Figure 28](#)).

Figure 28 Major Fatal/Life-threatening CABG-related bleeding by days from last dose of study drug to CABG procedure



X-axis is days from last dose of study drug prior to CABG.
C Clopidogrel; CABG Coronary artery bypass graft; T Ticagrelor.

9.1.6 Summary and conclusions for PLATO analysis of bleeding

Despite the clear benefits of antiplatelet and antithrombotic agents in the treatment of CAD, bleeding remains an important safety risk associated with their use.

The ‘Total Major’ bleeding events on ticagrelor did not differ significantly from that of clopidogrel treatment (Kaplan-Meier [KM] estimate of % events 11.6% vs 11.2%, HR 1.04, [95% CI 0.95, 1.13]; $p=0.4336$) (Section 9.1.1). In addition, ticagrelor and clopidogrel did not differ significantly in fatal bleeding or fatal/life-threatening bleeding. Significantly more non-CABG bleeding, including non-procedural bleeding, was reported with ticagrelor treatment. Subgroup analyses do not identify particular patient factors that consistently predict more total bleeding, non-CABG bleeding or, more broadly, non-procedural bleeding with ticagrelor, including low body weight, advanced age, or sex.

There were numerically more ICH among ticagrelor-treated patients compared to clopidogrel-treated patients, and more of these events were fatal in the ticagrelor-treated group. However, there was an excess of fatal extracranial bleeding events in clopidogrel-treated patients.

9.2 Analysis of adverse events in PLATO

All safety analyses are reported for the safety population and generally present the adverse events (AEs) that occurred during randomized treatment unless otherwise noted. Analyses include events occurring on treatment, defined as the first dose of randomized treatment to the last dose of randomized treatment plus 7 days, inclusive. For the safety analyses, as per protocol, primary efficacy endpoint events and bleeding events that were sent for adjudication were not considered AEs and therefore not reported as such.

Ticagrelor-treated patients reported AEs more often than clopidogrel-treated patients (72.7% vs 69.6%, respectively). The excess of AEs with ticagrelor involves those mild or moderate in nature and does not extend to severe AEs or serious adverse events (SAEs); fewer ticagrelor-treated patients had an AE with an outcome of death during treatment (Table 23). Discontinuations due to an AE (including bleeding) occurred in more patients taking ticagrelor compared to patients taking clopidogrel.

Table 23 **Number (%) of patients within categories of AEs during the treatment period, including bleeding events – PLATO safety analysis set**

Category	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Any AE	6714 (72.7%)	6398 (69.6%)
Mild	5655 (61.2%)	5292 (57.6%)
Moderate	3322 (36.0%)	3073 (33.5%)
Severe	1019 (11.0%)	1061 (11.6%)
Any SAE	1864 (20.2%)	1866 (20.3%)
SAE excluding death	1712 (18.5%)	1685 (18.3%)
Death	218 (2.4%)	285 (3.1%)
Leading to study drug discontinuation	687 (7.4%)	500 (5.4%)
SAE	259 (2.8%)	218 (2.4%)

AE Adverse event; bid Twice daily dosing; qd Once daily dosing; SAE Serious adverse event.

The most common AEs reported during ticagrelor treatment, categorized using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT), were dyspnea, headache, dizziness, GI disturbances, and bleeding events such as epistaxis, bruising and bleeding events related to procedures (Table 24).

Table 24 **Number (%) of patients reporting the most common AEs (by PT), including bleeding AEs – PLATO safety analysis set**

Preferred term	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Patients with at least 1 event	6714 (72.7%)	6398 (69.6%)
Dyspnea ^a	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%)

Note: This table includes the 10 most frequently reported AEs based on the percentage in the ticagrelor group.

^a Dyspnea represents the individual PT. Section 9.3.1 presents an analysis of dyspnea that includes 5 combined PTs.

AE Adverse event; bid Twice daily dosing; PT Preferred term; qd Once daily dosing.

Dyspnea and epistaxis AEs leading to permanent discontinuation of study drug accounted for half of the excess discontinuations (93 of 187) with ticagrelor (Table 25). The remaining imbalance is spread across various PTs, most related to bleeding or GI disturbances.

Table 25 Summary by PT of the most common AEs leading to discontinuation of study treatment, including bleeding events – PLATO safety analysis set

Preferred term	Ticagrelor 90 mg bid N = 9235	Clopidogrel 75 mg qd N = 9186
Patients with at least 1 event	687 (7.4%)	500 (5.4%)
Dyspnea	77 (0.8%)	10 (0.1%)
Epistaxis	38 (0.4%)	12 (0.1%)
Atrial fibrillation	27 (0.3%)	37 (0.4%)
Intracardiac thrombus	22 (0.2%)	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%)	9 (0.1%)
Ecchymosis	13 (0.1%)	5 (0.1%)

Note: This table includes the 10 most frequently reported AEs leading to permanent discontinuation of study medication based on the percentages in the ticagrelor group.
AE Adverse event; bid Twice daily dosing; qd Once daily dosing.

Potential mechanisms for the various AEs reported in ticagrelor-treated patients have been explored, but these have yet to be definitively proven (Section 9.6).

9.3 Special safety topics

9.3.1 Dyspnea

Dyspnea, defined as a sensation of “shortness of breath” or “breathlessness,” is a common symptom of many medical conditions, including respiratory diseases (including COPD, asthma and pneumonia), cardiac ischemia and heart failure. Thus, many patients with ACS will report dyspnea due to underlying or concomitant diseases.

As a result, dyspnea is reported in association with administration of clopidogrel, prasugrel, and aspirin ([Effient Prescribing Information 2009](#), [Plavix Prescribing Information 2009](#), [Serebruany et al 2008](#)) and does not represent a major safety concern for those drugs. Of the 19185 patients in the CAPRIE study, 4.5% in the clopidogrel group and 4.7% in the aspirin group reported dyspnea. However, only 0.1% of the patients discontinued treatment due to dyspnea ([Plavix Prescribing Information 2009](#)).

An increase in reports of dyspnea associated with ticagrelor administration was first observed in Phase II studies. In the DISPERSE study, dyspnea was reported more frequently with

increasing doses of ticagrelor, a finding confirmed in DISPERSE2 in which 8% of patients in the ticagrelor 90 mg bid group and 12% of patients in the ticagrelor 180 mg bid group reported dyspnea, compared with 5% in the clopidogrel 75 mg qd group. An examination of a broader group of dyspnea PTs (dyspnea, dyspnea exertional, dyspnea exacerbated, dyspnea at rest, and nocturnal dyspnea) in the DISPERSE2 study showed that 10% of patients in the ticagrelor 90 mg bid group reported at least 1 of these PTs, compared to 6% of patients in the clopidogrel 75 mg qd group.

As a result of the dyspnea observations noted above, non-clinical studies were performed to investigate the possible mechanism for dyspnea with ticagrelor but none provided conclusive answers. Section 9.6 presents a discussion of possible mechanism of adverse effects.

These observations also led to 2 Phase I studies, 1 in healthy elderly volunteers and 1 in patients with COPD or asthma, to explore possible effects of ticagrelor on pulmonary function and inclusion of cardiopulmonary assessments in a subsequent Phase II study, ONSET-OFFSET, in patients with stable CAD. PLATO also included a pulmonary function substudy in patients with ACS. None of these clinical investigations revealed an effect of ticagrelor on cardiopulmonary function.

Analyses of dyspnea AEs in PLATO include an evaluation of intensity, seriousness and discontinuation of study medication; time to onset and resolution, relation of dyspnea to other diseases or factors, and CV outcomes in patients at risk for dyspnea. The data for dyspnea AEs are presented in an inclusive manner by combining the 5 MedDRA PTs that include the term dyspnea (dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, and dyspnea paroxysmal nocturnal) described subsequently as “dyspnea AEs” or “dyspnea.” The single PT of dyspnea is not used in any comparisons that follow unless specifically noted.

Dyspnea in PLATO

In PLATO, dyspnea AEs were reported more frequently with ticagrelor than clopidogrel (Table 26).

Table 26 **Number (%) of patients with dyspnea AEs on treatment – PLATO safety analysis set**

Preferred term	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Patients with at least 1 event	1270 (13.8%)	721 (7.8%)
Dyspnea	1104 (12.0%)	598 (6.5%)
Dyspnea exertional	176 (1.9%)	127 (1.4%)
Dyspnea at rest	9 (0.1%)	3 (0.0%)
Nocturnal dyspnea	8 (0.1%)	4 (0.0%)
Dyspnea paroxysmal nocturnal	6 (0.1%)	5 (0.1%)

AE adverse event; bid Twice daily; qd Once daily.

Dyspnea AEs were generally mild to moderate in intensity; relatively few were severe or SAEs. The increase in reports of dyspnea AEs with ticagrelor, compared to clopidogrel, occurred across all levels of AE intensity and in those leading to discontinuation of study drug (Table 27). The dyspnea AEs resolved after discontinuation of study drug in 67 (85%) of the 79 patients who discontinued because of a dyspnea AE. Of the 35 ticagrelor-treated patients reporting a severe dyspnea AE, 11 discontinued study drug. Additionally, 87% of the severe AEs resolved by the end of the study.

Table 27 **Number (%) of patients within categories of dyspnea AEs on treatment – PLATO safety analysis set**

Category	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Dyspnea AE	1270 (13.8%)	721 (7.8%)
Mild	890 (9.6%)	505 (5.5%)
Moderate	413 (4.5%)	218 (2.4%)
Severe	35 (0.4%)	18 (0.2%)
Dyspnea SAE	69 (0.7%)	39 (0.4%)
Death	1 (0.0%)	1 (0.0%)
Dyspnea AE leading to study drug discontinuation	79 (0.9%)	13 (0.1%)
Dyspnea SAE leading to study drug discontinuation	10 (0.1%)	1 (0.0%)

AE adverse event; bid Twice daily; qd Once daily; SAE Serious adverse event.

Most patients reporting dyspnea in both treatment groups reported 1 dyspnea AE: 87% of ticagrelor-treated patients and 92% of clopidogrel-treated patients. One ticagrelor-treated patient reported 5 dyspnea AEs, all of which were mild to moderate in intensity. The events were reported on Days 20, 21, 24, 25 and 26 after randomization; each event resolved the same day.

Dyspnea was reported earlier with ticagrelor (median time to onset of 20 days) than with clopidogrel (median time to onset of 33 days).

Dyspnea often resolved during continued ticagrelor treatment. The median duration of all dyspnea AEs was 56 days for ticagrelor vs 62 days for clopidogrel. Approximately two-thirds of all dyspnea AEs resolved by the end of the study. Among those dyspnea AEs that resolved, about half in both treatment groups (one-third of the total events) resolved within 1 week. For the remaining one-third of events that were reported as ongoing at the end of the study, approximately 30% were reported by patients who had a medical history of dyspnea at randomization.

Table 28 Resolution of dyspnea AEs – PLATO safety analysis set

Characteristic	Ticagrelor 90 mg bid	Clopidogrel 75 mg qd
Total number of dyspnea AEs	1463 (100%)	793 (100%)
Unresolved dyspnea AEs at end of study	468 (32.0%)	289 (36.4%)
Resolved dyspnea AEs	995 (68.0%)	504 (63.6%)
AEs resolved within 7 days	463/995 (46.5%)	240/504 (47.6%)
AEs resolved in 8-30 days	163/995 (16.4%)	70/504 (13.9%)
AEs resolved after 30 days	369/995 (37.1%)	194/504 (38.5%)

Note: this table includes events that resolved during and after discontinuation of treatment.
AE adverse event; bid Twice daily; qd Once daily.

Relation of dyspnea to other diseases or factors

Patients who reported dyspnea AEs during the study tended to be 2 to 3 years older than the general PLATO population, be ex-smokers, and have a prior history of dyspnea or cardiopulmonary diseases (congestive heart failure [CHF], COPD or asthma) at baseline regardless of treatment group. More than 3000 PLATO patients had a history of these cardiopulmonary diseases at study entry.

Ticagrelor-treated patients with baseline dyspnea or cardiopulmonary diseases are not disproportionately at risk of experiencing a dyspnea AE ([Table 29](#)). The patterns of onset, intensity, and number of episodes in these subgroups generally followed those of the overall PLATO population.

Table 29 Hazard ratios for dyspnea AEs in selected subgroups of patients – PLATO safety analysis set

Subgroup	Ticagrelor 90 mg bid n/N (%) patients	Clopidogrel 75 mg qd n/N (%) patients	Hazard ratio (95% CL)
Overall N=18421	1270/9235 (13.8%)	721/9186 (7.8%)	1.84 (1.68, 2.02)
Patients with dyspnea at baseline ^a n=3746 (20.3%)	353/1890 (18.7%)	247/1856 (13.3%)	1.49 (1.27, 1.76)
Patients without dyspnea at baseline ^a n=14675 (79.7%)	917/7345 (12.5%)	474/7330 (6.5%)	2.02 (1.81, 2.26)
Patients with COPD or asthma or CHF at baseline ^b n=3357 (18.2%)	300/1686 (17.8%)	191/1671 (11.4%)	1.64 (1.36, 1.96)
Patients without COPD or asthma or CHF at baseline ^b n=15064 (81.8%)	970/7549 (12.8%)	530/7515 (7.1%)	1.91 (1.72, 2.13)

^a Dyspnea at baseline is defined as history of, or current, dyspnea at baseline.

^b Subgroup defined by medical history of COPD, asthma or CHF or history of, or current, dyspnea at baseline with etiology COPD, asthma or CHF.

AE Adverse event; bid Twice daily; CHF Congestive heart failure; CL Confidence limit; COPD Chronic obstructive pulmonary disease; HR Hazard ratio; qd Once daily.

AEs of heart failure, COPD or asthma in PLATO were reported with similar incidence in both treatment groups (Table 30) and regardless of whether patients reported dyspnea. Therefore, the imbalance in dyspnea AEs observed with ticagrelor is not accounted for by AEs related to heart failure or lung disease. Furthermore, among patients reporting dyspnea, ticagrelor-treated patients used diuretics less often than clopidogrel-treated patients (46.1% vs 50.5%, respectively).

Table 30 AEs related to cardiopulmonary disease and diuretic use in all patients, patients with dyspnea and patients without dyspnea – PLATO safety analysis set

Event	All patients		Patients with dyspnea AEs on treatment		Patients without dyspnea AEs on treatment	
	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186	Ticagrelor 90 mg bid N = 1270	Clopidogrel 75 mg qd N = 721	Ticagrelor 90 mg bid N = 7965	Clopidogrel 75 mg qd N = 8465
AE of heart failure ^a	410 (4.4)	421 (4.6)	72 (5.7%)	61 (8.5%)	338 (4.2%)	360 (4.3%)
AE of asthma ^b	17 (0.2)	27 (0.3)	5 (0.4%)	3 (0.4%)	12 (0.2%)	24 (0.3%)
AE of COPD ^b	57 (0.6)	41 (0.4)	24 (1.9%)	10 (1.4%)	33 (0.4%)	31 (0.4%)
New onset diuretic use during PLATO	3180 (34.4%)	3075 (33.5%)	585 (46.1%)	364 (50.5%)	2604 (32.7%)	2711 (32.0%)

^a AEs in the heart failure higher level group term.

^b Single PT.

AE adverse event; bid Twice daily; COPD Chronic obstructive pulmonary disease; qd Once daily.

Pulmonary function testing and cardiopulmonary assessments

Overall, pulmonary function testing (PFT) across the ticagrelor development program demonstrated no differences between treatment groups or placebo in spirometry, diffusion, flow rates, or oxygenation in patients with asthma or COPD, in healthy elderly volunteers, in patients with stable CAD in the ONSET/OFFSET study, and in ACS patients in PLATO.

In the 2 Phase I studies (with durations of 4 days each), no changes in PFT parameters or other respiratory function tests were observed for ticagrelor compared to placebo in healthy elderly volunteers or in volunteers with asthma or COPD.

In DISPERSE2, pulmonary function testing was performed in all patients at baseline. Patients were asked to return for pulmonary function testing if they reported an AE of dyspnea. However, too few of the patients reporting dyspnea returned for testing to make meaningful conclusions from the data.

Cardiopulmonary assessments in stable CAD patients in ONSET/OFFSET, including measurement of ejection fraction and N-terminal pro-brain natriuretic peptide (NT pro-BNP), showed no changes from baseline in ticagrelor-treated patients and no effect of ticagrelor (compared to clopidogrel or placebo) after 6 weeks of ticagrelor treatment, including in 6 patients who reported dyspnea. These patients had cardiopulmonary testing at the time of a dyspnea episode or shortly after they reported dyspnea.

Patients in the pulmonary function substudy in PLATO (n=199) underwent testing at 1 month and after >6 months whether or not they reported dyspnea. The treatment groups did not differ for forced expiratory volume in 1 second (FEV₁), percent predicted normal FEV₁, or

other measurements (Table 31). No changes in pulmonary function occurred in either treatment group over the duration of the substudy.

Table 31 Summary of PLATO pulmonary function results – PLATO pulmonary function analysis set

Parameter Mean (SD)	Ticagrelor 90 mg bid		Clopidogrel 75 mg qd	
	30 days post-randomization n=100 ^a	End of treatment n=98 ^a	30 days post-randomization n=76 ^a	End of treatment n=86 ^a
FEV ₁ (L)	2.81 (0.727)	2.77 (0.7198)	2.70 (0.845)	2.73 (0.838)
FVC (L)	3.54 (0.874)	3.51 (0.838)	3.50 (1.007)	3.54 (0.965)
FEV ₁ /FVC	79.6 (8.69)	78.9 (7.98)	77.4 (9.09)	77.0 (8.93)
FEF _{25-75%} (L/s)	2.90 (1.256)	2.76 (1.158)	2.62 (1.325)	2.63 (1.374)
FRC (L)	3.59 (0.862)	3.58 (0.991)	3.47 (0.942)	3.66 (1.123)
TLC (L)	6.42 (1.281)	6.27 (1.268)	6.27 (1.359)	6.46 (1.396)
RV (L)	2.72 (0.849)	2.67 (0.820)	2.54 (0.892)	2.72 (0.896)
D _L CO (%)	80.4 (15.50)	82.9 (15.51)	79.8 (17.04)	82.2 (21.51)
SpO ₂ (%)	97.3 (3.16)	97.0 (3.49)	96.4 (2.47)	96.5 (1.70)

^a Numbers of patients represent those that had FEV₁ measurements. Not all patients had all parameters measured so the numbers of patients may be lower for some parameters.

bid Once daily; D_LCO Single breath diffusing capacity for lungs using carbon monoxide; FEF₂₅₋₇₅ Mean forced expiratory flow 25% and 75% of the FVC; FEV₁ Forced expiratory volume in 1 second; FRC Forced residual capacity; FVC Forced vital capacity; qd Once daily; RV Residual volume; SD Standard deviation; SpO₂ Blood oxygen saturation measured by pulse oximetry; TLC Total lung capacity.

Cardiovascular outcomes in selected subgroups of patients

Analyses of the primary efficacy endpoint (the composite of CV death, MI, or stroke) in patients with a baseline history of CHF, COPD or asthma and in patients with a baseline history of dyspnea suggest that these patients benefit at least as much from ticagrelor treatment as the entire PLATO population (Table 32). A similar post-hoc analysis of the patients who reported dyspnea AEs showed that the benefit of ticagrelor was also maintained in these patients.

Table 32 Primary composite efficacy endpoint in selected subgroups of patients–PLATO full analysis set

Subgroup	Ticagrelor 90 mg bid N=9235			Clopidogrel 75 mg qd N=9186			Hazard ratio (95% CI)
	N	n (%)	KM%	N	n (%)	KM%	
Patients with CHF, COPD, or asthma ^a	1708	249 (14.6%)	15.3%	1693	291 (17.2%)	18.8%	0.84 (0.71, 1.00)
Patients with dyspnea ^b at baseline	1921	267 (13.9%)	14.7%	1879	294 (15.6%)	17.1%	0.88 (0.75, 1.04)
Patients with dyspnea AEs ^c	1399	151 (10.8%)	11.9%	798	117 (14.7%)	15.7%	0.75 (0.59, 0.96)
Patients without dyspnea AEs	7994	713 (8.9%)	9.4%	8493	897 (10.6%)	11.3%	0.84 (0.76, 0.93)

^a Subgroup defined by medical history of COPD, asthma or CHF or history of, or current, dyspnea at baseline with etiology COPD, asthma or CHF.

^b Dyspnea at baseline is defined as a history of or current dyspnea at baseline.

^c Includes all patients with dyspnea AEs (on or off treatment) as this analysis is based on the full analysis set.

AE Adverse event; bid Twice daily; CHF Congestive heart failure; COPD Chronic obstructive pulmonary disease; CI Confidence interval; KM Kaplan-Meier; qd Once daily.

Summary of dyspnea with ticagrelor

- In PLATO, dyspnea was reported more frequently with ticagrelor (13.8%) compared to clopidogrel (7.8%).
- Dyspnea AEs were generally mild to moderate in intensity and relatively few were severe or SAEs; the increase in reports of dyspnea with ticagrelor occurred across all categories of AEs, including those that led to discontinuation of study drug.
- Patients reporting dyspnea AEs tended to be older, be ex-smokers, or have a history of dyspnea, CHF, COPD, or asthma at baseline regardless of treatment group. Ticagrelor-treated patients with these baseline cardiopulmonary diseases were not disproportionately at risk of a dyspnea AE compared to clopidogrel-treated patients.
- The imbalance in dyspnea AEs observed with ticagrelor is not accounted for by AEs related to heart failure or lung disease (COPD or asthma), as the incidence of these AEs and use of diuretics was similar in both treatment groups.
- The CV benefit of ticagrelor is maintained in patients with baseline CHF, COPD, asthma or dyspnea and in those who reported dyspnea AEs during PLATO.

- Pulmonary function testing across the ticagrelor development program demonstrated no differences between treatment groups or placebo in spirometry, diffusion, flow rates, or oxygenation in patients with asthma or COPD, in healthy elderly volunteers, in patients with stable CAD in the OFFSET study, and in ACS patients in PLATO.

AstraZeneca 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.

Information on the potential mechanism for dyspnea is presented in Section 9.6. Additional data for reports of dyspnea in the US and in subgroups of patients taking high and low maintenance doses of ASA appear in Section 9.5.

9.3.2 Renal effects

No signals for renal toxicity were identified during non-clinical development, based on repeat-dose toxicity studies and histopathological examination of renal tissues, or in Phase I clinical studies with ticagrelor. Patients with any level of renal impairment except those requiring dialysis were permitted into PLATO, which allows for analyses of the effect of ticagrelor in patients with varying levels of renal impairment. The assessment of ticagrelor's renal effects using the PLATO database may be confounded by the acute ACS event itself, including both interventions and complications, and subsequent treatment.

Laboratory data related to renal function

Initial serum creatinine values, obtained <24 hours from onset of the ACS event in most cases, predated almost all interventions and complications that occurred during the patient's course following the index ACS event. Subsequent values, obtained at approximately 30 days later, likely reflect renal effects resulting from the index ACS event, which might include either treatment interventions or complications (or both), such as the influences of hemodynamic instability, multiple medications with potential renal effects, intravascular dye loads, and other factors that can adversely affect renal function.

In this context, serum creatinine increased from baseline (less than 0.1 mg/dL) in both treatment groups (Table 33), corresponding to a mean percent change from baseline (using matched baseline values) of approximately 10%. Mean creatinine values increased more with ticagrelor (approximately 0.01 to 0.05 mg/dL). The differential between treatments was consistently smaller than the absolute increase in either treatment group. Almost all of the creatinine increases for both treatment groups occurred by Visit 2 (30 days following the ACS index event). Following discontinuation of treatment during the 30-day follow-up period, mean serum creatinine values did not continue to increase and the difference between treatment groups diminished.

Table 33 **Mean serum creatinine values over time – PLATO safety laboratory analysis set**

		Ticagrelor 90 mg bid		Clopidogrel 75 mg qd	
		Mean creatinine mg/dL		Mean creatinine mg/dL	
Visit schedule ^a		N	Mean (SD)	N	Mean (SD)
Visit 1	Index Event	4641	0.98 (0.31)	4624	0.98 (0.32)
Visit 2	1 month	4901	1.06 (0.35)	4870	1.04 (0.32)
Visit 3	3 months	4494	1.05 (0.33)	4496	1.03 (0.33)
Visit 4	6 months	4022	1.05 (0.33)	3998	1.04 (0.32)
Visit 5	9 months	229	1.08 (0.33)	222	1.03 (0.25)
Visit 6	12 months	3652	1.07 (0.41)	3643	1.04 (0.31)
	30 day follow-up	3595	1.06 (0.37)	3545	1.05 (0.34)

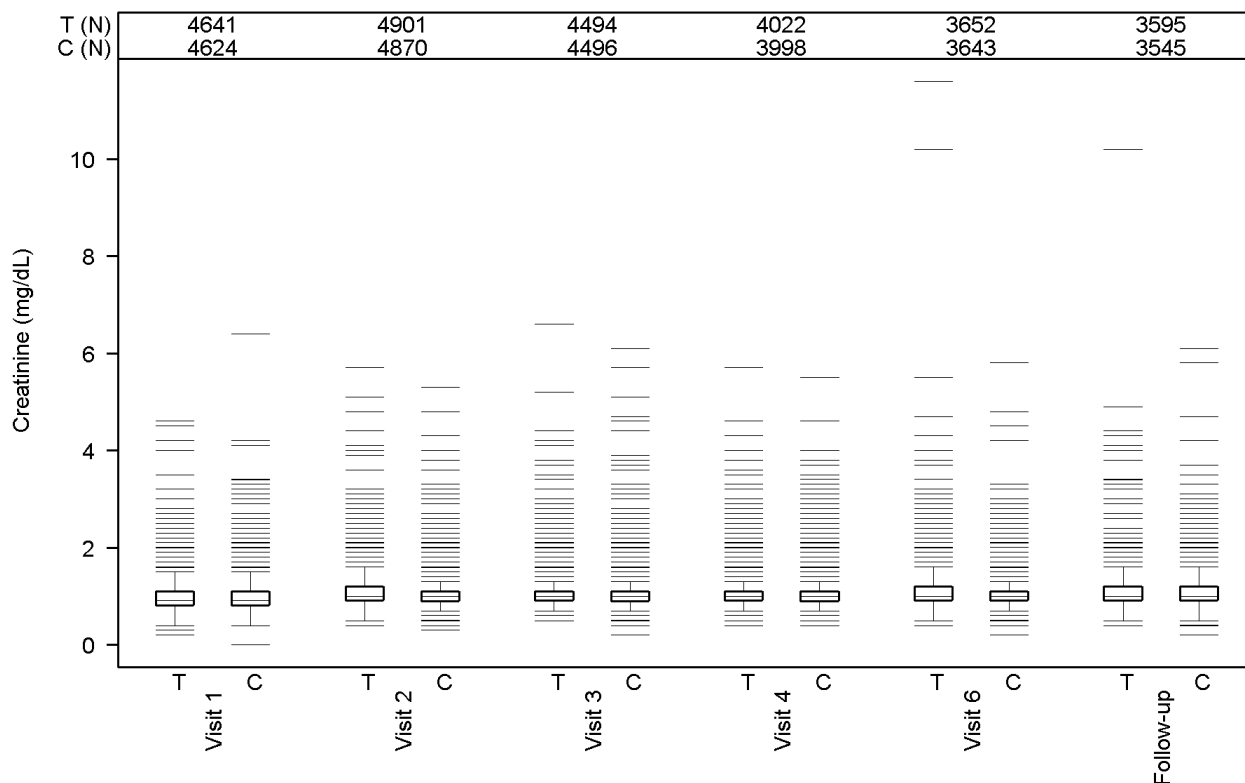
^a Baseline defined as date and time of first sample prior or equal to date and time of first dose. Visit 5 (9 months) was not a scheduled visit for serum creatinine measurement.

bid Twice daily; qd Once daily; SD Standard deviation.

The PLATO biomarker substudy measured the renal biomarker cystatin C in a subset of PLATO patients at baseline, 30 days, and 6 months only. Cystatin C reflects glomerular filtration rate (GFR) more reliably than serum creatinine ([Shlipak et al 2005](#)). Cystatin C increased similarly to creatinine in both treatment groups at 30 days and 6 months, with slightly greater increases in the ticagrelor group.

[Figure 29](#) shows the distribution of serum creatinine by treatment over time. The scale of the increase in serum creatinine is small compared to the range of the data. Few differences exist between ticagrelor and clopidogrel in the number of outliers or in the magnitude of their changes. The treatment effect differential in increased creatinine appears to be driven by a small increase in many patients rather than larger increases in only a portion.

Figure 29 **Box plots of serum creatinine over time - PLATO safety laboratory analysis set**

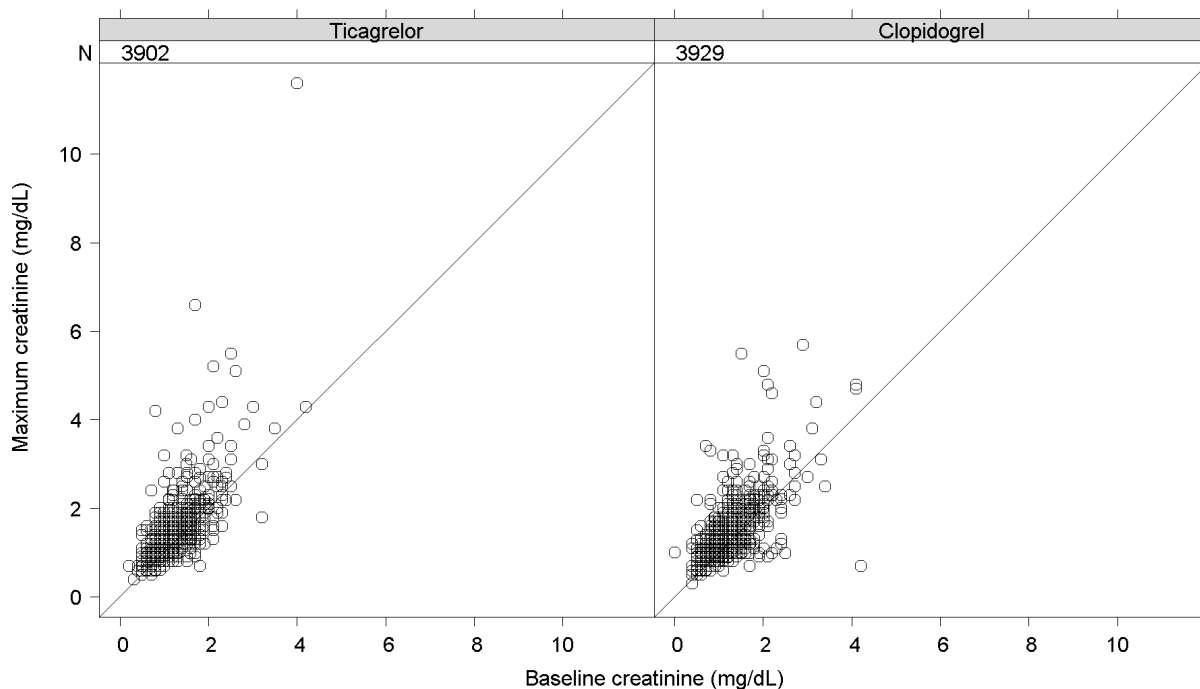


Note: In these box plots, the central line is the median, the boxes contain the 25th and 75th percentiles, the whiskers indicate 1.5 times the interquartile range from the edge of the box, with outlier values displayed as lines above and below the whiskers. All patients with routine creatinine measurements are displayed.
C Clopidogrel; T Ticagrelor.

In the box plots above, the 3 extreme outlier values occurred in 2 ticagrelor patients. One had a history of hypertension, diabetes mellitus, and baseline creatinine of 4.0 mg/dL, a 30-day measurement of 2.6 mg/dL, then steadily increasing values to 11.6 mg/dL on Day 364. Despite poor renal function at study entry this patient completed 12 months of study treatment. Then, 21 days later, the patient had azotemia reported as an SAE. This patient required ongoing dialysis. The second patient had heart failure, exacerbated by his episode of ACS. He received dopamine on Days 1 to 28, furosemide, a non-steroidal anti-inflammatory drug (NSAID), and vancomycin. The post-infarct period included major hemorrhage, urinary tract and other infections, reinfarction, and stent thrombosis. The patient received ticagrelor study medication only on Day 1 and Days 9 to 13 and received open-label clopidogrel multiple times during the study, including on Day 1 and Days 9 to 12. This patient's baseline creatinine was 4.2 mg/dL, rising to about 10 mg/dL at Visit 6, and remained there 30 days later.

Figure 30 displays on-treatment maximum serum creatinine levels for individual patients plotted against their baseline serum creatinine levels. Generally, the plots demonstrate a similar pattern of changes in both treatment groups, consistent with small changes in serum creatinine across the majority of patients regardless of their baseline serum creatinine levels rather than larger changes in a certain subgroup of patients. Furthermore, the data for patients with higher baseline serum creatinine values (eg, above 1.6 mg/dL), suggest no apparent treatment difference with respect to the pattern of maximum on-treatment serum creatinine values.

Figure 30 Individual patient scatter plot of on-treatment maximum serum creatinine levels vs baseline serum creatinine levels – PLATO safety laboratory analysis set



Note: Only patients who have both baseline and on-treatment creatinine measurements are displayed; therefore, the number of patients represented in this figure is different from Figure 29.

Table 34 presents the numbers of patients with categorical increases in serum creatinine, excluding patients whose baseline sample did not precede their first dose of study medication. Few patients, 35 ticagrelor-treated vs 34 clopidogrel-treated patients, had a creatinine value that more than doubled, ie, an increase >100%. Of these, 27 and 24 patients, respectively, had maximal values that exceeded 1.6 mg/dL, the upper limit of normal (ULN). The number of patients with smaller creatinine increases (>30% to ≤100%) was greater with ticagrelor vs

clopidogrel, as was the number of patients with creatinine values above the ULN within these categories.

Table 34 **Number (%) of patients with categorical changes in serum creatinine and eGFR – PLATO safety laboratory set**

Criteria ^a	Ticagrelor 90 mg bid N=4031	Clopidogrel 75 mg qd N=4035
Change in serum creatinine (baseline to maximum value)^b		
Decrease	372 (9.2%)	426 (10.6%)
Creatinine increase 0 to ≤30%	2632 (65.3%)	2750 (68.2%)
Creatinine increase >30% to ≤50%	692 (17.2%)	588 (14.6%)
Creatinine increase >50% to ≤100%	300 (7.4%)	237 (5.9%)
Creatinine increase >100% to ≤200%	28 (0.7%)	29 (0.7%)
Creatinine increase 200%	7 (0.2%)	5 (0.1%)
Creatinine increase >30% to ≤50% and above ULN ^c	89 (2.2%)	62 (1.5%)
Creatinine increase >50% to ≤100% and above ULN ^c	95 (2.4%)	59 (1.5%)
Creatinine increase >100% and above ULN ^c	27 (0.7%)	24 (0.6%)
Change in eGFR^d (baseline to minimum value)^b		
Increase	372 (9.2%)	426 (10.6%)
0 to ≤30% decrease in eGFR	2903 (72.0%)	2990 (74.1%)
>30% to ≤50% decrease in eGFR	667 (16.5%)	559 (13.9%)
>50% decrease in eGFR	89 (2.2%)	60 (1.5%)

^a Baseline defined as date and time of first sample prior to date and time of first dose. For creatinine, maximum on-treatment value used and for eGFR minimum on-treatment value used.

^b Safety laboratory values were not collected after Visit 1 (Baseline) in patients randomized on or after 1 February 2008 according to a protocol-specified DSMB evaluation. No data are available for 1579 ticagrelor and 1547 clopidogrel patients whose samples were collected after first dose or for whom data entry for date or time at sample collection was missing.

^c ULN is defined as >1.6 mg/dL.

^d eGFR-MDRD is the estimated glomerular filtration rate calculated per the Modification of Diet in Renal Disease equation (Levey et al 1999).

bid Twice daily dosing; eGFR Estimated glomerular filtration rate; qd Once daily dosing; ULN Upper limit of normal.

Renal-related AEs

More patients had renal-related AEs with ticagrelor compared to clopidogrel (Table 35), while renal-related SAEs (including deaths) and renal-related AEs leading to permanent discontinuation were similar in the 2 treatment groups.

Table 35 **Number (%) of patients within categories of renal-related AEs on treatment – PLATO safety analysis set**

Category	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Renal-related AE	449 (4.9%)	345 (3.8%)
Renal-related SAE	73 (0.8%)	60 (0.7%)
SAEs other than death	71 (0.8%)	57 (0.6%)
Deaths	2 (0.0%)	4 (0.0%) ^a
Renal-related AE leading to permanent discontinuation of study drug	15 (0.2%)	14 (0.2%)
Renal-related SAE leading to permanent discontinuation of study drug	4 (0.0%)	8 (0.1%)

^a Included among the renal-related deaths is 1 patient on clopidogrel treatment who died due to metabolic acidosis.

AE adverse event; bid twice daily dosing; qd once daily dosing; SAE serious adverse event.

Table 36 shows that hematuria partly accounts for the increase in renal-related AEs with ticagrelor. Most hematuria resolved during treatment, 155/174 (89%) ticagrelor-treated patients vs 137/147 (93%) clopidogrel-treated patients, and was infrequently associated with renal-related AEs (<0.3% in both groups) or significant renal laboratory events, defined as creatinine >50% and >1.6 mg/dL, (<0.1% in both groups).

In addition to hematuria, imbalances occurred in reports of renal failure, blood creatinine increased, and renal impairment. The previously described treatment differences in serum creatinine increases exceeding ULN (laboratory measurements) may potentially relate to the numerical imbalance in reports of renal-related AEs.

Table 36 **Number (%) of patients with the most frequently reported renal-related AEs by PT on treatment – PLATO safety analysis set**

Preferred term	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Patients with at least 1 event	449 (4.9%)	345 (3.8%)
Hematuria	174 (1.9%)	147 (1.6%)
Renal failure	93 (1.0%)	64 (0.7%)
Blood creatinine increased ^a	49 (0.5%)	26 (0.3%)
Renal failure acute	46 (0.5%)	42 (0.5%)
Renal impairment	33 (0.4%)	19 (0.2%)
Renal failure chronic	28 (0.3%)	21 (0.2%)
Proteinuria	13 (0.1%)	14 (0.2%)

Note: Events occurring in $\geq 0.2\%$ of patients in either treatment group are presented by decreasing frequency in the ticagrelor group.

^a Blood creatinine increased is the PT that indicates an increase in serum creatinine.

AE Adverse event; bid Twice daily dosing; PT Preferred term; qd Once daily dosing.

The imbalance in renal-related AEs persists when considering the subset of ‘renal function AEs,’ consisting of ‘renal failure,’ ‘renal failure acute,’ ‘renal failure chronic,’ ‘renal impairment,’ and ‘blood creatinine increased’: 244 (2.6%) for ticagrelor vs 167 (1.8%) for clopidogrel. Renal function SAEs were reported in 55 patients (0.6%) for ticagrelor compared to 47 patients (0.5%) for clopidogrel.

Reports of renal-related AEs increased with age in both treatment groups. A larger imbalance occurred with ticagrelor vs clopidogrel in patients ≥ 65 to < 75 years of age (6.2% with ticagrelor vs 4.5% with clopidogrel) and in patients ≥ 75 years of age (10.1% with ticagrelor vs 6.8% with clopidogrel). This imbalance, however, is not accounted for by any specific PT. Similar patterns occurred for renal-related SAEs.

Table 37 shows that 39 ticagrelor (0.4%) and 31 clopidogrel (0.3%) patients underwent dialysis in PLATO. Among patients reported to have a renal-related AE or SAE, the frequency of dialysis was similar in both treatment groups. Therefore, the increased frequency of renal-related AEs with ticagrelor vs clopidogrel did not appear to translate into a difference in outcomes with respect to dialysis.

Table 37 **Number (%) of patients who underwent dialysis, and with renal-related AEs or SAEs - PLATO safety analysis set**

Patient category	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Patients who underwent dialysis	39 (0.4%)	31 (0.3%)
With renal-related AEs	26 (0.3%)	25 (0.3)
With renal-related SAE	23 (0.2%)	22 (0.2%)

Note: Case report form limitations required that dialysis events be identified from a free text search of relevant terms in the database.

AE Adverse event; bid Twice daily dosing; qd Once daily dosing; SAE Serious adverse event.

Renal-related AE incidence by baseline renal impairment

Overall, a higher percentage of patients reported renal-related AEs in both treatment groups in association with worsening degrees of renal impairment at baseline (Table 38). The imbalance in renal-related AEs described in Table 35 occurred mostly in patients with mild to moderate baseline renal impairment, not in those patients with severe renal impairment at baseline, for whom there was no imbalance (Table 38). Baseline renal function did not reliably associate with higher rates or larger imbalances in SAEs or deaths with ticagrelor, although the number of patients with severe baseline renal impairment who reported events was relatively small.

Table 38 **Number (%) of patients with renal-related AEs, SAEs, deaths, or discontinuations due to an AE on treatment by baseline renal function– PLATO safety analysis set**

Category	Baseline renal function							
	Normal (≥ 90 mL/min/1.73 m ²)		Mild (≥ 60 to < 90 mL/min/1.73 m ²)		Moderate (≥ 30 to < 60 mL/min/1.73 m ²)		Severe (< 30 mL/min/1.73 m ²)	
	Ticagrelor 90 mg bid N=2807	Clopidogrel 75 mg qd N=2775	Ticagrelor 90 mg bid N=3542	Clopidogrel 75 mg qd N=3546	Ticagrelor 90 mg bid N=1178	Clopidogrel 75 mg qd N=1224	Ticagrelor 90 mg bid N=88	Clopidogrel 75 mg qd N=93
AE	56 (2.0%)	43 (1.5%)	142 (4.0%)	110 (3.1%)	147 (12.5%)	105 (8.6%)	19 (21.6%)	23 (24.7%)
SAE	5 (0.2%)	4 (0.1%)	19 (0.5%)	13 (0.4%)	31 (2.6%)	23 (1.9%)	6 (6.8%)	10 (10.8%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	1 (0.1%)	0 (0.0%)	2 (2.2%)
Discontinuation due to AE	2 (0.1%)	1 (0.0%)	3 (0.1%)	5 (0.1%)	5 (0.4%)	0 (0.0%)	1 (1.1%)	7 (7.5%)

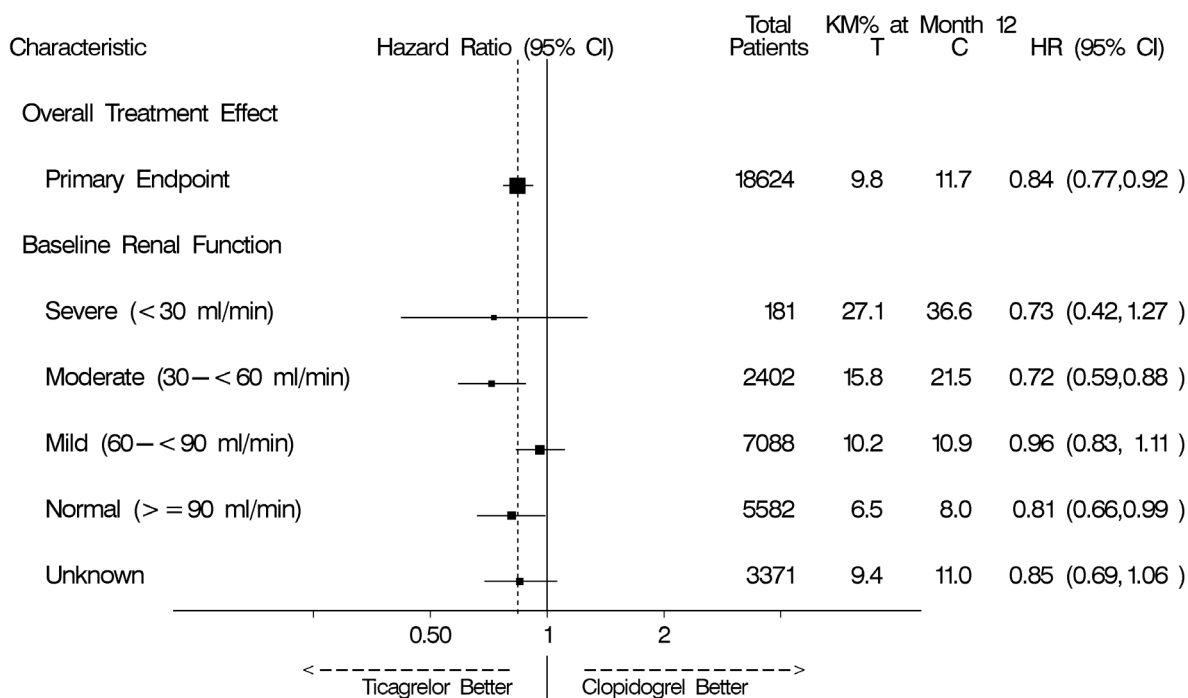
Note: Baseline renal function assessed by eGFR-MDRD, calculated per the Modification of Diet in Renal Disease equation ([Levey et al 1999](#)). Patients missing baseline eGFR-MDRD values included 1620 in the ticagrelor group and 1548 in the clopidogrel group. Missing includes patients whose samples were collected after first dose or if data entry for date or time at sample collection was missing. The total number of patients with renal-related events includes patients who did not have baseline renal function measured.

AE Adverse event; bid Twice daily dosing; eGFR-MDRD Estimated glomerular filtration rate calculated per the Modification of Diet in Renal Disease equation; qd Once daily dosing; SAE Serious adverse event.

Association of renal impairment with primary endpoint events

Figure 31 displays the primary efficacy composite outcome (CV death, MI, or stroke) according to renal function at baseline, as measured by calculated creatinine clearance. Patients with moderate or severe baseline renal impairment are at a high risk for CV events, as shown by the absolute KM event rates. While subgroups are small and treatment effect CIs overlap substantially, this analysis suggests that the CV benefit of ticagrelor is generally maintained in patients with varying degrees of baseline renal impairment. The mildly impaired subgroup deviates from an otherwise apparent relationship of point estimates; the treatment by factor interaction is not significant. Patients with moderate renal impairment at baseline had a 5.7% yearly ARR.

Figure 31 **Adjudicated primary clinical endpoint events by baseline renal function - PLATO full analysis set**



Note: Baseline renal function assessed by eGFR-MDRD, calculated per the Modification of Diet in Renal Disease equation (Levey et al 1999).

C Clopidogrel; CI Confidence interval; HR Hazard ratio; KM Kaplan-Meier; T Ticagrelor

Table 39 summarizes the results of a post-hoc evaluation of the primary efficacy composite outcome in patients who did or did not experience on-treatment increases of >30% in serum creatinine levels. The data from this non-randomized comparison (with small event numbers) are consistent with a benefit for ticagrelor-treated patients with serum creatinine increases compared to clopidogrel-treated patients with such increases.

Table 39 Primary composite efficacy endpoint according to the change in serum creatinine levels on treatment – PLATO safety laboratory analysis set

Change in serum creatinine from baseline to maximum post-baseline value	Ticagrelor 90 mg bid N=5610			Clopidogrel 75 mg qd N=5582			Hazard ratio (95% CI)
	N	n (%) patients with event	KM%	N	n (%) patients with event	KM%	
Decrease or increase ≤30%	3004	227 (7.6%)	7.5	3176	301 (9.5%)	9.5	0.79 (0.67, 0.94)
Increase >30%	1027	86 (8.4%)	8.3	859	76 (8.8%)	8.9	0.95 (0.69, 1.29)

Note: 1579 ticagrelor and 1547 clopidogrel patients were missing post-baseline measurements of serum creatinine because safety laboratory values were not collected after Visit 1 (Baseline) in patients randomized on or after 1 February 2008 according to a protocol-specified DSMB evaluation.

bid Twice daily; CI Confidence interval; KM Kaplan-Meier; qd Once daily.

Summary of ticagrelor's renal effects

- Small increases in serum creatinine from baseline occurred in both treatment groups, likely reflecting renal effects resulting from the index ACS event, its treatment and/or complications, including the influences of hemodynamic instability, multiple medications, intravascular dye loads, and other factors that can adversely affect renal function. These increases in serum creatinine were slightly higher for ticagrelor compared to clopidogrel. The differential between treatments was consistently smaller than the absolute increase in either treatment arm. By 30 days after discontinuation of study medication, the difference in creatinine between treatment groups diminished.
- Cystatin C data demonstrated a similar pattern as serum creatinine.
- Ticagrelor-treated patients reported more renal-related AEs (mostly non-serious), compared to clopidogrel-treated patients, but did not have an increase in clinically important outcomes such as death, discontinuation of study drug, and dialysis.
- Patients with severe and moderate renal impairment at baseline were more likely to report a renal-related AE than those with mild or no impairment. The imbalance in reports of renal-related AEs (more AEs with ticagrelor) occurred mostly in patients with mild to moderate baseline renal impairment, not in those patients with severe renal impairment at baseline, for whom there was no imbalance.
- Analyses of the primary clinical endpoint (composite of CV death, MI, or stroke) in patients with renal impairment and in patients with on-treatment creatinine increases suggest that these patients benefit from ticagrelor treatment.

Discussion of potential mechanism for the observed increase in serum creatinine and renal-related AEs is presented in Section 9.6. Additional data for creatinine increases and

renal-related AEs in the US and in patients taking high and low maintenance doses of ASA appear in Section 9.5.

Guidance to physicians for the clinical management of adverse effects is presented in Section 11. No renal monitoring is recommended beyond the standard of care for patients with ACS.

9.3.3 Cardiac arrhythmias and conduction abnormalities

Arrhythmias occur commonly during ACS. They range from benign premature ventricular beats to more malignant arrhythmias, such as sustained ventricular tachycardia, ventricular fibrillation, and complete atrioventricular (AV) block.

In ACS, bradycardic events, ie, bradyarrhythmias and conduction disturbances, follow some common patterns. Etiology, prognosis, and management vary according to the site and extent of MI (Ryan et al 1996). Sinus bradycardia occurs in up to one-third of patients, particularly after reperfusion of STEMI involving the right coronary artery, related to increased vagal tone (Bezold-Jarisch reflex) and ongoing ischemia of nodal and conduction tissue. Both sinus and AV node dysfunction are observed following ACS. Generally, bradycardia following anterior wall MI indicates extensive damage to the conduction system and often requires placement of a permanent pacemaker; bradycardia following non-anterior wall MIs resolve spontaneously within a few days.

Non-clinical studies with ticagrelor revealed no concerns related to cardiac arrhythmias or conduction abnormalities. Ticagrelor produced no significant adverse effects on the CV system in safety pharmacology studies. ECG monitoring in dogs and marmosets revealed no ticagrelor-related abnormalities. A “Thorough QT study” concluded that ticagrelor had no cardiac ventricular repolarization effect and no plasma concentration-related increases in the QTc interval. However, 1 healthy volunteer in this study, who received 900 mg ticagrelor, demonstrated AV block and a sinus pause without symptoms. One healthy volunteer in a Single Ascending Dose study, who received 1260 mg ticagrelor, had a symptomatic prolonged sinus pause that resolved.

Phase II studies disclosed no differences between ticagrelor and clopidogrel in heart rates or blood pressure, but did reveal an imbalance of ventricular pauses and bradycardia AEs with ticagrelor. DISPERSE2 employed continuous ECG (Holter) monitoring in 990 patients to comprehensively detect any recurrent ischemia. A post-hoc analysis of Holter data instead revealed an imbalance of mostly asymptomatic ventricular pauses >2.5 seconds: 5.6% with ticagrelor vs 4.4% with clopidogrel.

Based on these observations, PLATO excluded patients who, at enrollment, carried an increased risk of bradycardic events unless treated with a pacemaker: known sick sinus syndrome, second- or third-degree AV block, or previous documented syncope suspected to be due to bradycardia. In addition, PLATO included prospective Holter monitoring beginning at randomization in a subset of 2908 patients and prespecified analyses of cardiac arrhythmias.

Ventricular pauses detected by Holter monitoring in PLATO

Holter monitoring (3-lead digital cECG recording) occurred for up to 7 days immediately after randomization (Visit 1) and again 30 days after randomization (Visit 2). The substudy primary variable, ventricular pauses ≥ 3 seconds, included sinoatrial (SA) node, AV node, and other pauses; the substudy also explored ventricular pauses ≥ 5 seconds separately. Analyses of ventricular pauses ≥ 3 seconds included data for ventricular pauses ≥ 5 seconds. These variables were selected because patients with symptomatic ventricular pauses ≥ 3 seconds are often candidates for pacemaker insertion. Ventricular pauses ≥ 5 seconds, also a criterion for pacemaker insertion, are more likely to be symptomatic ([Epstein et al 2008](#)).

The primary prespecified analysis included patients with Holter measurements at both Visit 1 and Visit 2 so that comparisons were based on the same patient population: these paired readings allow the assessment of whether increases in ventricular pauses associate only with the initial ACS event, while the patient is in-hospital and usually monitored, or persist into the convalescent ambulatory phase.

Of the 2908 patients, 1949 had paired readings at Visit 1 and Visit 2, with mean recording durations of 6 days in both treatment groups at both visits. Forty-two patients had monitoring during Visit 2 only. After Visit 1, 917 patients did not return for Visit 2 monitoring: 35 had died (18 ticagrelor vs 17 clopidogrel); 34 had withdrawn consent (20 ticagrelor vs 14 clopidogrel); 302 had prematurely discontinued study drug (164 ticagrelor vs 138 clopidogrel); and 533 had unknown reasons (278 ticagrelor vs 255 clopidogrel) but remained in the study. Additionally, 7 ticagrelor and 6 clopidogrel patients had unreadable Visit 2 recordings.

Ventricular pauses of ≥ 3 seconds and ≥ 5 seconds occurred more commonly during Visit 1 compared to Visit 2 for both treatment groups, consistent with the natural history of ACS ([Table 40](#)). At both visits, more ticagrelor patients had ventricular pauses ≥ 3 seconds and ≥ 5 seconds compared to clopidogrel; this difference was statistically significant for ventricular pauses ≥ 3 seconds at Visit 1 only: relative risk=1.74 [95% CI 1.15, 2.64].

The results in all Holter patients are consistent with those observed in patients with paired readings. Of the 1451 ticagrelor patients and 1415 clopidogrel patients with Visit 1 Holter recordings, 5.8% and 3.6% had ventricular pauses ≥ 3 seconds, respectively; ventricular pauses ≥ 5 seconds occurred in 2.0% vs 1.2% of patients taking ticagrelor and clopidogrel, respectively. Of the 985 ticagrelor patients and 1006 clopidogrel patients with Visit 2 Holter recordings, 2.0% and 1.7% had ventricular pauses ≥ 3 seconds, respectively; ventricular pauses ≥ 5 seconds occurred infrequently during Visit 2 monitoring: 0.8% vs 0.6% of ticagrelor and clopidogrel patients, respectively.

Table 40 **Bradyarrhythmias at Visit 1 and Visit 2 for patients with paired readings – PLATO Holter analysis set**

Characteristic		Visit 1 (Index event)		Visit 2 (30 days post-randomization)	
		Ticagrelor 90 mg bid N=964	Clopidogrel 75 mg qd N=985	Ticagrelor 90 mg bid N=964	Clopidogrel 75 mg qd N=985
Heart rate in patients with paired readings	Mean (SD)	68.0 (10.52)	67.9 (10.09)	68.1 (10.21)	67.9 (10.22)
	Median	67.0	67.0	67.0	67.0
Patients with at least 1 bradyarrhythmia ^a		571 (59.2%)	531 (53.9%)	556 (57.7%)	498 (50.6%)
Ventricular pauses ≥ 3 secs		58 (6.0%)	34 (3.5%)	21 (2.2%)	16 (1.6%)
AV node pause ≥ 3 secs		15 (1.6%)	11 (1.1%)	6 (0.6%)	7 (0.7%)
SA node pause ≥ 3 secs		43 (4.5%)	22 (2.2%)	17 (1.8%)	11 (1.1%)
Ventricular pauses ≥ 5 secs		20 (2.1%)	10 (1.0%)	8 (0.8%)	5 (0.5%)
AV node pause ≥ 5 secs		6 (0.6%)	5 (0.5%)	2 (0.2%)	1 (0.1%)
SA node pause ≥ 5 secs		15 (1.6%)	4 (0.4%)	7 (0.7%)	4 (0.4%)

^a This total includes dropped beats and other bradyarrhythmias in addition to ventricular pauses. All terms refer to the cECG findings detected by Holter monitoring, not clinical events.

AV Atrioventricular; bid Twice daily dosing; cECG Continuous electrocardiogram; qd Once daily dosing; SA Sinoatrial; SD Standard deviation; sec Seconds.

SA node pauses were the most common type in both treatment groups for both visits and accounted for most of the imbalance in ventricular pauses between ticagrelor and clopidogrel. The guidelines for pacemaker implantation ([Epstein et al 2008](#)) do not recommend pacemaker implantation for asymptomatic sinus node dysfunction, based on lack of correlation with survival or sudden cardiac death.

Heart rates did not change over time in ticagrelor patients in the substudy, nor did they differ between treatment groups throughout both Holter recording periods.

Demographic analyses of patients with ventricular pauses showed that these patients in both treatment groups had slightly higher mean body weights and BMI; these observations were more apparent with ticagrelor.

Adverse events in patients with ventricular pauses

The Holter substudy analyses included prespecified bradyarrhythmia-related clinical events. [Table 41](#) displays those AEs if they were reported on the same date as a ventricular pause. Nine ticagrelor-treated patients (10.1%) reported these events, compared to 12 clopidogrel-treated patients (19.4%). Note that the event and the ventricular pause did not necessarily occur at or close to the same time within that day. Also patient numbers are small and from non-randomized subgroups; therefore, warranting caution in interpretation. Still, the Holter-detected excess of ventricular pauses with ticagrelor did not translate into more bradycardia-related AEs.

A similar summary of bradyarrhythmia-related AEs occurring at any time throughout PLATO in patients with ventricular pauses ≥ 3 seconds displayed an increase in bradycardia with ticagrelor (20 patients) vs clopidogrel (8 patients). Six patients in each treatment group with Holter-detected ventricular pauses ≥ 3 seconds died at any time during PLATO. Similar numbers of patients with ventricular pauses had syncope, heart block, cardiac output, or pacemaker insertion.

Overall, these revealed no increase in adverse clinical consequences associated with the increase in ventricular pauses with ticagrelor vs clopidogrel.

**Table 41 Bradyarrhythmia-related AEs (by PT) in patients with ventricular pauses
≥3 seconds that occurred on the same date – PLATO Holter analysis set**

Characteristic Preferred term	Ticagrelor 90 mg bid N=89	Clopidogrel 75 mg qd N=62
Patients with at least 1 bradycardia-related AE	17 (19.1%)	14 (22.6%)
Patients with at least 1 asymptomatic ^b AE	9	3
Bradycardia/bradyarrhythmia	7	2
Atrioventricular block complete	1	1
Sinus arrest	1	0
Patients with at least 1 symptomatic ^b AE	9	12
Bradycardia/bradyarrhythmia	4	4
Cardiac arrest	2	2
Atrioventricular block complete	1	3
Atrioventricular block second degree	1	1
Hypotension	1	3
Syncope	1	1
Dizziness	0	2
Orthostatic hypotension	0	1

^a Patients may be counted in more than 1 category but are counted only once within each category.

^b AEs of bradycardia/bradyarrhythmia, atrioventricular block complete/second degree or sinus arrest were considered asymptomatic unless the investigator specifically described them as 'symptomatic;' other PTs are counted as 'symptomatic.'

AE Adverse event; bid Twice daily dosing; HR Hazard ratio; qd Once daily dosing; PT Preferred term.

Arrhythmia AEs in PLATO

In PLATO, the overall occurrence of cardiac arrhythmia AEs was generally similar between treatment groups (Table 42), as were SAEs and discontinuations of study drug due to cardiac arrhythmia AEs.

Table 42 **Number (%) of patients reporting selected arrhythmia AEs – PLATO safety analysis set**

MedDRA HLGT Preferred Term	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
AEs in Cardiac Arrhythmias HLGT	1312 (14.2%)	1338 (14.6%)
Atrial fibrillation	390 (4.2%)	418 (4.6%)
Bradycardia	269 (2.9%)	270 (2.9%)
Ventricular tachycardia	184 (2.0%)	193 (2.1%)
Ventricular fibrillation	71 (0.8%)	88 (1.0%)
SAEs in Cardiac Arrhythmias HLGT	240 (2.6%)	266 (2.9%)
Discontinuations due to AEs in Cardiac Arrhythmias HLGT	53 (0.6%)	61 (0.7%)

AE Adverse event; bid Twice daily dosing; HLGT Higher level group term; MedDRA Medical Dictionary for Regulatory Activities; qd Once daily dosing; SAE Serious adverse event.

Other AEs possibly related to bradyarrhythmias in PLATO

[Table 43](#) displays prespecified analyses of categories of clinical events of interest that are possibly related to bradycardia or bradyarrhythmias. Numerically more patients taking ticagrelor compared to those taking clopidogrel reported bradycardia, dizziness and syncope; however, reports of hypotension, loss of consciousness, heart block, cardiac arrest, or pacemaker insertion were similar between groups or fewer with ticagrelor.

Table 43 **Number (%) of patients with bradyarrhythmia-related AEs on treatment – PLATO safety analysis set**

Categories of bradyarrhythmia-related AEs	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Total patients with ≥ 1 event	1238 (13.4%)	1200 (13.1%)
Dizziness	428 (4.6%)	368 (4.0%)
Hypotension	328 (3.6%)	345 (3.8%)
Bradycardia ^a	409 (4.4%)	372 (4.0%)
Syncope	100 (1.1%)	76 (0.8%)
Cardiac arrest	59 (0.6%)	88 (1.0%)
Heart block	67 (0.7%)	66 (0.7%)
Loss of consciousness	7 (0.1%)	13 (0.1%)
Pacemaker placement ^b	82 (0.9%)	79 (0.9%)
Temporary pacemaker	61 (0.7%)	52 (0.6%)
Permanent pacemaker	35 (0.4%)	37 (0.4%)
Pre-syncope	20 (0.2%)	13 (0.1%)
Vaso-vagal syncope	28 (0.3%)	35 (0.4%)

^a These categories of AEs include more than 1 PT, so the percent of patients with bradycardia do not match with the AEs reported by PT in Table 42.

^b Patients can be counted in both temporary and permanent pacemaker placement categories, but each patient is counted only once for 'pacemaker placement.' Pacemaker placement includes data from both AEs and from the bradycardic event eCRF page.

AE Adverse event; bid Twice daily dosing; qd Once daily dosing.

More patients in the ticagrelor group experienced AEs of syncope, but SAEs of syncope did not differ between ticagrelor and clopidogrel (26 vs 23). One ticagrelor patient and zero clopidogrel patients discontinued due to syncope. AEs of syncope, pre-syncope, vasovagal syncope, and loss of consciousness, when combined, occurred with a similar incidence in ticagrelor and clopidogrel patients: 154 (1.7%) and 136 (1.5%), respectively.

Heart rates in PLATO decreased by an average of 7 to 8 beats/minute from baseline to end of treatment visit; blood pressures decreased by 2 mmHg for systolic and 6 mmHg for diastolic. These changes occurred in both treatment groups.

Efficacy outcomes in patients at risk for ventricular pauses and who had Holter-detected ventricular pauses in PLATO

As patients with an increased risk of bradycardic events were excluded from PLATO, it is difficult to examine efficacy results in patients with an increased risk of ventricular pauses. Demographic analyses of patients with pauses showed that patients with pauses had higher

mean weight and BMI. The prespecified efficacy subgroup analyses included these 2 groups; and the benefit of ticagrelor treatment was apparent in these subgroups (Section 8.7).

Table 44 shows the primary composite efficacy endpoint in the Holter substudy, grouped by those with and without ventricular pauses ≥ 3 seconds. The group of patients with ventricular pauses is small and thus the results should be interpreted with caution; however, patients with ≥ 3 second ventricular pauses appear to have no disadvantage as a result of ticagrelor treatment compared to clopidogrel.

Table 44 Rate of primary endpoint for patients with or without a ventricular pause ≥ 3 seconds - PLATO Holter analysis set

Patient subgroup	Ticagrelor 90 mg bid			Clopidogrel 75 mg qd		
	N	n (%) patients with event	KM%	N	n (%) patients with event	KM%
With ventricular pauses ≥ 3 seconds	89	11 (12.4%)	11.3%	62	15 (24.2%)	24.5%
Without ventricular pauses ≥ 3 seconds	1383	154 (11.1%)	11.2%	1374	163 (11.9%)	12.0%

Note: 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.
bid twice daily dosing; KM Kaplan-Meier; qd Once daily dosing.

Summary of cardiac arrhythmias and conduction abnormalities

- The “Thorough QT study” demonstrated no cardiac ventricular repolarization effect with ticagrelor and no apparent ticagrelor plasma concentration-related increases in the QTc interval.
- Holter monitoring data from a subset of PLATO patients showed that the risk for having a ventricular pause ≥ 3 seconds was statistically greater with ticagrelor than clopidogrel during Visit 1 and this risk was numerically greater during Visit 2. These patterns were apparent regardless of whether the analysis included all patients in the Holter analysis set or only patients with paired readings.
- Ventricular pauses detected by Holter monitoring were predominantly asymptomatic and infrequently coincided with clinically important events such as syncope, heart block, cardiac arrest or pacemaker insertion, regardless of treatment group.
- No increase in symptomatic AEs was associated with the increased incidence in ventricular pauses with ticagrelor compared to clopidogrel.

- In PLATO, the number of patients with cardiac arrhythmia AEs was generally similar between treatment groups, as were cardiac arrhythmia-related SAEs and discontinuations due to an AE.
- Numerically more patients taking ticagrelor compared to those taking clopidogrel reported bradycardia, dizziness, and syncope, but not hypotension, loss of consciousness, heart block, cardiac arrest, or pacemaker insertion.
- Although the numbers of patients and events are small, it appears that patients with ≥ 3 second ventricular pauses benefit from ticagrelor treatment.

The mechanism responsible for the increase in ventricular pauses with ticagrelor is not yet known, but a potential mechanism is discussed in Section 9.6.

Guidance to physicians with respect to patients at increased risk of bradycardic events is presented in Section 11.

9.3.4 Increases in serum uric acid

Increased serum uric acid with ticagrelor administration was first noted in the Phase II DISPERSE and DISPERSE2 studies. A Phase I study in healthy volunteers, performed to examine the effect of ticagrelor on serum uric acid levels and urinary uric acid excretion under controlled conditions of diet, fluid intake, and activity, demonstrated that the small increases in serum uric acid with ticagrelor were reversible within 60 hours after the last dose of ticagrelor. Uric acid is not routinely measured in non-clinical studies because the enzyme uricase, which is present in most preclinical species but is not active in humans, converts uric acid to urea. Routine monitoring of urea levels in repeat-dose toxicity studies, however, did not demonstrate any consistent effects related to ticagrelor.

Changes in serum uric acid in PLATO

Serum uric acid increased from baseline up to 0.7 mg/dL with ticagrelor and 0.3 mg/dL with clopidogrel (Table 45). This increase corresponds to a mean percent change from baseline (using individual baseline-matched values) of approximately 15% for ticagrelor compared to an approximately 7.5% increase for clopidogrel. Serum uric acid levels decreased after discontinuation of treatment in ticagrelor-treated patients but not in clopidogrel-treated patients so that the 2 treatment groups were similar with respect to serum uric acid levels within 30 days after discontinuation of study treatment.

Table 45 **Mean serum uric acid by study visit - PLATO safety laboratory analysis set**

Timepoint	Ticagrelor 90 mg bid		Clopidogrel 75 mg qd	
	n	Mean (SD) mg/dL	n	Mean (SD) mg/dL
Visit 1 (baseline ^a)	4642	5.77 (1.630)	4624	5.81 (1.591)
Visit 2	4901	6.36 (1.759)	4870	5.97 (1.563)
Visit 3	4494	6.44 (1.743)	4496	6.04 (1.602)
Visit 4	4021	6.42 (1.747)	3998	6.01 (1.578)
Visit 5	229	6.41 (1.534)	222	6.10 (1.625)
Visit 6	3652	6.37 (1.739)	3642	6.00 (1.554)
30-day Follow-up	3595	5.95 (1.559)	3546	6.01 (1.593)

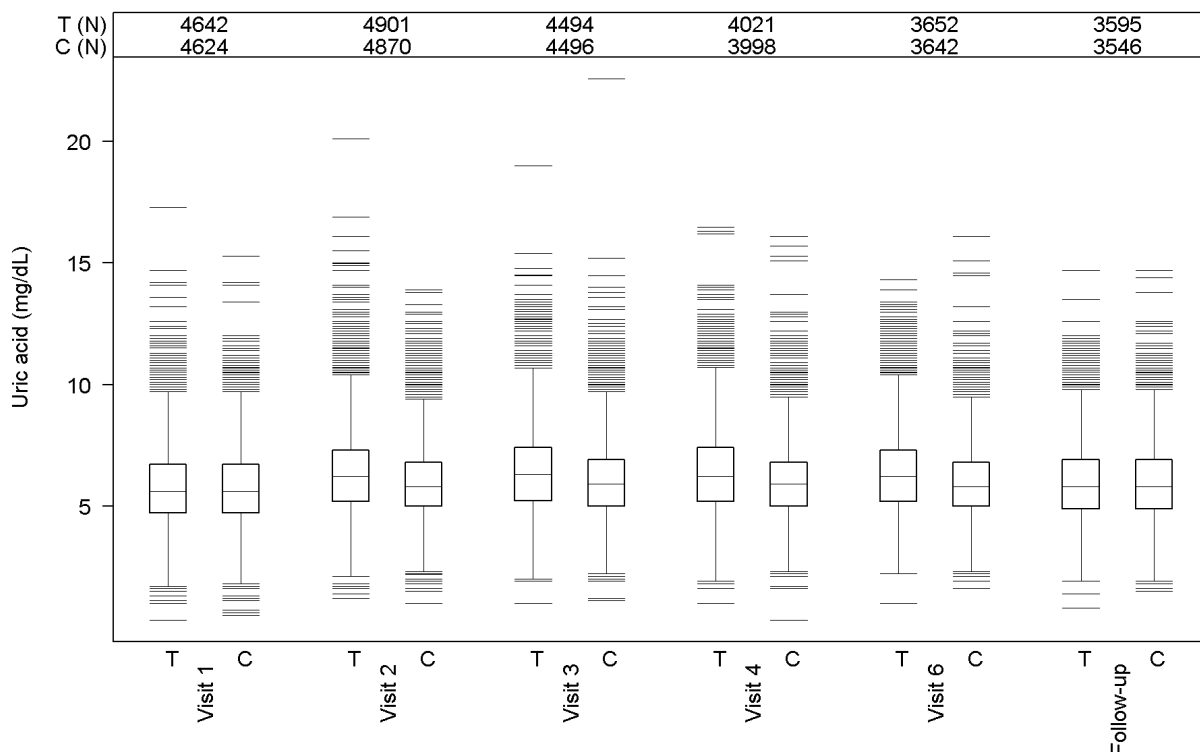
Note: Numbers of patients represented in laboratory analyses are lower than the safety laboratory analysis set because some patients did not have samples taken at all study visits.

^a Baseline defined as first sample date and time \leq first dose date and time.

bid Twice daily dosing; qd Once daily dosing; SD Standard deviation.

Box plots of serum uric acid ([Figure 32](#)) show that the scale of the increase in serum uric acid is small compared to the range of the data, and the differences between ticagrelor and clopidogrel are small as shown in the number of outliers and magnitude of change. The treatment effect noted for mean change in serum uric acid over time appears to be driven by a small increase in the majority of patients rather than a small number of larger changes.

Figure 32 Box plots of serum uric acid – PLATO safety laboratory analysis set



Note: All patients with routine uric acid measurements are displayed.
C Clopidogrel; T Ticagrelor

The 3 ticagrelor outlier values occurred in 2 ticagrelor-treated patients. The outlier values at Visit 1 and Visit 2 occurred in the same patient, who entered the trial with a serum uric acid value of 17.3 mg/dL. This patient, with a past medical history of chronic kidney disease, suffered acute renal failure on Day 2; this AE resolved on Day 9. The patient's uric acid level increased to 20 mg/dL by Day 30. The patient died on Day 40 due to an MI. The ticagrelor outlier at Visit 3 represents a patient who entered the trial with uric acid level of 7.4 mg/dL, suffered gout on Day 82 and acute renal failure on Day 84, which resolved on Day 166. The patient completed 363 days of study medication. At the follow-up visit, the patient's uric acid level was 7.2 mg/dL.

Uric acid-related AEs

Few patients reported uric acid-related AEs (2.1% taking ticagrelor vs 1.8% taking clopidogrel; [Table 46](#)). A small numerical imbalance in uric-acid related AEs occurred for ticagrelor-treated compared to clopidogrel-treated patients, primarily in the PT 'hyperuricemia.'

AEs of gout (Table 46) as well as the combined terms of gout and gouty arthritis occurred with similar frequency in the 2 treatment groups: 73 (0.8%) with ticagrelor vs 63 (0.7%) with clopidogrel. Of 1296 ticagrelor patients with serum uric acid above the ULN, 33 (2.5%) reported an AE, compared to 19 of 852 (2.2%) of clopidogrel patients, with most imbalances in the AEs based laboratory terms. Among those patients with serum uric acid >ULN, 7 patients in each treatment group reported gout or gouty arthritis.

Table 46 **Number (%) of patients with the most commonly reported uric acid-related AEs (by PT) on treatment – PLATO safety analysis set**

Preferred term	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Patients with at least 1 event	195 (2.1%)	164 (1.8%)
Gout	59 (0.6%)	58 (0.6%)
Hyperuricemia	42 (0.5%)	19 (0.2%)
Calculus urinary	21 (0.2%)	24 (0.3%)
Blood uric acid increased	18 (0.2%)	12 (0.1%)
Joint swelling	17 (0.2%)	18 (0.2%)
Nephrolithiasis	16 (0.2%)	23 (0.3%)
Gouty arthritis	15 (0.2%)	6 (0.1%)

Note: Because there is no single MedDRA SOC or SMQ that captures all relevant terms, specific and non-specific terms potentially related to uric acid excess were compiled from Metabolism and nutrition disorders, Renal and urinary disorders, Musculoskeletal and connective tissue disorders, and Investigations SOCs.

AE Adverse event; bid Twice daily dosing; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred term; qd Once daily dosing; SMQ Standardized MedDRA query; SOC System Organ Class.

The effect of diuretics (excluding xanthine derivatives and most ‘other’ low ceiling diuretics) on serum uric acid was explored since some diuretics are known to increase serum uric acid. Using a diuretic ≥50% of the time during the study increased serum uric acid levels similarly in both treatment groups but did not increase the likelihood of having an episode of gout with ticagrelor compared with clopidogrel.

Patients with a medical history of gout at randomization reported gout AEs during PLATO more frequently than those without a prior history, but without a differential with respect to study treatment: 25 of 267 (9.4%) for ticagrelor vs 29 of 260 (11.2%) for clopidogrel. In contrast, those with no past history of gout report new events of gout with a frequency of approximately 0.5% in both treatment groups. These data suggest that reports of gout or gouty arthritis may be independent of uric acid levels and instead more strongly associated with prior history of gout.

Summary of increases in uric acid with ticagrelor

- Ticagrelor-treated patients had increases in mean serum uric acid of approximately 15% (mean percent increase from baseline) compared to an approximately 7.5% increase for clopidogrel-treated patients.
- Serum uric acid levels were similar in both treatment groups within 30 days after discontinuation of study treatment.
- Few ticagrelor-treated patients reported uric acid-related AEs, which occurred similarly the 2 groups.
- Diuretic use and prior history of gout were associated with increases in uric acid-related AEs in both treatment groups.

Potential mechanisms for the adverse effects reported during ticagrelor treatment are discussed in Section 9.6.

9.3.5 Hepatic function

Throughout the ticagrelor clinical development program, data pertaining to hepatic safety were scrutinized for signs of drug-induced liver injury (DILI) with ticagrelor.

Changes in liver enzymes, albumin, total protein and bilirubin occurred in rodents without histological evidence of hepatocellular injury. In marmosets, ticagrelor did not increase liver weight, plasma/serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), cholesterol, albumin or total protein; no hepatocellular hypertrophy occurred. Although female rats fed high doses of ticagrelor (180 mg/kg/day) showed a slight increase in the incidence of hepatocellular adenomas and carcinomas, this reflects a known species effect in hepatic adaptive responses that is not relevant for humans (Graham and Lake 2008; Greaves 2007).

In a Phase I study, patients with mild hepatic impairment (Child Pugh A) had modestly increased ticagrelor exposure (C_{max} increased by 12% and AUC increased by 23%) compared to healthy volunteers (Section 5.4), suggesting no need for a ticagrelor dose adjustment for patients with mild hepatic impairment. Patients with moderate to severe hepatic impairment have not been studied in clinical pharmacology studies.

Despite exclusion criteria in PLATO for patients with moderate and severe hepatic impairment, some of these patients likely enrolled, given the urgent nature of ACS, which permitted collection of only limited information to gauge the severity of hepatic impairment (ie, no Child Pugh scores were obtained).

Aspartate aminotransferase (AST) elevations accompany ACS, typically exceeding the ULN within 8 to 12 hours and reach peak elevation (2x to 10x ULN) at 36 hours, then declining to normal over the next 3 to 4 days (Sobel and Shell 1972). In PLATO, AST levels followed this

pattern with increases at the time of the initial ACS event and subsequent decrease for the remainder of the treatment period in both treatment groups.

Liver function test (LFT) abnormalities occurred similarly in the 2 treatment groups, with 219 (3.9%) ticagrelor and 210 (3.8%) clopidogrel patients in the safety laboratory analysis set with at least 1 abnormal LFT. Individual LFT measurements showed similar proportions of ticagrelor and clopidogrel patients with LFT abnormalities, except for total bilirubin, for which 25 ticagrelor (0.4%) and 10 clopidogrel (0.2%) patients had increases >2x ULN. Resolution of the bilirubin increase, ie, a decrease to below ULN, occurred in 6 of the 25 ticagrelor patients and 2 of the 10 clopidogrel patients.

In PLATO, hepatocellular, mixed, and cholestatic event type hepatic injury occurred similarly in the 2 treatment groups (1.4% for ticagrelor and 1.5% for clopidogrel; [Table 47](#)).

Table 47 Liver function test abnormalities by type of hepatic injury – PLATO safety laboratory analysis set

Type of injury	LFT Abnormality	Ticagrelor 90 mg bid N=5610	Clopidogrel 75 mg qd N=5582
Any injury	Patients with at least 1 event	80 (1.4%)	85 (1.5%)
Hepatocellular	Patients with at least 1 hepatocellular event	39 (0.7%)	43 (0.8%)
	+ ALT or AST >10xULN	8 (0.1%)	7 (0.1%)
Mixed	Patients with at least 1 mixed event	4 (0.1%)	5 (0.1%)
	+ ALT or AST >10xULN	0 (0.0%)	2 (0.0%)
Cholestatic	Patients with at least 1 cholestatic event	42 (0.7%)	42 (0.8%)
	+ ALT or AST >10x ULN	1 (0.0%)	3 (0.1%)

Note: Definitions of types of hepatic injury (hepatocellular, mixed, and cholestatic) are derived from [Abboud and Kaplowitz 2007](#). Hepatocellular is defined as: ALT $\geq 3 \times$ ULN and (ALT/ULN)/(ALP/ULN) ≥ 5 ; Mixed is defined as: ALT $\geq 3 \times$ ULN and ALP $\geq 2 \times$ ULN with (ALT/ULN)/(ALP/ULN) >2 to <5xULN; Cholestatic is defined as: ALP $\geq 2 \times$ ULN and (ALT/ULN)/(ALP/ULN) ≤ 2 .

ALP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; bid Twice daily dosing; LFT Liver function test; qd Once daily dosing; ULN Upper limit of normal.

The overall frequency of hepatic-related AEs (1.7% of patients in each treatment group), SAEs (including those with an outcome of death), and the patterns of individual hepatic-related AEs were similar between the ticagrelor and clopidogrel groups in the PLATO study. Therefore, these data provide no evidence of drug-induced liver injury during treatment with ticagrelor.

Summary of hepatic function with ticagrelor

- In patients with mild hepatic impairment, the exposure (C_{\max} and AUC) for ticagrelor increased modestly in patients with mild hepatic impairment, compared to matched healthy volunteers.
- In PLATO, the overall patterns of liver function test abnormalities were similar in the ticagrelor and clopidogrel treatment groups.
- Hepatocellular, mixed, and cholestatic event type hepatic injury occurred similarly in the ticagrelor and clopidogrel treatment groups in PLATO.
- The overall frequency of hepatic-related AEs and the patterns of hepatic-related AEs were similar in the ticagrelor and clopidogrel groups.
- Overall, there is no evidence of DILI with ticagrelor during the development program.

Ticagrelor is contraindicated in patients with severe hepatic impairment because of an increased risk of bleeding with antiplatelet agents in these patients. Caution is advised in patients with moderate hepatic impairment as these patients have not been studied.

9.3.6 Neoplasms and gynecological cancer

In female rats (but not in male rats or in mice), ticagrelor produced a change in the tumor incidence pattern at the high dose only (180 mg/kg/day), consisting of increased incidence of uterine tumors (adenocarcinomas) associated with a reduced incidence of mammary tumors and reduced incidence of pituitary adenomas and hyperplasia, as well as a mild increased incidence of hepatic tumors. The mid-dose did not show any effect and represents an 8-fold margin of safety. The hepatocellular tumors seen in high-dose female rats reflect a known species effect in hepatic adaptive responses that is not relevant for humans. The pattern of tumor formation (increased uterine tumors with concurrent decreased pituitary and mammary tumors) is consistent with a sustained reduction in circulating prolactin, as has been documented for drugs like bromocryptine, and is not relevant to humans.

Because of the non-clinical finding of rat-specific uterine tumors and recent clinical studies on prasugrel showing a higher incidence of neoplasms ([FDA 2009](#)), the incidence of neoplasms was examined in PLATO and across the ticagrelor development program.

Monitoring of abnormal vaginal bleeding in PLATO

Abnormal vaginal bleeding, which may occur in association with gynecological cancer, was thoroughly evaluated across the ticagrelor development program as a result of the non-clinical findings described above. AEs related to abnormal vaginal bleeding occurred similarly in the ticagrelor and clopidogrel treatment groups in the PLATO study: 23 AEs and 1 SAE for ticagrelor vs 18 AEs and 2 SAEs for clopidogrel. One patient who took ticagrelor for 14 days was diagnosed with endometrial adenocarcinoma. This patient discontinued taking study medication; the investigator considered the endometrial cancer not related to study treatment.

Incidence of neoplasms in PLATO

In PLATO, benign neoplasms and non-benign neoplasms occurred similarly in the ticagrelor and clopidogrel treatment groups (Table 48). Of patients with a baseline history of malignant neoplasms, fewer ticagrelor patients than clopidogrel patients developed a treatment-emergent (TE) neoplasm. Of the patients without such baseline history, similar numbers of patients developed treatment-emergent neoplasms. Deaths due to cancer did not differ between treatment groups: 15 ticagrelor patients (0.2%) and 17 clopidogrel patients (0.2%). The PLATO data indicate no increased risk of neoplasia with ticagrelor during the 1-year treatment and follow-up period.

Table 48 **Number (%) of patients with neoplasms - on treatment and overall – PLATO safety analysis set**

	On treatment		Overall (on + off treatment)	
	Ticagrelor 90 mg bid	Clopidogrel 75 mg qd	Ticagrelor 90 mg bid	Clopidogrel 75 mg qd
Safety analysis set	N=9235	N=9186	N=9235	N=9186
Patients with TE ^a neoplasm (includes Investigations SOC)	132 (1.4%)	155 (1.7%)	166 (1.8%)	179 (1.9%)
Patients with TE malignancy (Malignancy SMQ)	115 (1.2%)	121 (1.3%)	142 (1.5%)	144 (1.6%)
Patients with TE malignancy (excl. non-melanomatous skin cancer)	103 (1.1%)	112 (1.2%)	128 (1.4%)	133 (1.4%)
Patients with TE benign neoplasm (everything in Neoplasm SOC subtracting out Malignancy SMQ)	18 (0.2%)	35 (0.4%)	26 (0.3%)	37 (0.4%)
Patients with history of non-benign neoplasm at baseline	N=299 (3.2%)	N=316 (3.4%)	N=299 (3.2%)	N=316 (3.4%)
Patients with pre-existing non-benign neoplasm who had TE neoplasm	14 (4.7%)	26 (8.2%)	18 (6.0%)	28 (8.9%)
Patients without history of non-benign neoplasm at baseline	N=8936	N=8870	N=8936	N=8870
Patients without history of non-benign neoplasm with new TE neoplasm	118 (1.3%)	129 (1.5%)	148 (1.7%)	151 (1.7%)

^a Treatment emergent (TE) neoplasms are defined as neoplasms occurring after the start of study treatment and include gynecological cancers.

AE Adverse event; bid Twice daily dosing; qd Once daily dosing; MedDRA Medical dictionary for regulatory activities; SMQ Standardized MedDRA queries; SOC System organ class; TE Treatment-emergent.

Summary of neoplasms for ticagrelor

- Non-clinical studies with ticagrelor showed an increase in uterine epithelial tumors and in hepatocellular tumors in female rats but not in mice; these findings are not considered relevant to humans.
- AEs related to abnormal vaginal bleeding occurred similarly in the ticagrelor and clopidogrel treatment groups in the PLATO study.
- The clinical data from the PLATO study revealed no imbalances in the reports of neoplasm AEs (including gynecological cancers) during the PLATO study, which followed patients for up to 1 year. These clinical data are, however, limited by the relatively short duration of observation.

9.4 Laboratory and vital sign data

Ticagrelor treatment did not associate with changes in either hematologic parameters or the following clinical chemistry parameters: glycosylated hemoglobin A1c, total cholesterol, LDL-C (calculated), HDL-C, or glucose. Data for serum creatinine, serum uric acid, and liver enzyme function tests are presented in Section 9.3.2, Section 9.3.4 and Section 9.3.5, respectively. No treatment differences occurred in measurements of heart rate or blood pressure or in physical examination findings.

9.5 Safety in special populations (subgroups)

The analyses of safety data from the ticagrelor development program demonstrated that the safety profile of ticagrelor with respect to AEs was generally consistent across subgroups studied, including age, sex, race and geographic region.

The analysis of AEs by geographic region is further explored below because of the treatment by region interaction seen for the efficacy outcomes (Section 8.8).

Overview of safety by geographic region

Table 49 summarizes the percentages of patients with AEs by category in the US and Table 50 summarizes the most common AEs by PT in the US. Both tables include bleeding AEs.

A higher percentage of patients reported AEs in the US population in both treatment groups (82.3% vs 78.5% for ticagrelor and clopidogrel, respectively) compared to the overall PLATO study, but patients in both treatment groups within and outside the US reported similar patterns of AEs.

Table 49 **Number (%) of patients in the US within categories of AEs on treatment, including bleeding events – PLATO safety analysis set**

Category	Ticagrelor 90 mg bid N=682	Clopidogrel 75 mg qd N=675
Any AE	561 (82.3%)	530 (78.5%)
Mild	438 (64.2%)	409 (60.6%)
Moderate	359 (52.6%)	333 (49.3%)
Severe	117 (17.2%)	98 (14.5%)
Any SAE	173 (25.4%)	161 (23.9%)
SAE excluding death	167 (24.5%)	154 (22.8%)
Death	8 (1.2%)	13 (1.9%)
AE leading to study drug discontinuation	82 (12.0%)	54 (8.0%)
SAE	35 (5.1%)	30 (4.4%)

AE Adverse event; bid Twice daily dosing; qd Once daily dosing; SAE Serious adverse event; US United States.

The US and overall PLATO safety population share most of the same PTs for the most commonly reported AEs. Of these, some AEs were reported more frequently in the US for both treatment groups, such as dyspnea.

Table 50 **Number (%) of patients reporting the most common AEs (by PT) in the US, including bleeding AEs – PLATO safety analysis set**

Preferred term	Ticagrelor 90 mg bid N=682	Clopidogrel 75 mg qd N=675
Patients with at least 1 event	561 (82.3%)	530 (78.5%)
Dyspnea (single PT)	128 (18.8%)	59 (8.7%)
Headache	51 (7.5%)	40 (5.9%)
Epistaxis	35 (5.1%)	32 (4.7%)
Cough	30 (4.4%)	30 (4.4%)
Dizziness	56 (8.2%)	36 (5.3%)
Nausea	59 (8.7%)	39 (5.8%)
Atrial fibrillation	29 (4.3%)	32 (4.7%)
Contusion	47 (6.9%)	32 (4.7%)
Hypertension	33 (4.8%)	24 (3.6%)
Non-cardiac chest pain	41 (6.0%)	42 (6.2%)

AE Adverse event; bid Twice daily dosing; qd Once daily dosing; PT Preferred term; US United States.

Analysis of AEs across geographic regions disclosed no new safety concerns for ticagrelor in specific regions. The safety topics of bleeding, dyspnea, and renal effects are addressed in more detail below.

Bleeding, dyspnea, and renal effects by region

[Table 51](#) displays adjudicated bleeding events and AEs of special interest for ticagrelor in the US and non-US cohorts. A division by NA and non-NA yielded similar results. The small size of the US cohort and smaller numbers of patients with events warrants caution in interpreting results shown in [Table 51](#).

Aside from slightly higher incidences, the US cohort displayed similar adjudicated bleeding results to that of the non-US cohort and overall PLATO population, regardless of severity, ie, Major or Major+Minor, and regardless of clinical context, ie, overall or only non-procedural.

Dyspnea was reported more frequently in the US vs the non-US in both treatment groups, with more dyspnea AEs for ticagrelor than for clopidogrel. This treatment differential was slightly greater in the US than in the overall PLATO population.

The pattern of renal-related AEs and of clinically meaningful changes in creatinine in the US and non-US both reflected the observations in the overall PLATO population. Both treatment groups had more patients with creatinine increases >50% in the US subgroup.

Table 51 **Number (%) of patients in the US and non-US with bleeding events, dyspnea AEs or renal-related AEs– PLATO safety analysis set**

Adverse effect	US		Non-US	
	Ticagrelor 90 mg bid N=682	Clopidogrel 75 mg qd N=675	Ticagrelor 90 mg bid N=8553	Clopidogrel 75 mg qd N=8511
Major bleeding	77 (11.3%)	74 (11.0%)	884 (10.3%)	855 (10.0%)
Major+Minor	101 (14.8%)	92 (13.6%)	1238 (14.5%)	1123 (13.2%)
Non-procedural Major bleeding	20 (2.9%)	17 (2.5%)	215 (2.5%)	163 (1.9%)
Non-procedural Major+Minor bleeding	35 (5.1%)	28 (4.1%)	422 (4.9%)	304 (3.6%)
Dyspnea AE (5 PTs ^a)	146 (21.4%)	65 (9.6%)	1124 (13.1%)	656 (7.7%)
Renal-related AE	36 (5.3%)	26 (3.9%)	413 (4.8%)	319 (3.7%)
Creatinine increase >50%	35/271 (12.9%)	20/258 (7.8%)	300/3760 (8.0%)	251/3777 (6.6%)

^a Dyspnea AEs include these 5 dyspnea PTs: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, and dyspnea paroxysmal nocturnal.
AE Adverse event; bid Twice daily dosing; qd Once daily dosing; PT Preferred Term; US United States.

Overview of safety by ASA maintenance doses

Table 52 summarizes the percentages of patients with AEs by category in the high and low ASA maintenance dose subgroups and Table 53 summarizes the most common AEs by PT in the high and low ASA maintenance dose subgroups. Both tables include bleeding AEs.

Patients taking high maintenance doses of ASA reported more AEs compared to the AE frequency in the overall PLATO study. The incidence of AEs in the low ASA maintenance dose subgroup in both treatment groups was similar to the overall PLATO population.

Table 52 **Number (%) of patients within categories of AEs on treatment, including bleeding events, by ASA maintenance dose – PLATO safety analysis set**

Category	High-dose ASA ^a (≥300 mg)		Low-dose ASA ^a (<300 mg)	
	Ticagrelor 90 mg bid N=464	Clopidogrel 75 mg qd N=492	Ticagrelor 90 mg bid N=8258	Clopidogrel 75 mg qd N=8233
Any AE	368 (79.3%)	373 (75.8%)	6009 (72.8%)	5704 (69.3%)
Mild	287 (61.9%)	301 (61.2%)	5135 (62.2%)	4774 (58.0%)
Moderate	212 (45.7%)	205 (41.7%)	2931 (35.5%)	2715 (33.0%)
Severe	82 (17.7%)	70 (14.2%)	835 (10.1%)	897 (10.9%)
Any SAE	121 (26.1%)	115 (23.4%)	1621 (19.6%)	1636 (19.9%)
SAE excluding death	115 (24.8%)	110 (22.4%)	1512 (18.3%)	1496 (18.2%)
Death	10 (2.2%)	12 (2.4%)	166 (2.0%)	228 (2.8%)
AE Leading to study drug discontinuation	52 (11.2%)	38 (7.7%)	577 (7.0%)	418 (5.1%)
SAE	26 (5.6%)	22 (4.5%)	209 (2.5%)	170 (2.1%)

^a Median ASA based on ASA usage from Day 2 to end of study drug period (or censored at primary event) for patients with at least 2 days of ASA.

AE Adverse event; ASA Acetylsalicylic acid; bid Twice daily dosing; qd Once daily dosing, SAE Serious adverse event.

The most common AEs in both ASA dose subgroups reflected those AEs that occurred in the overall PLATO population. Of these, some AEs were reported more frequently in the high ASA maintenance dose subgroup, such as dyspnea. The patterns of AEs in the low ASA maintenance dose subgroup in both treatment groups were similar to the overall PLATO population.

Table 53 **Number (%) of patients reporting the most common AEs (by PT), including bleeding AEs, by ASA maintenance dose – PLATO safety analysis set**

Preferred term	High-dose ASA ^a (≥300 mg)		Low-dose ASA ^a (<300 mg)	
	Ticagrelor 90 mg bid N=464	Clopidogrel 75 mg qd N=492	Ticagrelor 90 mg bid N=8258	Clopidogrel 75 mg qd N=8233
Dyspnea (single PT)	81 (17.5%)	44 (8.9%)	966 (11.7%)	533 (6.5%)
Headache	40 (8.6%)	29 (5.9%)	531 (6.4%)	488 (5.9%)
Epistaxis	23 (5.0%)	26 (5.3%)	510 (6.2%)	271 (3.3%)
Cough	24 (5.2%)	21 (4.3%)	408 (4.9%)	392 (4.8%)
Dizziness	27 (5.8%)	22 (4.5%)	372 (4.5%)	316 (3.8%)
Nausea	32 (6.9%)	23 (4.7%)	343 (4.2%)	309 (3.8%)
Atrial fibrillation	21 (4.5%)	17 (3.5%)	348 (4.2%)	376 (4.6%)
Contusion	24 (5.2%)	18 (3.7%)	320 (3.9%)	164 (2.0%)
Hypertension	19 (4.1%)	17 (3.5%)	325 (3.9%)	332 (4.0%)
Non-cardiac chest pain	24 (5.2%)	29 (5.9%)	310 (3.8%)	265 (3.2%)

^a Median ASA based on ASA usage from Day 2 to end of study drug period (or censored at primary event) for patients with at least 2 days of ASA.

AE Adverse event; ASA Acetylsalicylic acid; bid Twice daily dosing; qd Once daily dosing

Bleeding, dyspnea, and renal effects by ASA dose

The safety topics of bleeding, dyspnea, and renal effects were explored stratified by high and low maintenance ASA dose (high ≥300, low <300; [Table 54](#)) given the potential interaction of ASA in relation to efficacy results in the NA subgroup (Section 8.8). The small size of the high ASA maintenance dose subgroup, even smaller than that of the US subgroup, warrants caution in interpreting results in [Table 54](#).

The high ASA maintenance dose subgroup is comprised of patients in both the US and non-US. In the US, over half the patients received a high maintenance dose of ASA (>300 mg) while the majority of the remaining patients received a low maintenance dose (<100 mg).

Patients receiving high and low maintenance doses of ASA displayed similar adjudicated bleeding results to that of the overall PLATO population, regardless of severity, ie, Major or Major+Minor, and regardless of clinical context, ie, overall or only non-procedural.

Dyspnea was reported more frequently in the high ASA maintenance dose subgroup than in the low ASA maintenance dose subgroup for both ticagrelor and clopidogrel. The incidence of dyspnea in the low ASA maintenance dose subgroup in both treatment groups was similar to the overall PLATO population.

The pattern of renal-related AEs and of clinically meaningful changes in creatinine in the high and low ASA maintenance dose subgroups both generally reflected the observations in the overall PLATO population. Both treatment groups had more patients with creatinine increases >50% in the high maintenance dose ASA subgroup. In both treatment groups, creatinine increases >50% in the low ASA maintenance dose subgroup were similar to the overall PLATO population.

Table 54 **Number (%) of patients with bleeding events, dyspnea AEs or renal-related AEs, by treatment and ASA maintenance dose – PLATO safety analysis set**

Adverse effect	High-dose ASA ^a (≥300 mg)		Low-dose ASA ^a (<300 mg)	
	Ticagrelor 90 mg bid N=464	Clopidogrel 75 mg qd N=492	Ticagrelor 90 mg bid N=8258	Clopidogrel 75 mg qd N=8233
Major bleeding	46 (9.9%)	46 (9.3%)	834 (10.1%)	804 (9.8%)
Major+Minor bleeding	64 (13.8%)	58 (11.8%)	1176 (14.2%)	1064 (12.9%)
Non-procedural Major bleeding	14 (3.0%)	14 (2.8%)	207 (2.5%)	155 (1.9%)
Non-procedural Major+Minor bleeding	27 (5.8%)	22 (4.5%)	405 (4.9%)	290 (3.5%)
Dyspnea AE (5 PTs ^b)	91 (19.6%)	50 (10.2%)	1115 (13.5%)	649 (7.9%)
Renal-related AE	25 (5.4%)	20 (4.1%)	395 (4.8%)	307 (3.7%)
Creatinine increase >50%	26/173 (15.0%)	15/160 (9.4%)	299/3734 (8.0%)	246/3767 (6.5%)

^a Median ASA based on ASA usage from Day 2 to end of study drug period (or censored at primary event) for patients with at least 2 days of ASA.

^b Dyspnea AEs include these 5 dyspnea PTs: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, and dyspnea paroxysmal nocturnal.

AE Adverse event; ASA Acetylsalicylic acid; bid Twice daily dosing; qd Once daily dosing.

Demographic factors and baseline medical history

For both the ticagrelor and clopidogrel treatment groups, the frequency of AE reports increases with age, probably reflecting underlying background morbidity. Women have more AE reports than men. Caucasians and non-Caucasians report AEs with similar frequencies. Habitual smokers in PLATO had a similar AE frequency to non-habitual smokers.

Overall, AEs were more frequent in patients with moderate or severe renal impairment at baseline. For both treatment groups, AEs overall were reported with a similar frequency in patients with a history of diabetes at baseline and those without.

9.6 Potential mechanisms for clinical adverse effects observed with ticagrelor

Adverse effects potentially related to adenosine

Ticagrelor is not an adenosine analog and only weakly stimulates adenosine receptors (with greatest activity as an agonist of the adenosine A₃ receptor). It does block the uptake of adenosine into erythrocytes, potentially increasing local concentrations of endogenous adenosine and prolonging its effects.

Although the mechanism for the increased incidence of dyspnea reported by patients taking ticagrelor is not known, a hypothesis is that it results from an excess of endogenous adenosine due to ticagrelor's inhibition of adenosine reuptake in the red blood cells, which may cause dyspnea via activation of cell surface adenosine receptors and stimulation of the pulmonary or vagal c-fibers. Furthermore, intravenous adenosine and intravenous dipyridamole are both associated with dyspnea, providing support for such a mechanism. Several non-clinical studies have been conducted as part of AstraZeneca's efforts to elucidate the mechanism. In an initial safety pharmacology study in rats, a slight but significant and dose dependent increase in respiratory rates and decreases in expiration rates were seen, which may not necessarily correlate with human dyspnea. Further studies in rats failed to show effects at similar or higher exposure levels. Because of the mild and transient nature of the majority of dyspnea episodes, it is difficult to elucidate a mechanism for dyspnea clinically. Ticagrelor showed no effect on pulmonary function in clinical studies (for both healthy volunteers and patients with CAD or ACS), and pulmonary function data from patients experiencing dyspnea was difficult to obtain due to the nature of the symptom (mild and often transient or intermittent).

The increase in ventricular pauses with ticagrelor could also be related to the effect of an increase in endogenous adenosine, which decreases SA node activity and AV node conduction. This may be especially apparent in the setting of ACS, where there may be increased release of adenosine due to ischemia. Adenosine depresses SA node activity, AV node conduction, and ventricular automaticity, and attenuates cardiac stimulatory action of catecholamines and the release of norepinephrine from nerve terminals ([Belardinelli and Lerman 1991](#)). However, other mechanisms may be involved in addition to an adenosine mediated effect, eg, increased vagal tone.

Many non-clinical studies have been conducted to examine the mechanism of the adverse effects seen with ticagrelor and the possible involvement of adenosine. Since adenosine is evanescent in blood, it is difficult to measure directly ([Eltzschig 2009](#)). As a result, data from the ticagrelor development program are not able to definitively answer whether the adverse effects are adenosine-mediated, despite some evidence that adenosine may play a role.

Possible mechanism of other adverse effects

Although the exact mechanism for the renal effects of ticagrelor is not known, the data do not suggest that the increases in creatinine and non-serious renal-related AEs with ticagrelor are a result of kidney injury. Most importantly, the mild increases in creatinine are non-progressive

over time. The observed increases in serum creatinine, which were confirmed using measurements of cystatin C (a more accurate biomarker for GFR) from PLATO suggest that ticagrelor and clopidogrel may increase creatinine via a functional effect on GFR rather than on tubular secretion of creatinine.

Increased uric acid with ticagrelor is likely secondary to a combination of increased turnover and decreased excretion of uric acid. Increased adenosine is converted to inosine after deamination and is later degraded into hypoxanthine and xanthine, and ultimately uric acid. Following observations of increased uric acid in clinical trials, *in vitro* studies were performed in non-clinical models designed to investigate the potential of ticagrelor to affect the transport of uric acid across human renal proximal tubules. These *in vitro* studies demonstrate an inhibition of renal organic anion transporters (OAT 1 and 3) which are responsible for secretion of uric acid into the nephron. In addition, ticagrelor showed a potential weak inhibitory effect ($IC_{50} > 100 \mu\text{mol/L}$) and no trans-stimulatory effect on URAT1-mediated uric acid transport.

9.7 Safety conclusions

Bleeding

The most recognized adverse effect of any anti-thrombotic therapy is the increased risk of bleeding. During ticagrelor treatment, 'Total Major' bleeding (the primary safety endpoint in PLATO), did not differ from that of clopidogrel treatment (11.6% vs 11.2%, HR 1.04, [95% CI 0.95, 1.13]; $p=0.4336$). In subgroup analyses of the bleeding events, there was consistency of the results across a range of subgroups including age, weight, gender and prior TIA and stroke (non-hemorrhagic stroke). 'Major Fatal/Life-threatening' and fatal bleeding with ticagrelor also did not differ significantly from that of clopidogrel treatment across the different clinical contexts, including CABG, non-CABG, and non-procedural bleeding. Additionally, when bleeding was assessed using different bleeding scales, the results were consistent, demonstrating the robustness of the bleeding evaluation.

More non-CABG bleeding, including non-procedural bleeding, was reported with ticagrelor treatment across the less severe bleeding categories. No particular subgroup could be identified at particular risk for non-CABG bleeding. Likewise, clinicians cannot easily predict who will undergo CABG while receiving dual antiplatelet therapy, or when that will occur. Thus, the most clinically relevant comparisons focus on all bleeding events, including those occurring in the context of CABG.

More patients in the ticagrelor group had ICH, and more of these events were fatal with ticagrelor than with clopidogrel (11 vs 2), but fewer patients had fatal extracranial hemorrhages (9 vs 21). Other fatal bleeding events such as GI bleeding events were fewer with ticagrelor compared to clopidogrel. The percentage of patients with ICH, however, was low in both treatment groups given the significant comorbidity and CV risk factors of the population under study. No specific group of patients could be identified in the cohort that was at higher risk of ICH with ticagrelor, however; a previous history of ICH was associated with an increased risk of ICH in both groups.

Because of the risks associated with bleeding, patients with active pathological bleeding or with a history of ICH should not be treated with ticagrelor. In addition, caution is advised in patients with an increased propensity to bleed or who are taking medications known to increase the risk of bleeding. Section 11 presents guidance to physicians.

In summary, the analysis of the primary safety endpoint, 'Total Major' bleeding, showed that, overall, ticagrelor treatment did not differ from that of clopidogrel treatment for PLATO-defined 'Major' bleeding.

Other safety

More ticagrelor-treated patients reported AEs, compared to clopidogrel-treated patients. The excess of AEs with ticagrelor involves those mild or moderate in nature and does not extend to severe AEs or to SAEs. Discontinuations due to an AE occurred in more patients taking ticagrelor compared to patients taking clopidogrel; half of the excess discontinuations with ticagrelor were because of AEs of dyspnea and epistaxis.

The most common AEs reported during ticagrelor treatment are dyspnea, headache, dizziness, GI disturbances, and bleeding events (such as epistaxis, bruising and bleeding events related to procedures).

Dyspnea is reported commonly in patients with ACS, in PLATO, more so with ticagrelor treatment than with clopidogrel; 13.8% vs 7.8%, respectively. In PLATO, dyspnea was usually mild or moderate in intensity. More ticagrelor-treated patients than clopidogrel-treated patients discontinued due to dyspnea. Studies measuring pulmonary function and cardiopulmonary assessments have not shown any evidence of an effect of ticagrelor on pulmonary function or cardiac output in patients or healthy volunteers. The ticagrelor-associated dyspnea may be a result of increases in endogenous adenosine, which may cause dyspnea via activation of cell surface adenosine receptors and stimulation of the pulmonary or vagal C-fibers; however, this theory has yet to be proven. Patients with a history of dyspnea, heart failure, asthma, or COPD at study entry were more likely to develop dyspnea during the trial regardless of treatment group. However, these patients did not have a disproportionately greater increase in dyspnea with ticagrelor and still experienced a reduction in CV events with ticagrelor compared to clopidogrel. Therefore, AstraZeneca proposes that if a patient reports dyspnea, physicians should rule out underlying causes of dyspnea. If no cause is identified, patients should continue on ticagrelor treatment unless they cannot tolerate the dyspnea.

Increases in serum creatinine occurred in both treatment groups, likely reflecting renal effects resulting from the ACS event and treatment, including the influences of hemodynamic instability, multiple medications, intravascular dye loads, and other factors that can adversely affect renal function. These increases were slightly higher for ticagrelor compared to clopidogrel. By 30 days after discontinuation of study medication, the difference in creatinine between treatment groups diminished. The observed changes in serum creatinine, supported by cystatin C data, are not progressive and do not suggest that ticagrelor treatment results in kidney injury, but rather it may have an effect on GFR that is slightly greater than the effect of

clopidogrel. Ticagrelor-treated patients also reported more renal-related AEs (most of which were reported as non-serious), compared to clopidogrel-treated patients but did not have an increase in clinically important outcomes such as death, discontinuation of study drug, and dialysis. The increase in creatinine may account for the increase in reporting of non-serious renal-related AEs in ticagrelor-treated patients. Regardless of treatment group, patients with baseline renal impairment are at greater risk of having renal-related AEs as well as cardiovascular events than those without; however, in PLATO, the CV benefits of ticagrelor were generally maintained in patients with baseline renal impairment.

In the PLATO Holter substudy, more patients had ventricular pauses with ticagrelor than with clopidogrel, though these pauses were not associated with an increase in adverse clinical consequences such as syncope, heart block, cardiac arrest or pacemaker insertion. The increase in ventricular pauses may also be related to an increase in endogenous adenosine, which decreases SA node activity and AV node conduction. In the entire PLATO study, reports of cardiac arrhythmias and other possibly related AEs were generally similar between treatment groups. Ventricular pauses were largely asymptomatic and the occurrence of symptomatic pauses was not greater with ticagrelor. An analysis of the primary composite efficacy endpoint, although limited by the small number of patients and events, suggests that patients with ≥ 3 second ventricular pauses derive CV benefit from ticagrelor treatment. Patients with ventricular pauses observed during ECG monitoring following an ACS event should be treated according to appropriate guidelines. Patients with an increased risk of bradycardic events (eg, patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) were excluded from the PLATO study; therefore, caution is advised given the limited clinical experience in these patients.

Increases in serum uric acid occurred in both treatment groups, with a greater increase for ticagrelor-treated patients compared to clopidogrel-treated patients. The 2 treatment groups were similar with respect to serum uric acid levels within 30 days after discontinuation of study treatment. Relatively few ticagrelor-treated patients reported uric acid-related AEs and the incidence of these events was generally similar between the 2 groups. Results from the PLATO study do not support a causal association between elevated uric acid levels and increased risk of gout. However, the long-term impact of hyperuricemia on gout cannot be assessed in patients enrolled in the PLATO study since they were only followed for up to 1 year, which is insufficient to evaluate the long-term impact on gout and uric acid nephropathy.

A review of the clinical data revealed no evidence of drug-induced liver injury with ticagrelor. However, the use of ticagrelor is contraindicated in patients with severe hepatic impairment due to the potential for an increased risk of bleeding with the use of an antiplatelet agent. Caution is advised in patients with moderate hepatic impairment as these patients have not been specifically studied.

The clinical data from the PLATO study revealed no imbalances in the reports of neoplasm AEs (including gynecological cancers) during the PLATO study, which followed patients for

up to 1 year. These clinical data are, however, limited by the relatively short duration of observation.

In both treatment groups, reports of AEs in patients taking low maintenance doses of ASA were consistent with those in the overall PLATO study. Patients taking high maintenance doses of ASA in both treatment groups reported more AEs compared to those taking low maintenance doses of ASA and to the overall PLATO study, with a higher incidence in ticagrelor-treated patients. These findings are consistent with published data for AEs in previous ACS trials (Bainey and Mehta 2010). Analysis of AEs in the US population identified no new safety concerns for ticagrelor in this subgroup. A higher percentage of AEs were reported in the US population compared to the overall PLATO study, but similar patterns of AEs in the 2 treatment groups were reported within and outside the US.

In conclusion, despite the significant disease burden, interventions, and concomitant medications in the target population of ACS patients, the observed safety and tolerability profile of ticagrelor demonstrates that ticagrelor does not substantially add to the background morbidity or pose a safety concern considerably different from that for the current standard of care for patients with ACS. The safety and tolerability of ticagrelor should be balanced with the potential efficacy benefits of ticagrelor, including its effect on CV mortality (see Section 13).

10. PLATO GENETICS SUBSTUDY

A genetics substudy in PLATO explored the hypothesis that ticagrelor is superior to clopidogrel across all CYP2C19 and/or ABCB1 genotypes in appropriately defined genotypically predicted phenotypic subgroups. The analysis included the primary efficacy and safety outcomes in PLATO as well as the prespecified combined efficacy and safety endpoint (net clinical benefit).

Ticagrelor, an orally active agent, does not require CYP enzyme activity to inhibit platelet aggregation. Clopidogrel, a prodrug, must undergo metabolism by CYP enzymes to produce its active metabolite. The CYP2C19*1 allele corresponds to normal functional metabolism, while the CYP2C19*2 through *8 alleles result in loss of function. The *17 allele confers a gain of function.

Another gene, ABCB1, also known as multi-drug resistance (MDR1), codes for the P-glycoprotein transport enzyme, affecting movement of drugs between various body compartments. High ABCB1 expressivity accelerates excretion of the clopidogrel active metabolite, decreasing antiplatelet activity. A single nucleotide polymorphism C3435T creates 3 classes: high, intermediate (heterozygote), and low expressivity. As a P-glycoprotein substrate, ticagrelor may interact with ABCB1 phenotypes in efficacy and bleeding.

In PLATO, 10285 patients provided genetic samples for genotype determination of CYP2C19 and ABCB1 loci. An exploratory analysis provided these associations of genotype groupings on efficacy and safety outcomes in PLATO:

- Ticagrelor reduced major CV events compared to clopidogrel independently of CYP2C19 or ABCB1 genotype – that is, the superiority of ticagrelor over clopidogrel is not significantly affected by patient CYP2C19 or ABCB1 genotype.
- Total PLATO major bleeding did not differ between ticagrelor and clopidogrel groups independent of CYP2C19 or ABCB1 genotype, reflecting the overall PLATO study results.
- Net benefit overall was similar to the main PLATO study results independent of genotype.

11. GUIDANCE TO PHYSICIANS

Active pathological bleeding

The use of ticagrelor is contraindicated in patients with active pathological bleeding such as peptic ulcer or ICH.

Intracranial hemorrhage

The use of ticagrelor is contraindicated in patients with a medical history of ICH.

Moderate and severe hepatic impairment

Caution is advised in patients with moderate hepatic impairment because ticagrelor has not been studied in these patients. The use of ticagrelor is contraindicated in patients with severe hepatic impairment.

General bleeding risk

As with other antiplatelet agents, the use of ticagrelor in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events. If clinically indicated, ticagrelor should be used with caution in the following patient groups:

- Patients with a propensity to bleed (eg, due to recent trauma, recent surgery, active or recent GI or moderate hepatic impairment). The use of ticagrelor is contraindicated in patients with active pathological bleeding and in those with history of ICH, and severe hepatic impairment.
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (eg, non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics within 24 hours of ticagrelor dosing).

No data exist with ticagrelor regarding a hemostatic benefit of platelet transfusions; circulating ticagrelor may inhibit transfused platelets. Since co-administration of ticagrelor with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may augment hemostasis. Ticagrelor may be resumed after the cause of bleeding has been identified and controlled.

Surgery

If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 5 days prior to surgery.

Patients at risk for bradycardic events

Patients with an increased risk of bradycardic events (eg, patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) were excluded from PLATO. Therefore, due to the limited clinical experience in these patients, caution is advised.

Dyspnea

Dyspnea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation, is reported in patients treated with ticagrelor (13.8%). The mechanism has not yet been elucidated. If a patient reports new, prolonged or worsened dyspnea, this should be investigated for other causes. If not tolerated, treatment with ticagrelor should be stopped.

Other

Co-administration of ticagrelor with strong CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, nefazadone, ritonavir, and atazanavir) should be avoided as co-administration may lead to a substantial increase in exposure to ticagrelor.

Genetic testing

It is not necessary to test CYP2C19 or ABCB1 genotype in patients before considering ticagrelor treatment.

Discontinuations

Patients who require discontinuation of ticagrelor are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If ticagrelor must be temporarily stopped due to an adverse event(s), it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution.

ASA dose

Ticagrelor is most effectively used in combination with low maintenance doses of ASA.

12. POST-MARKETING RISK MANAGEMENT

AstraZeneca has conducted an extensive pre-marketing risk assessment to develop the ticagrelor risk management plan and to contribute to the post-marketing risk planning framework. The Risk Management Plan (RMP) encompasses both a pharmacovigilance program and a Risk Evaluation and Mitigation Strategy (REMS), and defines elements to mitigate specific risks identified in the proposed labeling.

The post-marketing risk management and pharmacovigilance activities consist of:

- Pharmacovigilance plan - describes the activities involved in monitoring safety and acquiring additional safety data.
- Risk minimization - describes activities designed to minimize risk to patients.

The elements proposed by AstraZeneca in the RMP will be discussed and agreed with the FDA during the NDA review.

12.1 Pharmacovigilance and ongoing evaluation of safety information

12.1.1 Routine pharmacovigilance practices for ticagrelor

AstraZeneca employs routine pharmacovigilance and has standard processes and systems for collecting and recording information about all events potentially related to drug/product safety, and for expedited and periodic reporting, are in compliance with current local regulations.

12.1.2 Enhanced pharmacovigilance

Detailed data collection on targeted prespecified SAEs reported to the AstraZeneca safety database from clinical trials and post marketing surveillance will be monitored. AstraZeneca proposes to request additional information on patients reporting key AEs. These include ICH, renal failure, and nephropathy. For the cases of renal failure and nephropathy, this will include a request for any available serum uric acid levels. In addition, in future clinical trials with ticagrelor, further information will be obtained either by dedicated case report forms or questionnaires for the SAEs of ICH, renal failure, and nephropathy. Bleeding events will be assessed using a standardized scale.

12.2 Risk minimization

The Full Prescribing Information (FPI), including a Medication Guide, is the primary vehicle through which risks associated with ticagrelor will be communicated to health care practitioners and patients.

12.2.1 Risk evaluation and mitigation strategy

The goal of the REMS is to communicate to patients with ACS the risks of taking ticagrelor to ensure awareness of:

- The risk of bleeding relative to the potential benefits of ticagrelor and what precautions are necessary to minimize the risk
- The risk of dyspnea associated with the use of ticagrelor and when to seek appropriate medical attention if dyspnea occurs
- The risk of premature discontinuation of ticagrelor unless specifically recommended by a physician.

AstraZeneca will incorporate a ticagrelor Medication Guide into the FPI, which will be dispensed with each ticagrelor prescription. To assess patients' understanding of the risks associated with ticagrelor as it relates to bleeding, dyspnea and premature discontinuation of ticagrelor as communicated in the ticagrelor Medication Guide, AstraZeneca will conduct a patient survey. The survey will evaluate the patients' level of knowledge regarding the key messages in the Medication Guide.

13. BENEFIT RISK ASSESSMENT

13.1 Summary of benefits

In a large randomized controlled study in 18624 patients with ACS, ticagrelor reduced the rate of the composite efficacy endpoint of CV death, MI, or stroke after ACS events, with ARR 1.9%, RRR 16%, and number needed to treat (NNT) of 54, relative to the active comparator clopidogrel, the current standard of care for patients with ACS. This result is driven by reductions in both CV death and MI, with no contribution from stroke. Ticagrelor also reduced the risk of stent thrombosis, an important benefit for many ACS patients treated with PCI and stenting. Analysis of all-cause mortality (ARR 1.4%, RRR 22%, nominal $p=0.0003$) confirms the CV death benefit (ARR 1.1%, RRR 21%, $p=0.0013$). Ticagrelor prevented 1 CV death for every 91 patients treated with ticagrelor instead of clopidogrel for 12 months.

The efficacy of ticagrelor was consistent in nearly all prespecified subgroup analyses, with a notable exception of a regional interaction in North America, driven by results in the US. While the US observation may be due to play of chance, additional analyses of the data show that efficacy of ticagrelor increases when used with low ASA maintenance doses compared to high ASA maintenance doses. Although these insights come from post-hoc analyses, these data show a lower event rate for ticagrelor compared to clopidogrel for all patients, both in the US and non-US, when taken with low ASA maintenance doses.

The PLATO genetic substudy demonstrates that the benefit of ticagrelor over clopidogrel persists regardless of patient genotype for the gene encoding the CYP2C19 enzyme and for the ABCB1 gene that codes the intestinal P-glycoprotein transporter.

PLATO tested ticagrelor in clinically relevant settings. Therefore, the results of the PLATO study apply to the broad, inclusive population of ACS patients with or without ST segment

elevation on the ECG, whether or not intended for invasive management. The benefit of ticagrelor appears early in the course of treatment and a continued reduction in events is apparent throughout the 12-month treatment period, suggesting that it is appropriate to treat patients with ticagrelor for at least 12 months.

13.2 Summary of risks

The important identified clinical risks related to ticagrelor are bleeding and dyspnea.

Despite the clear benefits of antiplatelet and antithrombotic agents in the treatment of CAD, bleeding remains an important safety risk associated with their use. The ‘Total Major’ bleeding events with ticagrelor did not differ significantly from that of clopidogrel treatment (11.6% vs 11.2%, HR 1.04, [95% CI 0.95, 1.13]; $p=0.4336$). In addition, ticagrelor and clopidogrel did not differ significantly in fatal bleeding, or fatal/life-threatening bleeding. However, more major non-CABG major bleeding, including non-procedural bleeding, was reported with ticagrelor treatment. Overall, ticagrelor had a similar number of fatal bleeding events as clopidogrel. More patients in the ticagrelor group had fatal ICHs than those in the clopidogrel group (11 vs 2), but fewer had fatal extracranial hemorrhages (9 vs 21). No particular patient subgroup had an increased risk for bleeding as a whole or for ICH while taking ticagrelor; patients with a prior history of ICH had an increased risk of subsequent ICH in both treatment groups.

Dyspnea was reported commonly in patients with ACS, more so with ticagrelor treatment, 13.8% vs 7.8% with clopidogrel in PLATO. Dyspnea was usually rated mild to moderate in intensity. It led 9 in 1000 ticagrelor-treated patients to discontinue therapy. Older patients and those with dyspnea, heart failure, asthma, or COPD at baseline were more likely to develop dyspnea during the trial. Pulmonary function testing in the ticagrelor development program revealed no effect of ticagrelor on pulmonary function.

Other safety observations in patients given ticagrelor include ventricular pauses (largely asymptomatic), increases in serum uric acid concentrations; and increases in serum creatinine.

AE reporting in patients receiving low maintenance doses of ASA in both treatment groups was consistent with those in the overall PLATO study. Patients taking high maintenance doses of ASA reported more AEs compared to those taking low maintenance doses of ASA, and with a higher incidence in ticagrelor-treated patients. The finding of an increase in adverse effects with high maintenance doses of ASA is consistent with published data for AEs in previous ACS trials, ([Bainey and Mehta 2010](#)). Analysis of AEs in the US population identified no new risks in this subgroup. A higher percentage of AEs were reported in the US population compared to the overall PLATO study, but similar patterns of AEs in both ticagrelor and clopidogrel treatment groups were reported within and outside the US.

13.3 Special populations

The elderly, women, and patients of low body weight obtain the same efficacy benefit as others do from ticagrelor, with no increased risk of major bleeding or of other identifiable clinically important safety events. Preservation of the primary efficacy and primary safety

results applies in the elderly to the category of patients at least 65 years old and also to those at least 75 years old; these results apply by body weight. Patients with prior stroke or TIA, and those with renal impairment each benefit from ticagrelor at least as much as those with normal organ function and carry no clinically important additional safety risks.

13.4 Net benefit evaluation

A prespecified exploratory analysis using the PLATO full analysis set utilized time to first occurrence of any event from the composite of CV death, MI, stroke, and a major bleeding event, excluding non-life-threatening bleeding occurring in the setting of CABG surgery. The FDA requested additional exploratory analyses of clinically relevant composite endpoints (including all-cause mortality) to be included.

Thus, combined efficacy and safety composite were explored for the 4 combinations that can be obtained for 2 efficacy and 2 safety composite endpoints:

- Efficacy endpoints:
 - CV death, MI, stroke, OR
 - All-cause mortality, MI, stroke.
- Safety endpoints:
 - PLATO-defined major bleeding excluding non-life threatening bleeding in the setting of CABG surgery OR
 - All PLATO-defined major bleedings (including non-life threatening bleeding in the setting of CABG surgery).

The findings in [Table 55](#) demonstrate the clinical benefit of ticagrelor compared to clopidogrel over 12 months after ACS events. Sensitivity analyses of this composite, substituting (1) all-cause mortality for CV death; (2) all CABG major bleeding for only those fatal or life-threatening bleeding events; and, (3) both of these substitutions, all support the prespecified analysis results. The results are consistent in that all combinations indicate a clinical benefit of ticagrelor over clopidogrel.

Table 55 Analysis of net clinical benefit (combined efficacy and safety composite) in PLATO study – full analysis set

	Ticagrelor 90 mg bid N=9333		Clopidogrel 75 mg qd N=9291			
	Patients with Events	KM%	Patients with Events	KM%	Hazard ratio (95% CI)	p- value
Excluding CABG-related bleeds that were not life-threatening						
Composite of MI/Stroke/CV Death/Major Bleed	1462	(15.7%)	1575	(17.0%)	0.92 (0.86, 0.99)	0.0257
Composite of MI/Stroke/All Cause Mortality/Major Bleed	1486	(16.6%)	1605	(18.2%)	0.92 (0.86, 0.99)	0.0201
Including all CABG-related bleeds (ie, those that were not life-threatening)						
Composite of MI/Stroke/CV Death/Major Bleed	1782	(19.9%)	1891	(21.3%)	0.94 (0.88, 1.00)	0.0449
Composite of MI/Stroke/All Cause Mortality/Major Bleed	1758	(19.6%)	1864	(21.0%)	0.94 (0.88, 1.00)	0.0493

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.

bid Twice daily; CABG Coronary artery bypass graft; CI Confidence interval; CV Cardiovascular; KM Kaplan-Meier; MI Myocardial infarction; qd Once daily.

In terms of therapeutic considerations, treating 1000 patients with ticagrelor instead of clopidogrel for a year results in: 14 fewer deaths, 11 fewer MIs and 6 to 8 fewer cases of stent thromboses. Those 1000 patients would be expected to experience no increase in overall ‘Fatal/Life-threatening’ bleeding, but 6 additional ‘Major’ non-CABG bleeding events and 9 discontinuations due to dyspnea. Overall, the treatment of 54 patients with ticagrelor instead of clopidogrel for a year will prevent 1 major CV event (MI, CV death, or stroke).

13.5 Benefit risk and overall conclusions

The PLATO study demonstrated that ticagrelor is superior to clopidogrel in reducing the rate of the primary efficacy endpoint of CV death, MI, or stroke in patients with ACS without an increase in 'Total Major' bleeding events. An increase in non-procedural bleeding in both the 'Major' and less severe categories was also observed. Another important safety consideration included dyspnea which was reported more frequently by ticagrelor patients and led to more discontinuations among those patients. This increase in dyspnea was not associated with increased reports of cardiopulmonary disease compared to clopidogrel.

The overall benefit to ACS patients treated with ticagrelor was driven by a reduction in both CV mortality and MI. The benefit of CV death reduction has been demonstrated in very few prior clinical trials of antiplatelet therapy in ACS, making ticagrelor an important potential therapeutic option for these patients. When efficacy and safety were analyzed together, ticagrelor provided a net clinical benefit over clopidogrel. Therefore, AstraZeneca is seeking approval of ticagrelor to reduce the rate of fatal and nonfatal CV events for patients with ACS.

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15. APPENDICES

See Appendices for additional tables and figures.



**Appendix to Advisory Committee Briefing
Document - Publications**

Drug	Ticagrelor
Study Code	D5130C00000
Edition	1
Date	23 June 2010

**BRILINTA Advisory Committee Briefing Document
Appendix A (Ticagrelor program key publications)**

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1. TICAGRELOR PROGRAM KEY PUBLICATIONS

Table 1 provides a list of the key publications and presentations resulting from studies conducted within the ticagrelor program to date.

Table 1 List of key publications and presentations from the ticagrelor clinical program to date

Study	Reference
PLATO study design	James S, Akerblom A, Cannon C, Emanuelsson H, Husted S, Katus, H, et al. Comparison of ticagrelor, the first reversible oral P2Y ₁₂ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. <i>Am Heart J</i> 2009;157:599-605.
PLATO overall results	Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held, C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. <i>N Engl J Med</i> 2009a;361:1045-57.
PLATO STEMI results (slides)	Steg PG, Becker RC, Cannon CP, et al. Comparison of ticagrelor: the first reversible oral P2Y ₁₂ receptor antagonist with clopidogrel in patients with ST-elevation acute coronary syndromes: results from the PLATelet inhibition and patient Outcomes (PLATO) trial. Late-breaking clinical trial abstract. [Presented at the American Heart Association annual congress, November 14-18, Orlando, FL]
PLATO INVASIVE management results	Cannon CP, Harrington RA, James S, et al; Ardissino D, Becker RC, Emanuelsson H, et al, for the PLATelet inhibition and patients Outcomes (PLATO) investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomized double-blind study. <i>Lancet</i> . 2010;375:283-93.
PLATO CABG results (slides)	Held C, Bassand J-P, Becker RC, et al. Ticagrelor Versus Clopidogrel In Patients With Acute Coronary Syndromes Undergoing Coronary Artery Bypass Surgery: Results From The PLATO Trial. 2009 [Abstract 3020-11 presented at the American College of Cardiology, March 14-16, Atlanta, GA].
ONSET/OFFSET results	Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. <i>Circulation</i> . 2009;120:2577-85
RESPOND results	Gurbel PA, Bliden KP, Butler K, Antonino MJ, Wei C, Teng R, et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. <i>Circulation</i> . 2010;121:1188-99.

Table 1 **List of key publications and presentations from the ticagrelor clinical program to date**

Study	Reference
DISPERSE2 results	Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, et al. DISPERSE-2 Investigators. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol. 2007;50:1844-51.
DISPERSE results	Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J. 2006;27:1038-47.

REFERENCE

James S, Akerblom A, Cannon C, Emanuelsson H, Husted S, Katus, H, et al. Comparison of ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J 2009;157:599-605

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Comparison of ticagrelor, the first reversible oral P2Y₁₂ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial

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Background Antiplatelet therapy is essential treatment for acute coronary syndromes (ACS). Current therapies, however, have important limitations affecting their clinical success. Ticagrelor, the first reversible oral P2Y₁₂ receptor antagonist, provides faster, greater, and more consistent adenosine diphosphate–receptor inhibition than clopidogrel. The phase III PLATelet inhibition and patient Outcomes (PLATO) trial is designed to test the hypothesis that ticagrelor compared with clopidogrel will result in a lower risk of recurrent thrombotic events in a broad patient population with ACS.

Methods PLATO is an international, randomized, double-blind, event-driven trial involving >18,000 patients hospitalized for ST-elevation ACS with scheduled primary percutaneous coronary intervention or for non-ST-elevation ACS. After loading doses of ticagrelor 180 mg or clopidogrel 300 mg in a double-blind, double-dummy fashion (with provision for additional 300 mg clopidogrel at percutaneous coronary intervention), patients will receive ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily for 6 to 12 months on top of acetylsalicylic acid. The primary efficacy end point is time to first occurrence of death from vascular causes, myocardial infarction, or stroke. The primary safety variable is PLATO-defined major bleeding. An extensive substudy program will explore the pathophysiology of ACS, indicators of prognosis and response to treatment, mechanisms of effect and safety of the study medications, health economics, and quality of life.

Conclusion The PLATO study will provide a pivotal comparison of the efficacy and safety of ticagrelor with those of clopidogrel in ACS patients, together with extensive information on treatment outcomes in different subsets of ACS in a broad patient population. (Am Heart J 2009;157:599-605.)

Background

Dual therapy with aspirin and the thienopyridine clopidogrel is a standard treatment in patients with acute

coronary syndromes (ACS) with or without ST-segment elevation and after stent procedures.¹⁻³ However, approximately 15% to 48% of patients have a poor platelet inhibition response to clopidogrel,⁴⁻⁸ a factor that contributes to a residual high risk of recurrent events.⁷

Clopidogrel is a prodrug that requires 2-step metabolism for conversion to its active metabolite, which irreversibly binds the platelet adenosine diphosphate (ADP) P2Y₁₂ receptor.^{4,6} Because of the metabolic activation, the onset of effect of clopidogrel is relatively slow, with steady-state platelet inhibition achieved 2 to 4 hours after a loading dose of 600 mg.⁵ Even during maintenance dosing, there is considerable interindividual variation in levels of inhibition of platelet aggregation (IPA) due to variable metabolic conversion to the active metabolite.^{7,8} Some of the limitations of clopidogrel have been overcome by the new thienopyridine prasugrel, which is more efficiently metabolized and exhibits faster,

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greater, and more consistent platelet inhibition.⁷ Recently, the TRial to assess Improvement in Therapeutic outcomes by Optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) study demonstrated a reduction in ischemic events with prasugrel compared with clopidogrel in percutaneous coronary intervention (PCI)-treated ACS patients.⁹ However, prasugrel was also associated with a significantly increased risk of major bleeding, including life-threatening and fatal bleeding.

The irreversible binding of the thienopyridines results in slow offset of effect, with a gradual recovery of platelet function after drug withdrawal based on the generation of fresh platelets.¹⁰ To avoid an increased risk for serious bleeding, an interval of 5 to 7 days off clopidogrel in patients undergoing coronary artery bypass grafting (CABG) is recommended.^{1,11} Thus, the development of P2Y₁₂ receptor antagonists that are reversible and that exhibit a better balance between efficacy and safety is desirable.

Ticagrelor is the first reversible oral P2Y₁₂ receptor antagonist.¹² Unlike the thienopyridines, ticagrelor is not a prodrug and does not require metabolic activation to inhibit the P2Y₁₂ receptor. Furthermore, ticagrelor has favorable pharmacokinetics and pharmacodynamics, including rapid peaking of plasma levels (1.5-3 hours) and rapid onset of antiplatelet effects (within 2 hours).^{12,13} The interindividual variability of response is low.¹² Importantly, the agent's half-life is 7 to 8 hours; and the antiplatelet effect is low 48 hours after the last dose.^{12,14} This reversibility might offer greater flexibility for surgical procedures. On the other hand, it may be a disadvantage in relation to possible poor compliance. However, still at 24 hours after maintenance dose of 90 mg, the mean percentage platelet aggregation was higher than that with 75 mg clopidogrel in patients with atherosclerosis.¹²

The phase IIb DISPERSE2 (Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs clopidogrel in non-ST-segment Elevation myocardial infarction) trial was a dose-guiding safety trial in which 990 patients with non-ST-elevation ACS received ticagrelor 90 or 180 mg twice daily or clopidogrel at a loading dose of 300 mg followed by 75 mg daily for up to 12 weeks.¹⁵ Major and minor bleeding rates at 4 weeks, the primary study outcome, did not differ among treatment groups. Ticagrelor treatment was associated with a favorable trend toward lower risk of myocardial infarction (MI). Ticagrelor inhibited platelet aggregation in a dose dependent fashion, with both doses producing greater IPA than clopidogrel in both clopidogrel-experienced and clopidogrel-naïve patients.¹⁶ Ticagrelor-treated patients had higher rates of dyspnea (6.4% with clopidogrel vs 10.5% and 15.8% with 90 and 180 mg of ticagrelor, respectively) and higher rates of mostly asymptomatic ventricular pauses than clopidogrel patients,¹⁵ prompting specific evaluation of these events in the phase III program.

The reversible P2Y₁₂ receptor antagonist ticagrelor is unique in its greater and more rapid and consistent, yet reversible, inhibition of the ADP receptor. The PLATelet inhibition and patient Outcomes (PLATO) study is designed to test the hypothesis that ticagrelor, compared with clopidogrel, will result in a lower risk of recurrent thrombotic events in a broad patient population with ACS and that this result can be achieved with a clinically acceptable bleeding rate and overall safety profile.

Study objectives

The primary objective of PLATO (D5130C05262) is to test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events (death from vascular causes, MI, or stroke) in patients with non-ST-elevation ACS or ST-elevation ACS.

The primary efficacy variable is time to first occurrence of any event from the composite of death from vascular causes, MI, or stroke. The rationale for choosing this composite end point was to use the most unbiased estimate of the effect regarding irreversible organ damage, that is, MI, ischemic and hemorrhagic stroke, and fatal bleeding. Death from vascular causes includes cardiovascular deaths, cerebrovascular deaths, and any other death for which there was no clearly documented nonvascular cause. In summary, *recurrent MI within 18 hours of a previous MI* is defined as recurrent cardiac ischemic symptoms and a new ST elevation. *Recurrent MI after 18 hours but before cardiac markers have returned to normal* is defined as symptoms and re-elevation of troponin or CK-MB of at least 50% over a previous value that was decreasing. *Myocardial infarction after cardiac biomarkers have returned to normal* is defined as elevation of biochemical markers above the upper limit of normal with either ischemic symptoms at rest, ECG changes or pathological findings of an acute MI. Finally *MI within 24 hours after PCI* defined as cardiac biomarker $\geq 3\times$ the local laboratory upper limit of normal from a normal or decreasing level and *after CABG* $\geq 10\times$ the upper limit of normal or ≥ 5 with new q-waves. A *stroke* is defined as a focal loss of neurological function caused by an ischemic or hemorrhagic event with residual symptoms at least 24 hours after onset or leading to death.

Secondary efficacy variables include (a) the primary efficacy outcome applied to the subgroup of patients with intent for invasive management at randomization; (b) all-cause mortality, MI, or stroke applied to the entire cohort; (c) the composite end point of death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, transient ischemic attack (TIA), or other arterial thrombotic event; (d) individual components of the primary composite efficacy end point; and (e) all-cause mortality. Another predefined objective is to compare the occurrence of stent thrombosis according to the Academic Research Consortium criteria¹⁷ (definite, probable,

and possible) between the ticagrelor and clopidogrel groups. The case report form (CRF) collects this information, and deaths and MI events are adjudicated for fulfilling the definitions of stent thrombosis.

Equally important are the objectives that assess the safety and tolerability of ticagrelor compared with clopidogrel. The primary safety variable is the time to first occurrence of any major bleeding event. Safety variables will be assessed separately in the subsets of patients undergoing CABG or PCI, especially in relation to the timing of these interventions. Additional safety variables include minor bleeding, dyspnea, arrhythmia, unanticipated clinical adverse events, and laboratory safety tests. In initially recruited patients ($n = 2,900$), ventricular pauses will be assessed by Holter monitoring for 7 days after randomization and at 1 month ($n = 2,000$).

Efficacy and safety variables will be assessed in patients with ST-elevation and non-ST-elevation MI and in subgroups based on age, gender, race, geographic region, clinical risk scores, body weight, diabetes mellitus, hypertension, current smoking, previous stroke or TIA, previous MI, revascularization history, renal dysfunction, prior antiplatelet therapy, concomitant IIb/IIIa inhibition, time to initiation of study therapy, type of stent implanted, any revascularization within the initial 30 days, and moderate CYP3A4 inhibitor use. Efficacy and safety outcomes also will be evaluated in relation to baseline laboratory risk markers (troponin, C-reactive protein, N-terminal pro-brain natriuretic peptide, cystatin C, and their combinations).

An additional study objective is to assess the pharmacokinetics of ticagrelor and its active metabolite AR-C1249XX, and explore its relationship with demographics, concomitant therapies, and disease states, as well as with efficacy and safety outcomes.

Substudies

An extensive substudy program is being conducted to enhance understanding of the pathophysiology of ACS and the mechanism of effect of the study medications, refine predictive models of clinical outcomes, correlate treatment effects with health economic and quality-of-life data, and identify new biomarkers that may be used to tailor current or future ACS therapies.

Baseline and discharge-day ECGs from the initially included 5,000 ST-elevation and 5,000 non-ST-elevation MI patients will be analyzed at a core laboratory for quantitative assessment of ST changes in combination with biomarkers, residual ST changes at discharge, and formation of new Q waves.

Blood samples to assess indicators of myocardial damage, myocardial function, renal function, coagulation, platelet activation, metabolism, lipoproteins, and inflammation and to allow proteomics analyses are being collected from all patients at randomization and from

4,000 patients at hospital discharge and after 1 and 6 months.

Angiograms and interventional procedures in 1,800 patients (900 with ST-elevation and 900 with non-ST-elevation ACS) performed at selected sites will be assessed qualitatively and quantitatively in a core laboratory. Myocardial perfusion and epicardial coronary blood flow will be evaluated by TIMI grading and related to the randomized treatment and outcomes.

Blood samples for pharmacokinetic analysis are being collected from the first 9,000 patients at any time within 6 hours postdose on the fourth day after enrollment or at discharge from the hospital, whichever is sooner, and after 1 month.

Genetic samples from 9,000 patients are being collected for future exploration of the effects of genetic polymorphisms on individual responses to ticagrelor and clopidogrel and outcome in ACS. Participation is voluntary and requires an additional signed informed consent, independent of consent to participate in the main study.

A platelet substudy is performed in a few centers comparing the effects of the study treatments on ADP-induced platelet aggregation, vasodilator-stimulated phosphoprotein (VASP) flow cytometry, and *VerifyNow* P2Y₁₂ assay (Accumetrics, San Diego, CA) in samples obtained after the loading dose and after 4 weeks of maintenance treatment.

The EuroQol-5D quality-of-life questionnaire¹⁸ will be administered at hospital discharge, at 6 months, and at the end-of-treatment visit. Health care resource utilization data related to the index event and any subsequent hospitalizations will be collected to assess treatment cost-effectiveness.

Study design and organization

The PLATO trial is a phase III multicenter randomized, double-blind, double-dummy, parallel-group, event-driven, international trial of approximately 18,000 patients hospitalized because of ACS. Patients are randomized to receive ticagrelor or clopidogrel in a 1:1 ratio using a randomization schedule blocked by site. Randomization must take place within 24 hours of onset of the most recent cardiac ischemic symptoms and before any planned or urgent PCI. Initial background assessments include demographics, cardiovascular risk factors, relevant medical and surgical histories, clinical characteristics, and laboratory data included in risk scores for ACS.^{1,19}

Randomized treatment continues from a minimum of 6 months to a maximum of 12 months with an estimated average follow-up of 11 months. The primary efficacy variable is the time from randomization to first occurrence of any event from the composite end point. The consistency of treatment effects over time will also be assessed by determining relative risk ratio (RRR) for time

Table I. Inclusion criteria

Hospitalized for potential ST-segment elevation or non-ST-segment elevation ACS, with onset during the previous 24 hours, documented by cardiac ischemic symptoms due to atherosclerosis of ≥ 10 minutes' duration at rest, ≥ 18 years of age, not pregnant, and with informed consent

And:

≥ 2 of the following:

1. ST-segment changes on ECG indicating ischemia. ST-segment depression or transient elevation ≥ 1 mm in two or more 2 contiguous leads
2. Positive biomarker indicating myocardial necrosis. Troponin I or T or CK-MB greater than the upper limit of normal
3. One of the following:
 - (a) ≥ 60 y of age
 - (b) Previous MI or CABG
 - (c) CAD with $\geq 50\%$ stenosis in ≥ 2 vessels
 - (d) Previous ischemic stroke, TIA (hospital-based diagnosis), carotid stenosis ($\geq 50\%$), or cerebral revascularization
 - (e) Diabetes mellitus
 - (f) Peripheral artery disease
 - (g) Chronic renal dysfunction

Or: Persistent ST-segment elevation ≥ 1 mm (not known to be preexisting or due to a coexisting disorder) in ≥ 2 contiguous leads or new LBBB plus primary PCI planned.

Urinary and/or blood pregnancy tests are to be performed in women of child-bearing potential and repeated at least every 6 months. Women of child-bearing potential must be using ≥ 2 forms of reliable contraception, including one barrier method. CAD, Coronary artery disease; LBBB, left bundle-branch block.

intervals from randomization to 30 days and from 31 to 360 days. Enrollment of 18,000 subjects will generate approximately 1,780 primary end point events, enabling reasonable power to detect both the primary and the initial secondary objectives. Study visits should occur at 1, 3, 6, 9, and 12 months after the index event, with a safety follow-up visit 1 month after the end-of-treatment visit.

The academic members of the executive committee designed the PLATO trial in collaboration with representatives from the sponsor (AstraZeneca, Mölndal, Sweden). The executive committee, together with an operations committee, including as well academic members as representatives from the sponsor, oversees the medical, scientific, and operational conduct of the study. An independent, external data and safety monitoring board (DSMB) monitors safety data on an ongoing basis and has access to unblinded data. An independent central adjudication committee adjudicates all end points and major and minor bleeding events. AstraZeneca Research and Development coordinates data management where information from the electronic clinical report form, central laboratory, and the clinical event committee is entered into separate databases. Source data verification, validation, and consistency checks are performed by AstraZeneca. After data lock, the database will be

Table II. Exclusion criteria

Drug related	<ol style="list-style-type: none"> 1. Contraindication to clopidogrel or other reason that study drug should not be administered (eg, hypersensitivity, moderate or severe liver disease, active bleeding or bleeding history, major surgery within 30 d) 2. Oral anticoagulation therapy that cannot be stopped 3. Fibrinolytic therapy planned or within the previous 24 h 4. Concomitant oral or IV therapy with strong CYP3A inhibitors (ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, grapefruit juice >1 L/d), CYP3A substrates with narrow therapeutic indices (cyclosporine, quinidine), or strong CYP3A inducers (rifampin/rifampicin, phenytoin, carbamazepine)
Treatment related	<ol style="list-style-type: none"> 1. Index event is an acute complication of PCI 2. PCI after index event and before first study dose
Medical	<ol style="list-style-type: none"> 1. Increased risk of bradycardiac events 2. Dialysis required 3. Known clinically important thrombocytopenia* 4. Known clinically important anemia* 5. Any other condition that may put the patient at risk or influence study results in the investigators' opinion (eg, cardiogenic shock, severe hemodynamic instability, active cancer)
General	<ol style="list-style-type: none"> 1. Participant in another investigational drug or device study within 30 d 2. Pregnancy or lactation 3. Any condition that increases the risk for noncompliance or being lost to follow-up 4. Involvement in the planning or conduct of the study 5. Previous enrollment or randomization in this study

* According to the investigator.

transferred for independent statistical analysis at Worldwide Clinical Trials Inc, Nottingham, United Kingdom. From this time, the database will also be available for analysis by a statistical working group consisting of the co-chairmen and one statistician from each of the academic institutions (UCR, Uppsala and DCRI, Duke University), and the sponsor for independent verification of the results.

The executive committee members are solely responsible for the reporting of the results and the drafting and editing of this and forthcoming manuscripts.

The study adheres fully to the ethical principles of the Declaration of Helsinki, to specifications of the International Conference of Harmonization, and to Good Clinical Practice. The study protocol undergoes approval by an Independent Ethics Committee or Institutional Review Board at each site. The protocol requires each subject's informed consent before initiating any study procedure.

Patient population

The PLATO study involves $>18,000$ patients recruited from approximately 800 sites in 43 countries. The primary enrollment criteria state that a patient must be ≥ 18 years

Table III. Definitions of bleeding events

Term		Associated decrease in hemoglobin	Transfusion of whole blood or PRBCs for bleeding
Major bleed—life threatening; meets any of these criteria:	Fatal or intracranial or intrapericardial with cardiac tamponade or hypovolemic shock or severe hypotension requiring pressors or surgery	>50 g/L (3.1 mmol/L)	≥4 U
Major bleed—other; meets any of these criteria:	Significantly disabling (eg, intraocular with permanent vision loss)	30-50 g/L (1.9-3.1 mmol/L)	2-3 U
Minor bleed	Requires medical intervention to stop or treat bleeding		
Minimal bleed	All others not requiring intervention or treatment		

If the bleeding event fulfills criteria in >1 category, the event will be assigned to the most severe category. PRBCs, Packed red blood cells.

and hospitalized with documented evidence of non-ST-elevation or ST-elevation ACS in the 24 hours before randomization. Inclusion and exclusion criteria details are shown in Tables I and II. Patients with ST-elevation ACS treated with fibrinolysis will be excluded because of lack of safety data with this combination of treatments.

Treatment regimens and concomitant medications

Patients are randomly assigned to oral maintenance treatment with ticagrelor 90 mg twice daily plus placebo (matched to clopidogrel) or clopidogrel 75 mg once daily plus placebo (matched to ticagrelor) as early as possible after the index event and not >24 hours postevent. The ticagrelor 90 mg dose was chosen because it is well tolerated and produces significantly greater IPA than clopidogrel 75 mg.^{15,16} Patients randomized to ticagrelor receive a loading dose of 180 mg (two 90 mg tablets) of ticagrelor study medication (active or placebo). Patients who have not received a loading dose of open-label clopidogrel or have not been taking clopidogrel or ticlopidine for ≥5 days before randomization will receive a 300 mg loading dose of clopidogrel study drug (active or placebo) and, otherwise, a maintenance dose of clopidogrel study drug as their first dose. Patients undergoing PCI >24 hours postrandomization should receive an additional loading dose of 90 mg ticagrelor study drug (active or placebo). Patients undergoing PCI may also receive an additional 300 mg loading dose of clopidogrel study drug (active or placebo) at the discretion of the investigator.

All patients should receive acetylsalicylic acid (ASA) 75 to 100 mg daily unless intolerant. For patients not previously receiving ASA, a loading dose of 325 mg is preferred (160-500 mg allowed). After stent placement, ASA up to 325 mg daily is allowed for up to 6 months, in recognition of the American College of Cardiology/

American Heart Association PCI guidelines.²⁰ Glycoprotein IIb/IIIa receptor antagonists and approved parenteral anticoagulants are allowed, but long-term treatment with low-molecular-weight heparin is not recommended. Oral anticoagulant drugs are not allowed; and if required, the study drug should be stopped.

Study treatment compliance will be assessed by the return of all unused investigational products and empty packages at each visit. Patients who have taken study medications for ≥80% of days between each visit are regarded as compliant.

Study end points and statistics

Efficacy

Sample size is based on an expected primary composite efficacy end point (death from vascular causes, MI, or stroke) event rate of 11% in the clopidogrel group over 12 months. This expected rate was based on the rate of 9.3% over an average of 9 months in the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study⁴ and by an event rate of 12% in ST-elevation ACS with primary PCI over a 6- to 18-month treatment period.² It is assumed that the hazard rate of an event in the clopidogrel group decreases over time such that approximately 50% of events will occur within the first month; a further 25% within the second, third, and fourth months; and the remaining 25% of events thereafter. Approximately 1,780 clinical events are needed to achieve 90% power to detect a relative risk reduction of 13.5% for ticagrelor. This leads to an estimated sample size of approximately 18,000 patients.

An interim efficacy analysis, confidentially reviewed by the DSMB, is planned after approximately 1,200 primary events have occurred.

The Cox proportional hazards model with a factor for treatment group will be used to analyze the primary and secondary end point results. All patients who have been randomized to study treatment will be included in the

Table IV. Baseline characteristics of the initial 10035 patients

	STEMI (n = 3736)	NSTE-ACS (n = 5791)	Total* (n = 10035)
Age, median	59	64	62
Gender, women, % (n)	25.3 (945)	31.4 (1818)	28.8 (2887)
Race, % (n)			
White	89.4 (3340)	91.4 (5293)	86.9 (8721)
Black	0.9 (32)	1.4 (82)	1.1 (114)
Asian	7.6 (284)	4.7 (271)	5.6 (565)
Other	2.1 (78)	2.5 (144)	2.2 (224)
History, % (n)			
Angina pectoris	35.3 (1320)	52.8 (3059)	43.7 (4382)
MI	13.5 (503)	25.2 (1459)	19.6 (1964)
Coronary artery disease	18.1 (678)	35.1 (2031)	27.0 (2712)
PCI	8.3 (311)	16.9 (979)	12.9 (1292)
CABG	2.5 (95)	8.4 (487)	5.8 (582)
TIA	1.8 (67)	3.3 (190)	2.6 (257)
Nonhemorrhagic stroke	3.0 (112)	4.2 (244)	3.5 (356)
Peripheral artery disease	4.4 (166)	7.6 (439)	6.0 (607)
Hypertension	57.4 (2143)	68.3 (3956)	60.8 (6106)
Diabetes mellitus	19.4 (726)	27.3 (1581)	23.0 (2308)
Congestive heart disease	3.3 (122)	7.0 (407)	5.3 (529)
Chronic renal disease	2.9 (110)	4.5 (260)	3.7 (370)
Habitual smoker, % (n)	45.0 (1681)	29.7 (1720)	34.0 (3407)
Troponin positive, % (n)	NA	78.5 (4546)	NA
ST-segment depression >1 mm, % (n)	42.8 (1598)	56.7 (3285)	48.7 (4883)
T-wave inversion >1 mm, % (n)	26.1 (974)	35.1 (2030)	29.9 (3004)
Invasive treatment intended, % (n)	90.6 (3386)	58.8 (3404)	71.7 (7200)
Clinical procedures during index hospitalization, % (n)			
Coronary angiography	90.8 (3394)	69.6 (4031)	74.1 (7434)
Percutaneous coronary revascularization	79.3 (2961)	45.8 (2653)	56.0 (5621)
Cardiac surgery	2.9 (108)	6.1 (354)	4.6 (462)
Pacemaker	1.2 (45)	0.6 (36)	0.8 (81)
Intracardial defibrillator	0.2 (8)	0.1 (6)	0.1 (14)

STEMI, ST-elevation MI; NSTE-ACS, non-ST-elevation acute coronary syndromes; NA, not applicable.

*Numbers for STEMI and NSTE-ACS are based on the investigators' initial classifications and not on final diagnosis. For 508 patients, this information is not yet available.

analyses (intent-to-treat analyses). A nominal significance level of 4.97% (2-tailed) for the primary end point will account for the planned interim analysis and preserve an overall significance level of 5% for comparison between treatment groups.

Safety

The primary safety end point is time to PLATO-defined and -adjudicated first major bleeding event. Table III shows the PLATO definitions of bleeding events, which are more inclusive than the CURE study and TIMI bleeding definitions. These criteria for bleeding events were identified as the most appropriate and clinically meaningful assessment of bleeding associated with chronic therapy. Occurrences of major, minor, and combined major and minor bleeding events will be compared between groups using the Cox proportional hazards model for each of the following categories: (a) total; (b) non-CABG; (c) non-procedure related; (d) CABG, PCI, and coronary angiography related; and (e) non-coronary procedure related.

All clinical adverse events including the Holter recordings from initially included patients, with specific

evaluation at a core laboratory of ventricular pauses >3 seconds, are transferred to the DSMB.

Present status

The first patient was enrolled in October 2006. By July 1, 2008, >18,000 patients had been enrolled; and enrollment ceased in mid-July 2008. The Holter program was ended according to the protocol in November 2007. The DSMB reviewed the emerging data on patient safety after enrollment of 12,889 patients in March 2008 and recommended continuation of enrollment without protocol alterations and that further follow-up on safety laboratory testing was not necessary. The statement to continue the trial without protocol alterations was repeated at the latest DSMB review in November 2008, 4 months after inclusion of all patients. The baseline characteristics of the first 10,035 patients are shown in Table IV.

Conclusion

The PLATO trial includes a broad ACS patient population recruited as early as possible after admission to the hospital, including patients with and without ST-

segment elevation and those managed early invasively and conservatively. The trial includes currently recommended doses of clopidogrel, including the 600-mg loading dose, and initiation of therapy before PCI.²⁰ The protocol also allows clopidogrel-exposed patients, both as maintenance treatment and loading dose. Therefore, the trial will reflect the full spectrum of ACS patients managed in different real-world clinical settings (with the exception of thrombolytic therapy) and will provide a definitive comparison of the efficacy and safety of ticagrelor versus optimal clopidogrel treatment in all ACS patients. The substudy program, which includes biomarker, genetic, angiography, and patient-reported outcomes and health economics, is one of the most extensive programs ever undertaken in patients across the spectrum of ACS. PLATO thus will also enhance our understanding of the pathophysiology of ACS and risk prediction; identify treatment effects in subpopulations; and create a database for identifying new laboratory, biochemical, and genetic markers that may be of value in tailoring treatment.

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Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

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ABSTRACT

BACKGROUND

Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y₁₂ that has a more rapid onset and more pronounced platelet inhibition than clopidogrel.

METHODS

In this multicenter, double-blind, randomized trial, we compared ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18,624 patients admitted to the hospital with an acute coronary syndrome, with or without ST-segment elevation.

RESULTS

At 12 months, the primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; $P<0.001$). Predefined hierarchical testing of secondary end points showed significant differences in the rates of other composite end points, as well as myocardial infarction alone (5.8% in the ticagrelor group vs. 6.9% in the clopidogrel group, $P=0.005$) and death from vascular causes (4.0% vs. 5.1%, $P=0.001$) but not stroke alone (1.5% vs. 1.3%, $P=0.22$). The rate of death from any cause was also reduced with ticagrelor (4.5%, vs. 5.9% with clopidogrel; $P<0.001$). No significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; $P=0.43$), but ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%, $P=0.03$), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types.

CONCLUSIONS

In patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding. (ClinicalTrials.gov number, NCT00391872.)

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*The Study of Platelet Inhibition and Patient Outcomes (PLATO) investigators are listed in the Appendix and the Supplementary Appendix, available with the full text of this article at NEJM.org.

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IN PATIENTS WHO HAVE ACUTE CORONARY syndromes with or without ST-segment elevation, current clinical practice guidelines¹⁻⁴ recommend dual antiplatelet treatment with aspirin and clopidogrel. The efficacy of clopidogrel is hampered by the slow and variable transformation of the prodrug to the active metabolite, modest and variable platelet inhibition,^{5,6} an increased risk of bleeding,^{7,8} and an increased risk of stent thrombosis and myocardial infarction in patients with a poor response.⁹ As compared with clopidogrel, prasugrel, another thienopyridine prodrug, has a more consistent and pronounced inhibitory effect on platelets,^{5,6} resulting in a lower risk of myocardial infarction and stent thrombosis, but is associated with a higher risk of major bleeding in patients with an acute coronary syndrome who are undergoing percutaneous coronary intervention (PCI).¹⁰

Ticagrelor, a reversible and direct-acting oral antagonist of the adenosine diphosphate receptor P2Y₁₂, provides faster, greater, and more consistent P2Y₁₂ inhibition than clopidogrel.^{11,12} In a dose-guiding trial, there was no significant difference in the rate of bleeding with the use of ticagrelor at a dose of 90 mg or 180 mg twice daily and the rate with the use of clopidogrel at a dose of 75 mg daily. However, dose-related episodes of dyspnea and ventricular pauses on Holter monitoring, which occurred more frequently with ticagrelor, led to the selection of the dose of 90 mg twice daily for further studies.¹³ We conducted the Study of Platelet Inhibition and Patient Outcomes (PLATO) to determine whether ticagrelor is superior to clopidogrel for the prevention of vascular events and death in a broad population of patients presenting with an acute coronary syndrome.

METHODS

STUDY DESIGN

PLATO was a multicenter, randomized, double-blind trial. The details of the design have been published previously.¹⁴ The executive and operations committee, consisting of both academic members and representatives of the sponsor, Astra-Zeneca, designed and oversaw the conduct of the trial. An independent data and safety monitoring board monitored the trial and had access to the unblinded data. The sponsor coordinated the data management. Statistical analysis was performed by Worldwide Clinical Trials, a contract research

organization, in collaboration with investigators at the academic centers and the sponsor, all of whom had full access to the final study data. The manuscript was drafted by the chairs of the executive and operations committee, who were academic authors and who vouch for the accuracy and completeness of the reported data. The study design was approved by the appropriate national and institutional regulatory authorities and ethics committees, and all participants provided written informed consent.

STUDY PATIENTS

Patients were eligible for enrollment if they were hospitalized for an acute coronary syndrome, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours. For patients who had an acute coronary syndrome without ST-segment elevation, at least two of the following three criteria had to be met: ST-segment changes on electrocardiography, indicating ischemia; a positive test of a biomarker, indicating myocardial necrosis; or one of several risk factors (age ≥ 60 years; previous myocardial infarction or coronary-artery bypass grafting [CABG]; coronary artery disease with stenosis of $\geq 50\%$ in at least two vessels; previous ischemic stroke, transient ischemic attack, carotid stenosis of at least 50%, or cerebral revascularization; diabetes mellitus; peripheral arterial disease; or chronic renal dysfunction, defined as a creatinine clearance of < 60 ml per minute per 1.73 m² of body-surface area). For patients who had an acute coronary syndrome with ST-segment elevation, the following two inclusion criteria had to be met: persistent ST-segment elevation of at least 0.1 mV in at least two contiguous leads or a new left bundle-branch block, and the intention to perform primary PCI. Major exclusion criteria were any contraindication against the use of clopidogrel, fibrinolytic therapy within 24 hours before randomization, a need for oral anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer.

STUDY TREATMENT

Patients were randomly assigned to receive ticagrelor or clopidogrel, administered in a double-blind, double-dummy fashion. Ticagrelor was given in a loading dose of 180 mg followed by a dose of 90 mg twice daily. Patients in the clopidogrel group who had not received an open-label

loading dose and had not been taking clopidogrel for at least 5 days before randomization received a 300-mg loading dose followed by a dose of 75 mg daily. Others in the clopidogrel group continued to receive a maintenance dose of 75 mg daily. Patients undergoing PCI after randomization received, in a blind fashion, an additional dose of their study drug at the time of PCI: 300 mg of clopidogrel, at the investigator's discretion, or 90 mg of ticagrelor for patients who were undergoing PCI more than 24 hours after randomization. In patients undergoing CABG, it was recommended that the study drug be withheld — in the clopidogrel group, for 5 days, and in the ticagrelor group, for 24 to 72 hours. All patients received acetylsalicylic acid (aspirin) at a dose of 75 to 100 mg daily unless they could not tolerate the drug. For those who had not previously been receiving aspirin, 325 mg was the preferred loading dose; 325 mg was also permitted as the daily dose for 6 months after stent placement.

Outpatient visits were scheduled at 1, 3, 6, 9, and 12 months, with a safety follow-up visit 1 month after the end of treatment. The randomized treatment was scheduled to continue for 12 months, but patients left the study at their 6- or 9-month visit if the targeted number of 1780 primary end-point events had occurred by that time. Initially, patients were to be assessed by means of Holter monitoring for 7 days after randomization, until a repeat assessment at 1 month had been obtained for 2000 of the enrolled patients.

END POINTS

Death from vascular causes was defined as death from cardiovascular causes or cerebrovascular causes and any death without another known cause. Myocardial infarction was defined in accordance with the universal definition proposed in 2007.^{14,15} Evaluation for stent thrombosis was performed according to the Academic Research Consortium criteria.¹⁶ Stroke was defined as focal loss of neurologic function caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 hours or leading to death.

We defined major life-threatening bleeding as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the hemoglobin level of 5.0 g per deciliter or more, or the need for transfusion of at least

4 units of red cells. We defined other major bleeding as bleeding that led to clinically significant disability (e.g., intraocular bleeding with permanent vision loss) or bleeding either associated with a drop in the hemoglobin level of at least 3.0 g per deciliter but less than 5.0 g per deciliter or requiring transfusion of 2 to 3 units of red cells. We defined minor bleeding as any bleeding requiring medical intervention but not meeting the criteria for major bleeding.

An independent central adjudication committee adjudicated all suspected primary and secondary efficacy end points as well as major and minor bleeding events.

STATISTICAL ANALYSIS

The primary efficacy variable was the time to the first occurrence of composite of death from vascular causes, myocardial infarction, or stroke. We estimated that 1780 such events would be required to achieve 90% power to detect a relative risk reduction of 13.5% in the rate of the primary end point in the ticagrelor group as compared with the clopidogrel group, given an event rate of 11% in the clopidogrel group at 12 months. Cox proportional-hazards models were used to analyze the data on primary and secondary end points. All patients who had been randomly assigned to a treatment group were included in the intention-to-treat analyses.

The principal secondary efficacy end point was the primary efficacy variable studied in the subgroup of patients for whom invasive management was planned at randomization. Additional secondary end points (analyzed for the entire study population) were the composite of death from any cause, myocardial infarction, or stroke; the composite of death from vascular causes, myocardial infarction, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, transient ischemic attack, or other arterial thrombotic events; myocardial infarction alone; death from cardiovascular causes alone; stroke alone; and death from any cause.

To address the issue of multiple testing, a hierarchical test sequence was planned. The secondary composite efficacy end points were tested individually, in the order in which they are listed above, until the first nonsignificant difference was found between the two treatment groups. Other treatment comparisons were examined in an exploratory manner. No multiplicity adjustment was made to the confidence intervals for

Table 1. Baseline Characteristics of the Patients, According to Treatment Group.*

Characteristic	Ticagrelor Group	Clopidogrel Group
Median age — yr	62.0	62.0
Age ≥75 yr — no./total no. (%)	1396/9333 (15.0)	1482/9291 (16.0)
Female sex — no./total no. (%)	2655/9333 (28.4)	2633/9291 (28.3)
Median body weight — kg (range)	80.0 (28–174)	80.0 (29–180)
Body weight <60 kg — no./total no. (%)	652/9333 (7.0)	660/9291 (7.1)
BMI — median (range)†	27 (13–68)	27 (13–70)
Race — no./total no. (%)‡		
White	8566/9332 (91.8)	8511/9291 (91.6)
Black	115/9332 (1.2)	114/9291 (1.2)
Asian	542/9332 (5.8)	554/9291 (6.0)
Other	109/9332 (1.2)	112/9291 (1.2)
Cardiovascular risk factor — no./total no. (%)		
Habitual smoker	3360/9333 (36.0)	3318/9291 (35.7)
Hypertension	6139/9333 (65.8)	6044/9291 (65.1)
Dyslipidemia	4347/9333 (46.6)	4342/9291 (46.7)
Diabetes mellitus	2326/9333 (24.9)	2336/9291 (25.1)
Other medical history — no./total no. (%)		
MI	1900/9333 (20.4)	1924/9291 (20.7)
Percutaneous coronary intervention	1272/9333 (13.6)	1220/9291 (13.1)
Coronary-artery bypass grafting	532/9333 (5.7)	574/9291 (6.2)
Congestive heart failure	513/9333 (5.5)	537/9291 (5.8)
Nonhemorrhagic stroke	353/9333 (3.8)	369/9291 (4.0)
Peripheral arterial disease	566/9333 (6.1)	578/9291 (6.2)
Chronic renal disease	379/9333 (4.1)	406/9291 (4.4)
History of dyspnea	1412/9333 (15.1)	1358/9291 (14.6)
Chronic obstructive pulmonary disease	555/9333 (5.9)	530/9291 (5.7)
Asthma	267/9333 (2.9)	265/9291 (2.9)
Gout	272/9333 (2.9)	262/9291 (2.8)
ECG findings at study entry — no./total no. (%)		
Persistent ST-segment elevation	3497/9333 (37.5)	3511/9291 (37.8)
ST-segment depression	4730/9333 (50.7)	4756/9291 (51.2)
T-wave inversion	2970/9333 (31.8)	2975/9291 (32.0)
Positive troponin I test at study entry — no./total no. (%)	7965/9333 (85.3)	7999/9291 (86.1)
Final diagnosis of ACS — no./total no. (%)		
ST-elevation MI	3496/9333 (37.5)	3530/9291 (38.0)
Non-ST-elevation MI	4005/9333 (42.9)	3950/9291 (42.5)
Unstable angina	1549/9333 (16.6)	1563/9291 (16.8)
Other diagnosis or missing data§	283/9333 (3.0)	248/9291 (2.7)
Risk factors for ST-elevation MI — no./total no. (%)		
Killip class >2	25/3496 (0.7)	41/3530 (1.2)
TIMI risk score ≥3	1584/3496 (45.3)	1553/3530 (44.0)

Table 1. (Continued.)

Characteristic	Ticagrelor Group	Clopidogrel Group
Risk factors for non-ST-elevation MI — no./total no. (%)¶		
Positive troponin I test	4418/5554 (79.5)	4455/5513 (80.8)
ST-segment depression >0.1 mV	3141/5554 (56.6)	3182/5513 (57.7)
TIMI risk score ≥5	1112/5554 (20.0)	1170/5513 (21.2)

* A positive result on testing for troponin I consisted of a troponin I level of 0.08 µg or more per liter for the first sample taken, as measured at the central laboratory with the use of the Advia Centaur TnI-Ultra Immunoassay (Siemens). ACS denotes acute coronary syndrome, ECG electrocardiographic, MI myocardial infarction, and TIMI Thrombolysis in Myocardial Infarction.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

‡ Race was self-reported. "Asian" does not include Indian or Southwest Asian ancestry.

§ This category includes patients with unspecified ACS or no ACS.

¶ Risk factors for non-ST-elevation MI were ascertained for patients with a final ACS diagnosis of non-ST-elevation MI or unstable angina.

the hazard ratios for the ticagrelor group as compared with the clopidogrel group.

The consistency of treatment effects over time was assessed by determining the relative risk ratios for the periods from randomization to 30 days and from 31 to 360 days. Another predefined objective was to compare the two treatment groups with respect to the occurrence of stent thrombosis. The primary safety end point was the first occurrence of any major bleeding event. Additional safety end points included minor bleeding, dyspnea, bradyarrhythmia, any other clinical adverse event, and results of laboratory safety tests. The consistency of effects on efficacy and safety end points was explored in 25 prespecified subgroups and 8 post hoc subgroups, without adjustment for multiple comparisons.

RESULTS

STUDY PATIENTS AND STUDY DRUGS

We recruited 18,624 patients from 862 centers in 43 countries from October 2006 through July 2008. The follow-up period ended in February 2009, when information on vital status was available for all patients except five. The two treatment groups were well balanced with regard to all baseline characteristics (Table 1) and non-study medications and procedures (Table 2). Both groups started the study drug at a median of 11.3 hours (interquartile range, 4.8 to 19.8) after the start of chest pain. In the clopidogrel group, taking into account both open-label and

randomized treatment, 79.1% of patients received at least 300 mg, and 19.6% at least 600 mg, of clopidogrel between the time of the index event and up to 24 hours after randomization. Premature discontinuation of the study drug was slightly more common in the ticagrelor group than in the clopidogrel group (in 23.4% of patients vs. 21.5%). The overall rate of adherence to the study drug, as assessed by the site investigators, was 82.8%, and the median duration of exposure to the study drug was 277 days (interquartile range, 179 to 365).

EFFICACY

The primary end point occurred significantly less often in the ticagrelor group than in the clopidogrel group (in 9.8% of patients vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; $P < 0.001$) (Table 3 and Fig. 1). The difference in treatment effect was apparent within the first 30 days of therapy and persisted throughout the study period. As shown in Table 3 (and Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), the hierarchical testing of secondary end points showed significant reductions in the ticagrelor group, as compared with the clopidogrel group, with respect to the rates of the composite end point of death from any cause, myocardial infarction, or stroke (10.2% vs. 12.3%, $P < 0.001$); the composite end point of death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, recurrent ischemia, transient ischemic attack, or other arterial throm-

Table 2. Randomized Treatment, Other Treatments, and Procedures, According to Treatment Group.*

Characteristic	Ticagrelor Group (N=9333)	Clopidogrel Group (N=9291)	P Value†
Start of randomized treatment			
Patients receiving treatment — no. (%)	9235 (98.9)	9186 (98.9)	
Time after start of chest pain — hr			0.89
Median	11.3	11.3	
IQR	4.8–19.8	4.8–19.8	
Time after start of hospitalization — hr			0.75
Median	4.9	5.3	
IQR	1.3–18.8	1.4–15.8	
Premature discontinuation of study drug — no. (%)	2186 (23.4)	1999 (21.5)	0.002
Because of adverse event	690 (7.4)	556 (6.0)	<0.001
Because of patient's unwillingness to continue	946 (10.1)	859 (9.2)	0.04
Other reason	550 (5.9)	584 (6.3)	0.27
Adherence to study drug — no. (%)‡	7724 (82.8)	7697 (82.8)	0.89
Exposure to study drug — days			0.11
Median	277	277	
IQR	177–365	181–365	
Clopidogrel administered in hospital before randomization — no. (%)	4293 (46.0)	4282 (46.1)	0.91
Clopidogrel dose given (as study drug or not) within 24 hours before or after randomization — no. (%)			0.65
No loading dose, or missing information	4937 (52.9)	94 (1.0)	
300–375 mg	1921 (20.6)	5528 (59.5)	
600–675 mg	1282 (13.7)	1822 (19.6)	
Other dose	697 (7.5)	1339 (14.4)	
Same dose as that given before index event§	496 (5.3)	508 (5.5)	
Antithrombotic treatment in hospital — no. (%)			
Aspirin			
Before randomization	8827 (94.6)	8755 (94.2)	0.31
After randomization	9092 (97.4)	9056 (97.5)	0.85
Unfractionated heparin	5304 (56.8)	5233 (56.3)	0.49
Low-molecular-weight heparin	4813 (51.6)	4706 (50.7)	0.21
Fondaparinux	251 (2.7)	246 (2.6)	0.89
Bivalirudin	188 (2.0)	183 (2.0)	0.83
Glycoprotein IIb/IIIa inhibitor	2468 (26.4)	2487 (26.8)	0.62
Other medication administered in hospital or at discharge — no. (%)			
Organic nitrate	7181 (76.9)	7088 (76.3)	0.30
Beta-blocker	8339 (89.3)	8336 (89.7)	0.42
ACE inhibitor	7090 (76.0)	6986 (75.2)	0.22
Angiotensin-II-receptor blocker	1143 (12.2)	1125 (12.1)	0.79
Cholesterol-lowering drug (statin)	8373 (89.7)	8289 (89.2)	0.27
Calcium-channel inhibitor	2769 (29.7)	2789 (30.0)	0.61
Proton-pump inhibitor	4233 (45.4)	4128 (44.4)	0.21

Table 2. (Continued.)

Characteristic	Ticagrelor Group (N=9333)	Clopidogrel Group (N=9291)	P Value [†]
Invasive procedure performed during index hospitalization — no. (%)			
Planned invasive treatment	6732 (72.1)	6676 (71.9)	0.68
Coronary angiography	7599 (81.4)	7571 (81.5)	0.91
PCI			
During index hospitalization	5687 (60.9)	5676 (61.1)	0.83
Within 24 hours after randomization	4560 (48.9)	4546 (48.9)	0.93
Cardiac surgery	398 (4.3)	434 (4.7)	0.19
Invasive procedure performed during study — no. (%)			
PCI	5978 (64.1)	5999 (64.6)	0.46
Stenting	5640 (60.4)	5649 (60.8)	0.61
With bare-metal stent only	3921 (42.0)	3892 (41.9)	0.87
With ≥ 1 drug-eluting stent	1719 (18.4)	1757 (18.9)	0.40
CABG	931 (10.0)	968 (10.4)	0.32
Time from first dose of study drug to PCI — hr			
Patients with ST-elevation MI			0.78
Median	0.25	0.25	
IQR	0.05–0.75	0.05–0.72	
Patients with non-ST-elevation MI			
Median	3.93	3.65	
IQR	0.48–46.9	0.45–50.8	

* ACE denotes angiotensin-converting enzyme, CABG coronary-artery bypass grafting, IQR interquartile range, and PCI percutaneous coronary intervention.

[†] P values were calculated with the use of Fisher's exact test.

[‡] Adherence to the study drug was defined as use of more than 80% of the study medication during each interval between visits, as assessed by the site investigator.

[§] Patients who had been receiving clopidogrel before the study were not eligible for a loading dose of the drug at study entry.

botic events (14.6% vs. 16.7%, $P<0.001$); myocardial infarction alone (5.8% vs. 6.9%, $P=0.005$); and death due to vascular causes (4.0% vs. 5.1%, $P=0.001$). This pattern was also reflected in a reduction in the rate of death from any cause with ticagrelor (4.5%, vs. 5.9% with clopidogrel; $P<0.001$). The rate of stroke did not differ significantly between the two treatment groups, although there were more hemorrhagic strokes with ticagrelor than with clopidogrel (23 [0.2%] vs. 13 [0.1%], nominal $P=0.10$). Concerning our first secondary objective of ascertaining the effect in patients for whom invasive treatment was planned, the rate of the primary end point was also lower with ticagrelor (8.9%, vs. 10.6% with clopidogrel; $P=0.003$). Among patients who received a stent during the study, the rate of defi-

nite stent thrombosis was lower in the ticagrelor group than in the clopidogrel group (1.3% vs. 1.9%, $P=0.009$).

The results regarding the primary end point did not show significant heterogeneity in analyses of the 33 subgroups, with three exceptions (Fig. 2 in the Supplementary Appendix). The benefit of ticagrelor appeared to be attenuated in patients weighing less than the median weight for their sex ($P=0.04$ for the interaction), those not taking lipid-lowering drugs at randomization ($P=0.04$ for the interaction), and those enrolled in North America ($P=0.045$ for the interaction).

BLEEDING

The ticagrelor and clopidogrel groups did not differ significantly with regard to the rates of major

Table 3. Major Efficacy End Points at 12 Months.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard Ratio for Ticagrelor Group (95% CI)	P Value†
Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001‡
Secondary end points — no./total no. (%)				
Death from any cause, MI, or stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77–0.92)	<0.001‡
Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event	1290/9333 (14.6)	1456/9291 (16.7)	0.88 (0.81–0.95)	<0.001‡
MI	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75–0.95)	0.005‡
Death from vascular causes	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69–0.91)	0.001‡
Stroke	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91–1.52)	0.22
Ischemic	96/9333 (1.1)	91/9291 (1.1)		0.74
Hemorrhagic	23/9333 (0.2)	13/9291 (0.1)		0.10
Unknown	10/9333 (0.1)	2/9291 (0.02)		0.04
Other events — no./total no. (%)				
Death from any cause	399/9333 (4.5)	506/9291 (5.9)	0.78 (0.69–0.89)	<0.001
Death from causes other than vascular causes	46/9333 (0.5)	64/9291 (0.8)	0.71 (0.49–1.04)	0.08
Severe recurrent ischemia	302/9333 (3.5)	345/9291 (4.0)	0.87 (0.74–1.01)	0.08
Recurrent ischemia	500/9333 (5.8)	536/9291 (6.2)	0.93 (0.82–1.05)	0.22
TIA	18/9333 (0.2)	23/9291 (0.3)	0.78 (0.42–1.44)	0.42
Other arterial thrombotic event	19/9333 (0.2)	31/9291 (0.4)	0.61 (0.34–1.08)	0.09
Death from vascular causes, MI, stroke — no./total no. (%)				
Invasive treatment planned§	569/6732 (8.9)	668/6676 (10.6)	0.84 (0.75–0.94)	0.003‡
Event rate, days 1–30	443/9333 (4.8)	502/9291 (5.4)	0.88 (0.77–1.00)	0.045
Event rate, days 31–360¶	413/8763 (5.3)	510/8688 (6.6)	0.80 (0.70–0.91)	<0.001
Stent thrombosis — no. of patients who received a stent/total no. (%)				
Definite	71/5640 (1.3)	106/5649 (1.9)	0.67 (0.50–0.91)	0.009
Probable or definite	118/5640 (2.2)	158/5649 (2.9)	0.75 (0.59–0.95)	0.02
Possible, probable, or definite	155/5640 (2.9)	202/5649 (3.8)	0.77 (0.62–0.95)	0.01

* The percentages are Kaplan–Meier estimates of the rate of the end point at 12 months. Patients could have had more than one type of end point. Death from vascular causes included fatal bleeding. Only traumatic fatal bleeding was excluded from the category of death from vascular causes. MI denotes myocardial infarction, and TIA transient ischemic attack.

† P values were calculated by means of Cox regression analysis.

‡ Statistical significance was confirmed in the hierarchical testing sequence applied to the secondary composite efficacy end points.

§ A plan for invasive or noninvasive (medical) management was declared before randomization.

¶ Patients with any primary event during the first 30 days were excluded.

bleeding as defined in the trial (11.6% and 11.2%, respectively; $P=0.43$) (Fig. 2 and Table 4). There was also no significant difference in the rates of major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) criteria (7.9% with ticagrelor and 7.7% with clopidogrel, $P=0.57$) or fatal or life-threatening bleeding (5.8% in both groups, $P=0.70$). The absence of a significant dif-

ference in major bleeding according to the trial definition was consistent among all subgroups, without significant heterogeneity, except with regard to the body-mass index ($P=0.05$ for interaction) (Fig. 4 in the Supplementary Appendix). The two treatment groups did not differ significantly in the rates of CABG-related major bleeding or bleeding requiring transfusion of red cells. How-

ever, in the ticagrelor group, there was a higher rate of non-CABG-related major bleeding according to the study criteria (4.5% vs. 3.8%, $P=0.03$) and the TIMI criteria (2.8% vs. 2.2%, $P=0.03$) (Fig. 3 in the Supplementary Appendix). With ticagrelor as compared with clopidogrel, there were more episodes of intracranial bleeding (26 [0.3%] vs. 14 [0.2%], $P=0.06$), including fatal intracranial bleeding (11 [0.1%] vs. 1 [0.01%], $P=0.02$). However, there were fewer episodes of other types of fatal bleeding in the ticagrelor group (9 [0.1%], vs. 21 [0.3%] in the clopidogrel group; $P=0.03$) (Table 4).

OTHER ADVERSE EVENTS

Dyspnea was more common in the ticagrelor group than in the clopidogrel group (in 13.8% of patients vs. 7.8%) (Table 4). Few patients discontinued the study drug because of dyspnea (0.9% of patients in the ticagrelor group and 0.1% in the clopidogrel group).

Holter monitoring was performed for a median of 6 days during the first week in 2866 patients and was repeated at 30 days in 1991 patients. There was a higher incidence of ventricular pauses in the first week, but not at day 30, in the ticagrelor group than in the clopidogrel group (Table 4). Pauses were rarely associated with symptoms; the two treatment groups did not differ significantly with respect to the incidence of syncope or pacemaker implantation (Table 4).

Discontinuation of the study drug due to adverse events occurred more frequently with ticagrelor than with clopidogrel (in 7.4% of patients vs. 6.0%, $P<0.001$) (Table 2). The levels of creatinine and uric acid increased slightly more during the treatment period with ticagrelor than with clopidogrel (Table 4).

DISCUSSION

PLATO shows that treatment with ticagrelor as compared with clopidogrel in patients with acute coronary syndromes significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke. A similar benefit was seen for the individual components of death from vascular causes and myocardial infarction, but not for stroke. The beneficial effects of ticagrelor were achieved without a significant increase in the rate of major bleeding.

The benefits of ticagrelor over clopidogrel

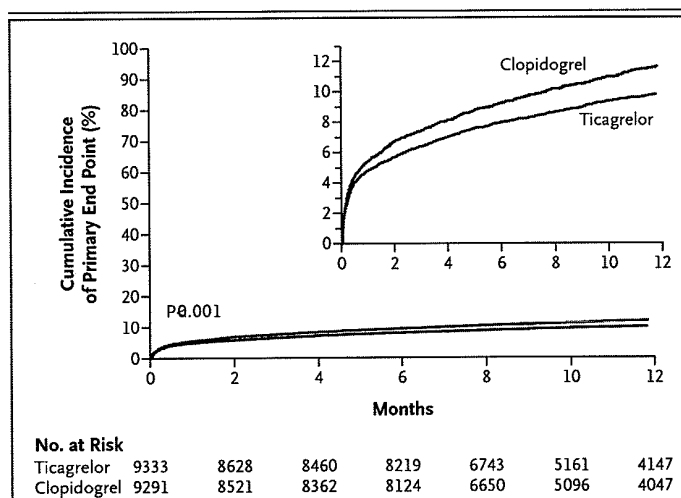


Figure 1. Cumulative Kaplan-Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point.

The primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval, 0.77 to 0.92; $P<0.001$).

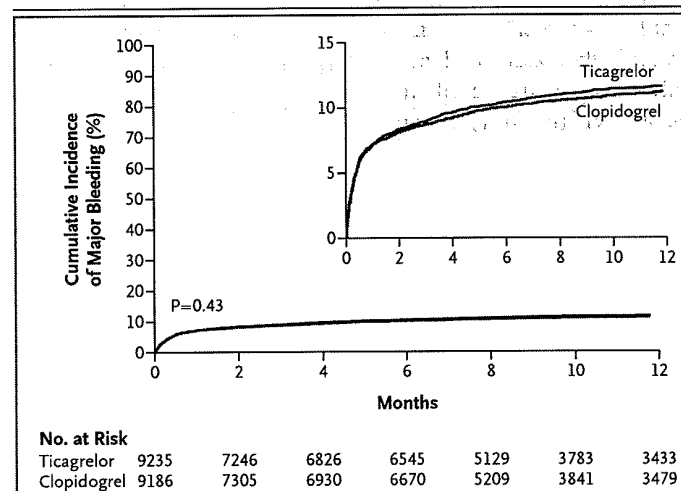


Figure 2. Cumulative Kaplan-Meier Estimates of the Time to the First Major Bleeding End Point, According to the Study Criteria.

The time was estimated from the first dose of the study drug in the safety population. The hazard ratio for major bleeding, defined according to the study criteria, for the ticagrelor group as compared with the clopidogrel group was 1.04 (95% confidence interval, 0.95 to 1.13).

were seen in patients who had an acute coronary syndrome with or without ST-segment elevation. Previous trials have shown benefits of clopidogrel in the same clinical settings.^{8,17-19} The advantages were seen regardless of whether patients had received appropriate initiation of treatment with the

currently recommended higher loading dose of clopidogrel and regardless of whether invasive or noninvasive management was planned.²⁰⁻²⁵ The treatment effects were the same in the short term (days 0 to 30) and in the longer term (days 31 to 360). This duration of treatment benefit has also been shown with clopidogrel.²⁶ Thus, ticagrelor appears to expand on the previously demonstrated benefits of clopidogrel across the spectrum of acute coronary syndromes.

Table 4. Safety of the Study Drugs.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI) [†]	P Value
Primary safety end points — no./total no. (%)				
Major bleeding, study criteria	961/9235 (11.6)	929/9186 (11.2)	1.04 (0.95–1.13)	0.43
Major bleeding, TIMI criteria [‡]	657/9235 (7.9)	638/9186 (7.7)	1.03 (0.93–1.15)	0.57
Bleeding requiring red-cell transfusion	818/9235 (8.9)	809/9186 (8.9)	1.00 (0.91–1.11)	0.96
Life-threatening or fatal bleeding, study criteria	491/9235 (5.8)	480/9186 (5.8)	1.03 (0.90–1.16)	0.70
Fatal bleeding	20/9235 (0.3)	23/9186 (0.3)	0.87 (0.48–1.59)	0.66
Nonintracranial fatal bleeding	9/9235 (0.1)	21/9186 (0.3)		0.03
Intracranial bleeding	26/9235 (0.3)	14/9186 (0.2)	1.87 (0.98–3.58)	0.06
Fatal	11/9235 (0.1)	1/9186 (0.01)		0.02
Nonfatal	15/9235 (0.2)	13/9186 (0.2)		0.69
Secondary safety end points — no./total no. (%)				
Non-CABG-related major bleeding, study criteria	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non-CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria [‡]	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33
Dyspnea — no./total no. (%)				
Any	1270/9235 (13.8)	721/9186 (7.8)	1.84 (1.68–2.02)	<0.001
Requiring discontinuation of study treatment	79/9235 (0.9)	13/9186 (0.1)	6.12 (3.41–11.01)	<0.001
Bradycardia — no./total no. (%)				
Pacemaker insertion	82/9235 (0.9)	79/9186 (0.9)		0.87
Syncope	100/9235 (1.1)	76/9186 (0.8)		0.08
Bradycardia	409/9235 (4.4)	372/9186 (4.0)		0.21
Heart block	67/9235 (0.7)	66/9186 (0.7)		1.00
Holter monitoring — no./total no. (%)				
First week				
Ventricular pauses ≥3 sec	84/1451 (5.8)	51/1415 (3.6)		0.01
Ventricular pauses ≥5 sec	29/1451 (2.0)	17/1415 (1.2)		0.10
At 30 days				
Ventricular pauses ≥3 sec	21/985 (2.1)	17/1006 (1.7)		0.52
Ventricular pauses ≥5 sec	8/985 (0.8)	6/1006 (0.6)		0.60
Neoplasm arising during treatment — no. of patients/total no. (%)				
Any	132/9235 (1.4)	155/9186 (1.7)		0.17
Malignant	115/9235 (1.2)	121/9186 (1.3)		0.69
Benign	18/9235 (0.2)	35/9186 (0.4)		0.02

Table 4. (Continued.)

End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI) [†]	P Value
Increase in serum uric acid from baseline value — %				
At 1 mo	14±46	7±44		<0.001
At 12 mo	15±52	7±31		<0.001
1 Mo after end of treatment	7±43	8±48		0.56
Increase in serum creatinine from baseline value — %				
At 1 mo	10±22	8±21		<0.001
At 12 mo	11±22	9±22		<0.001
1 Mo after end of treatment	10±22	10±22		0.59

* Plus-minus values are means ±SD. Data are shown for patients who received at least one dose of the study drug for events occurring up to 7 days after permanent discontinuation of the study drug. The percentages for the primary and secondary safety end points are Kaplan-Meier estimates of the rate of the end point at 12 months. Patients could have more than one type of end point. CABG denotes coronary-artery bypass grafting.

[†] Hazard ratios are shown for all safety end points except bleeding requiring red-cell transfusion, for which odds ratios are shown. P values for the odds ratios were calculated with the use of Fisher's exact test.

[‡] Major bleeding and major or minor bleeding according to Thrombolysis in Myocardial Infarction (TIMI) criteria refer to nonadjudicated events analyzed with the use of a statistically programmed analysis in accordance with previously used definitions.¹⁰

The incremental reduction in the risk of coronary thrombotic events (i.e., myocardial infarction and stent thrombosis) through more-intense P2Y₁₂ inhibition with ticagrelor is consistent with similar effects of prasugrel.¹⁰ As noted above, the benefits with ticagrelor were seen regardless of whether invasive or noninvasive management was planned; this issue has not been investigated with other P2Y₁₂ inhibitors. Treatment with ticagrelor was also associated with an absolute reduction of 1.4 percentage points and a relative reduction of 22% in the rate of death from any cause at 1 year. This survival benefit from more-intense platelet inhibition with ticagrelor is consistent with reductions in the mortality rate obtained by means of platelet inhibition with aspirin in patients who had an acute coronary syndrome^{27,28} and with clopidogrel in patients who had myocardial infarction with ST-segment elevation.²² In contrast, other contemporary trials involving patients with an acute coronary syndrome have not shown significant reductions in the mortality rate with the use of clopidogrel,⁸ prasugrel,¹⁰ or glycoprotein IIb/IIIa inhibitors.²⁹ The improved survival rate with ticagrelor might be due to the decrease in the risk of thrombotic events without a concomitant increase in the risk of major bleeding, as seen with other antithrombotic treatments in patients with an acute coronary syndrome.³⁰⁻³²

Since P2Y₁₂ inhibition with ticagrelor is revers-

ible, the antiplatelet effect dissipates more rapidly than with the thienopyridines, which are irreversible P2Y₁₂ inhibitors. Therefore, less procedure-related bleeding might be expected. Although the rates of major bleeding were not lower with ticagrelor than with clopidogrel, the more-intense platelet inhibition with ticagrelor was not associated with an increase in the rate of any major bleeding. In contrast to the experience with prasugrel,¹⁰ which is also a more effective platelet inhibitor than clopidogrel but is irreversible, there was no increased risk of CABG-related bleeding with ticagrelor. As with prasugrel,¹⁰ non-procedure-related bleeding (spontaneous bleeding), including gastrointestinal and intracranial bleeding, was more common with ticagrelor than with clopidogrel. Although the rare episodes of intracranial bleeding were often fatal, the rates of nonintracranial fatal bleeding, death from vascular causes, and death from any other cause were lower in the ticagrelor group than in the clopidogrel group, resulting in an overall reduction in the mortality rate with ticagrelor.

Dyspnea occurred more frequently with ticagrelor than with clopidogrel.¹³ Most episodes lasted less than a week. Discontinuation of the study drug because of dyspnea occurred in 0.9% of patients in the ticagrelor group. Holter monitoring detected more ventricular pauses during

the first week in the ticagrelor group than in the clopidogrel group,¹³ but such episodes were infrequent at 30 days and were rarely associated with symptoms. There were no significant differences in the rates of clinical manifestations of bradyarrhythmia between the two treatment groups.

The superiority of ticagrelor over clopidogrel with regard to the primary end point, as well as the similarity in rates of major bleeding, was consistent in 62 of 66 subgroups; the differences were significant in the remaining 4 subgroups ($P < 0.05$ for heterogeneity). These findings may have been due to chance, given the large number of tests performed. The difference in results between patients enrolled in North America and those enrolled elsewhere raises the questions of whether geographic differences between populations of patients or practice patterns influenced the effects of the randomized treatments, although no apparent explanations have been found.

In conclusion, in patients who had an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor, as compared with clopidogrel, significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke, without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding.

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APPENDIX

Members of select PLATO committees are as follows (with principal investigators at participating centers and members of other committees listed in the Supplementary Appendix): **Executive Committee** — Sweden: L. Wallentin (cochair), S. James, I. Ekman; H. Emanuelsson, A. Freij, M. Thorsen; United States: R.A. Harrington (cochair), R. Becker, C. Cannon, J. Horrow; Denmark: S. Husted; Germany: H. Katus; U.K.: A. Skene (statistician), R.F. Storey; France: P.G. Steg; **Steering Committee** — Italy: D. Ardissino; Australia: P. Aylward; Philippines: N. Babilonia; France: J.-P. Bassand; Poland: A. Budaj; Georgia: Z. Chapichadze; Belgium: M.J. Claeys; South Africa: P. Commerford; Netherlands: J.H. Cornel, F. Verheugt; Slovak Republic: T. Duris; China: R. Gao; Mexico: G.C. Armando; Germany: E. Giannitsis; United States: P. Gurbel, R. Harrington, N. Kleiman, M. Sabatine, D. Weaver; Spain: M. Heras; Denmark: S. Husted; Sweden: S. James; Hungary: M. Keltai; Norway: F. Kontny; Greece: D. Kremastinos; Finland: R. Lassila; Israel: B.S. Lewis; Spain: J.L. Sendon; Hong Kong: C. Man Yu; Austria: G. Maurer; Switzerland: B. Meier; Portugal: J. Morais; Brazil: J. Nicolau; Ukraine: A. Nikolaevich Parkhomenko; Turkey: A. Oto; India: P. Pais; Argentina: E. Paolasso; Bulgaria: D. Raev; Malaysia: D.S. Robaayah Zambahari; Russia: M. Ruda; Indonesia: A. Santoso; South Korea: K.-B. Seung; Singapore: L. Soo Teik; Czech Republic: J. Spinar; Thailand: P. Sritara; United Kingdom: R. Storey; Canada: P. Thérioux; Romania: M. Vintila; Taiwan: D.W. Wu; **Data Monitoring Committee** — United States: J.L. Anderson (chair), D. DeMets (statistician); the Netherlands: M. Simoons; United Kingdom: R. Wilcox; Belgium: F. Van de Werf.

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Steg PG, Becker RC, Cannon CP, et al. Comparison of ticagrelor: the first reversible oral P2Y₁₂ receptor antagonist with clopidogrel in patients with ST-elevation acute coronary syndromes: results from the PLATelet inhibition and patient Outcomes (PLATO) trial. Late-breaking clinical trial abstract. [oral presentation]

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PLATO STEMI

Ticagrelor compared with clopidogrel in patients with acute coronary syndromes
the PLATelet Inhibition and patient Outcomes trial

Outcomes in patients with STEMI and planned PCI

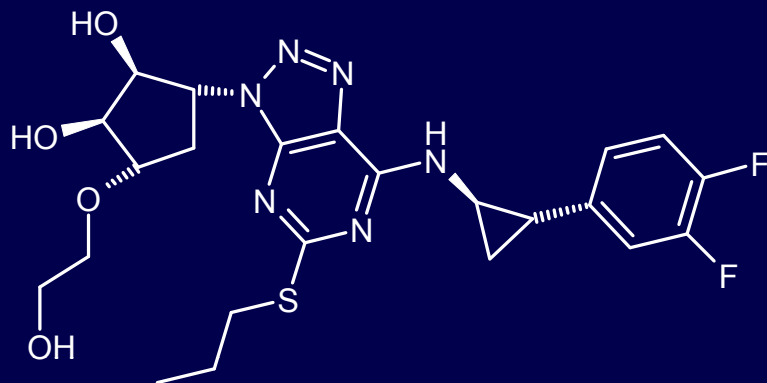
Ph. Gabriel Steg*, Stefan James, Robert A Harrington, Diego Ardissino, Richard C. Becker, Christopher P. Cannon, Håkan Emanuelsson, Ariel Finkelstein, Steen Husted, Hugo Katus, Jan Kilhamn, Sylvia Olofsson, Robert F. Storey, Douglas Weaver, Lars Wallentin, for the PLATO study group

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PG Steg: disclosures

- **Research Grant:** Sanofi-aventis (1999-2008), Servier (2009–2014)
- **Speaking:** AstraZeneca, Boehringer-Ingelheim, BMS, GSK, Menarini, Medtronic, Nycomed, Pierre Fabre, sanofi-aventis, Servier, The Medicines Company
- **Consulting/advisory board:** Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi-Sankyo, Endotis, GSK, Medtronic, MSD, Nycomed, Sanofi-aventis, Servier, The Medicines Company
- **Stockholding:** Aterovax

Ticagrelor (AZD 6140): an oral reversible $P2Y_{12}$ antagonist



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
 - Not a pro-drug; does not require metabolic activation
 - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
 - Greater inhibition of platelet aggregation than clopidogrel
- **Reversibly bound**
 - Degree of inhibition reflects plasma concentration
 - Faster offset of effect than clopidogrel
 - Functional recovery of circulating platelets within ~48 hours

PLATO study design



NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel (n=9291)
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor (n=9333)
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

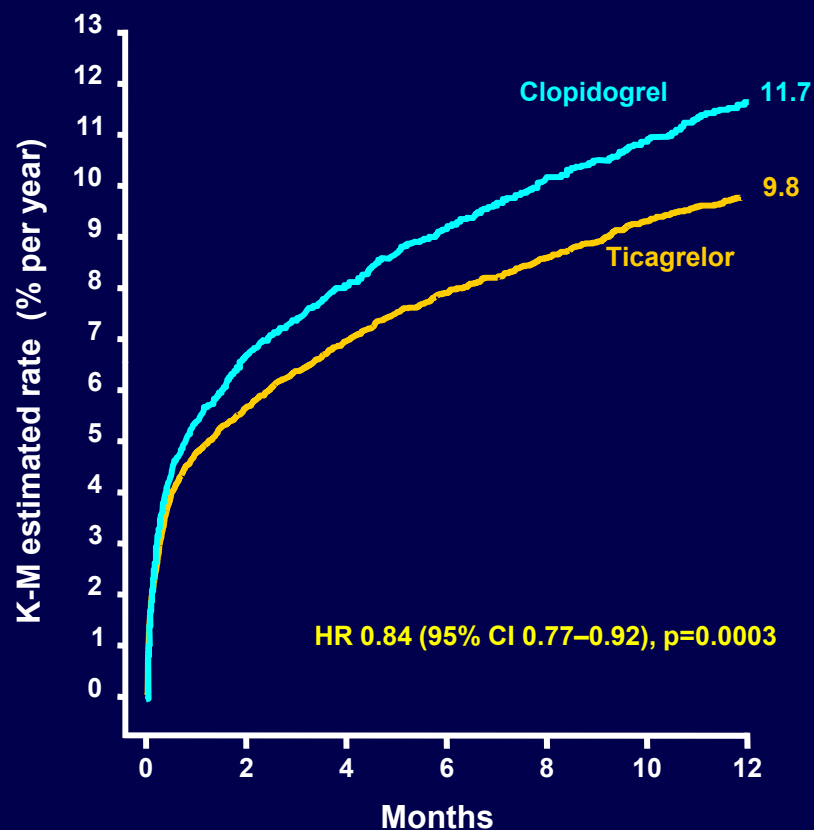
6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

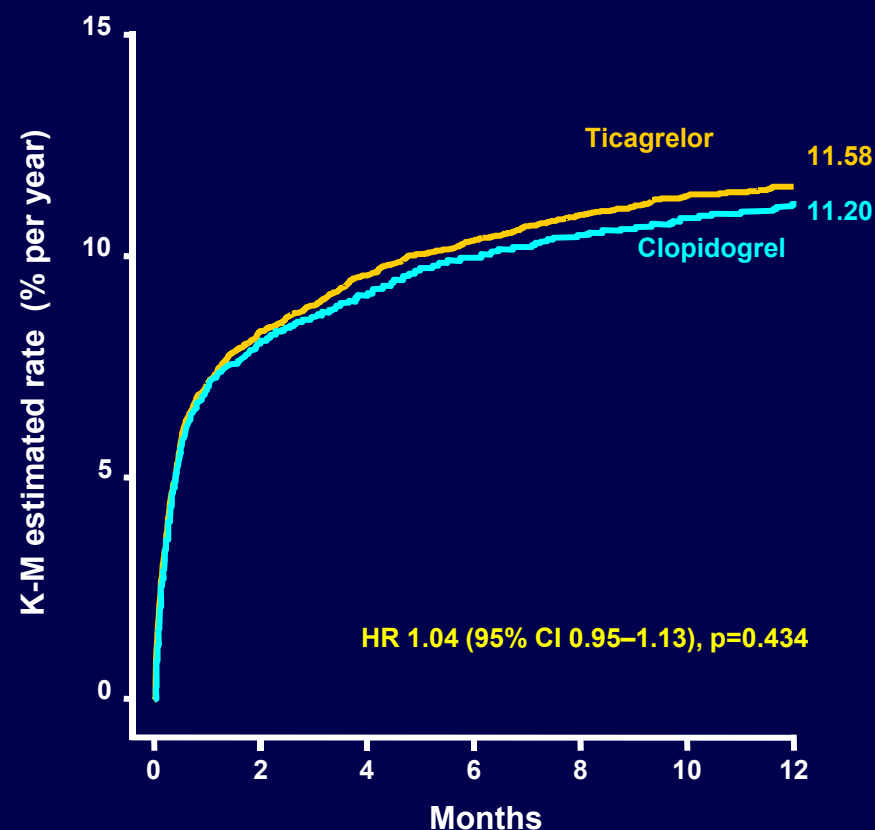
PLATO main endpoints



Primary efficacy endpoint



Primary safety endpoint



No. at risk

Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

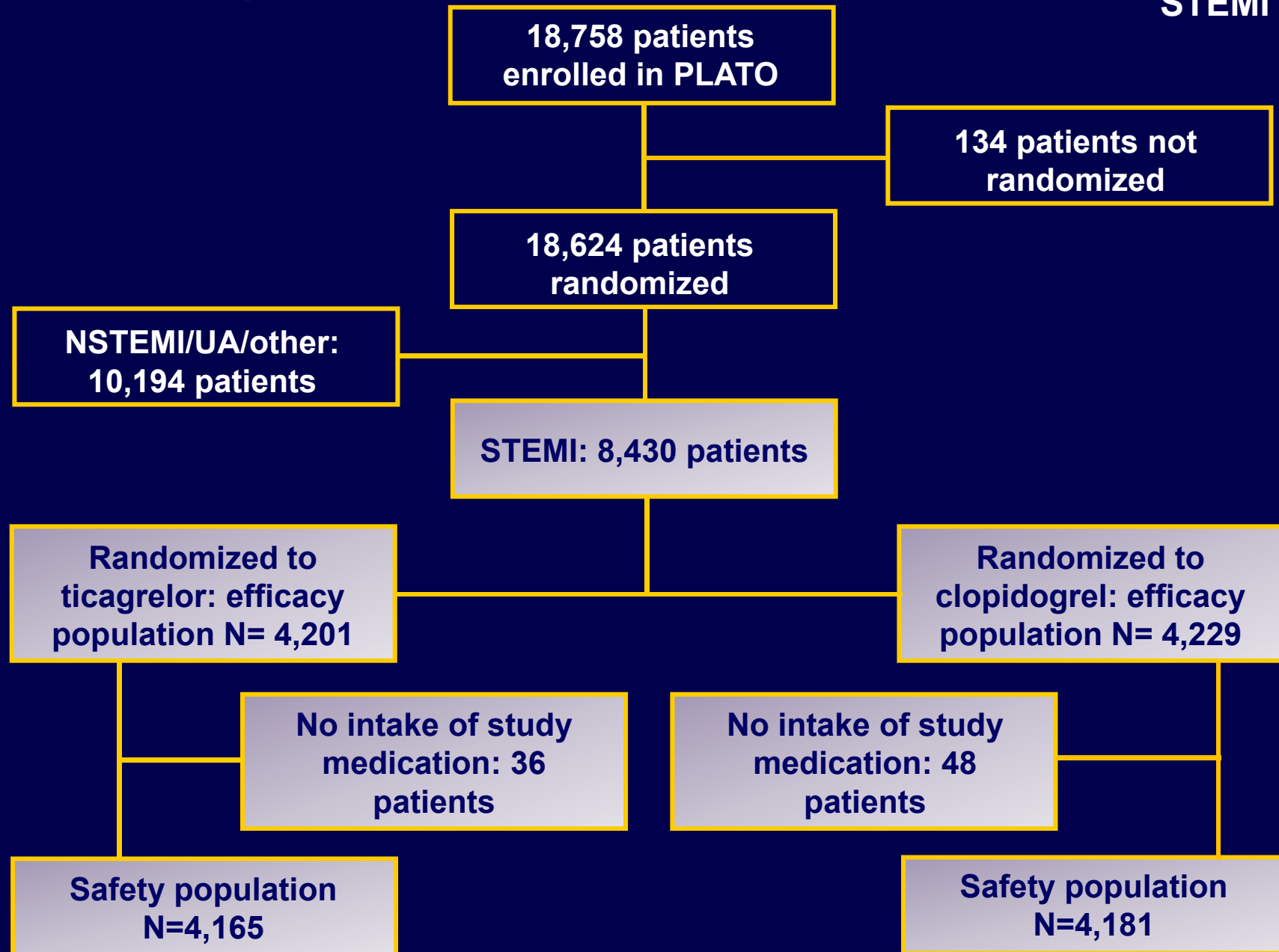
9,235	7,246	6,826	6,545	5,129	3,783	3,433
9,186	7,305	6,930	6,670	5,209	3,841	3,479

Wallentin et al., New Eng J Med. 2009;361:1045–1057

STEMI and primary PCI

- Primary PCI is the optimal reperfusion therapy for STEMI
- Patients with STEMI and planned primary PCI particularly require urgent and effective blockade of the P2Y₁₂ platelet receptor and also are potentially at greater risk of side effects from new therapies
- Therefore, the objective of this predefined analysis of the PLATO trial was to investigate the efficacy and safety of ticagrelor versus clopidogrel in patients with STEMI intended for reperfusion with primary PCI

Patient disposition



PLATO STEMI population



- **Inclusion criteria**

- Hospitalization for ST-segment elevation ACS, with onset during the previous 24 hours with either of the following
 - Persistent ST-elevation and planned primary PCI
 - New or presumed new LBBB and planned primary PCI
 - Or final diagnosis of STEMI

- **Main exclusion criteria**

- Contraindication to clopidogrel
- Fibrinolytic therapy within 24 hours prior to randomization
- Need for oral anticoagulation therapy
- STEMI as acute complication of PCI or PCI performed before the first study dose
- Increased risk of bradycardic events (e.g. no pacemaker and known sick sinus syndrome, 2nd degree A-V block, 3rd degree A-V block or previous documented syncope suspected to be due to bradycardia)
- Concomitant therapy with strong CYP3A inhibitors or inducers

Baseline and index event characteristics

Characteristic	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)
Median age, years	59	59
Women, %	24.1	23.5
CV risk factors, %		
Habitual smoker	45.5	44.3
Hypertension	59.3	57.8
Dyslipidemia	38.7	39.2
Diabetes mellitus	19.6	21.1
History, %		
Myocardial infarction	13.5	13.8
Percutaneous coronary intervention	8.8	7.9
Coronary-artery bypass graft	2.6	2.7
ECG findings at entry, %		
Persistent ST-segment elevation ≥ 1 mm	81.3	80.6
Left bundle branch block	8.0	9.0
Other*	10.7	10.3

*Final diagnosis of STEMI

Study medication and procedures

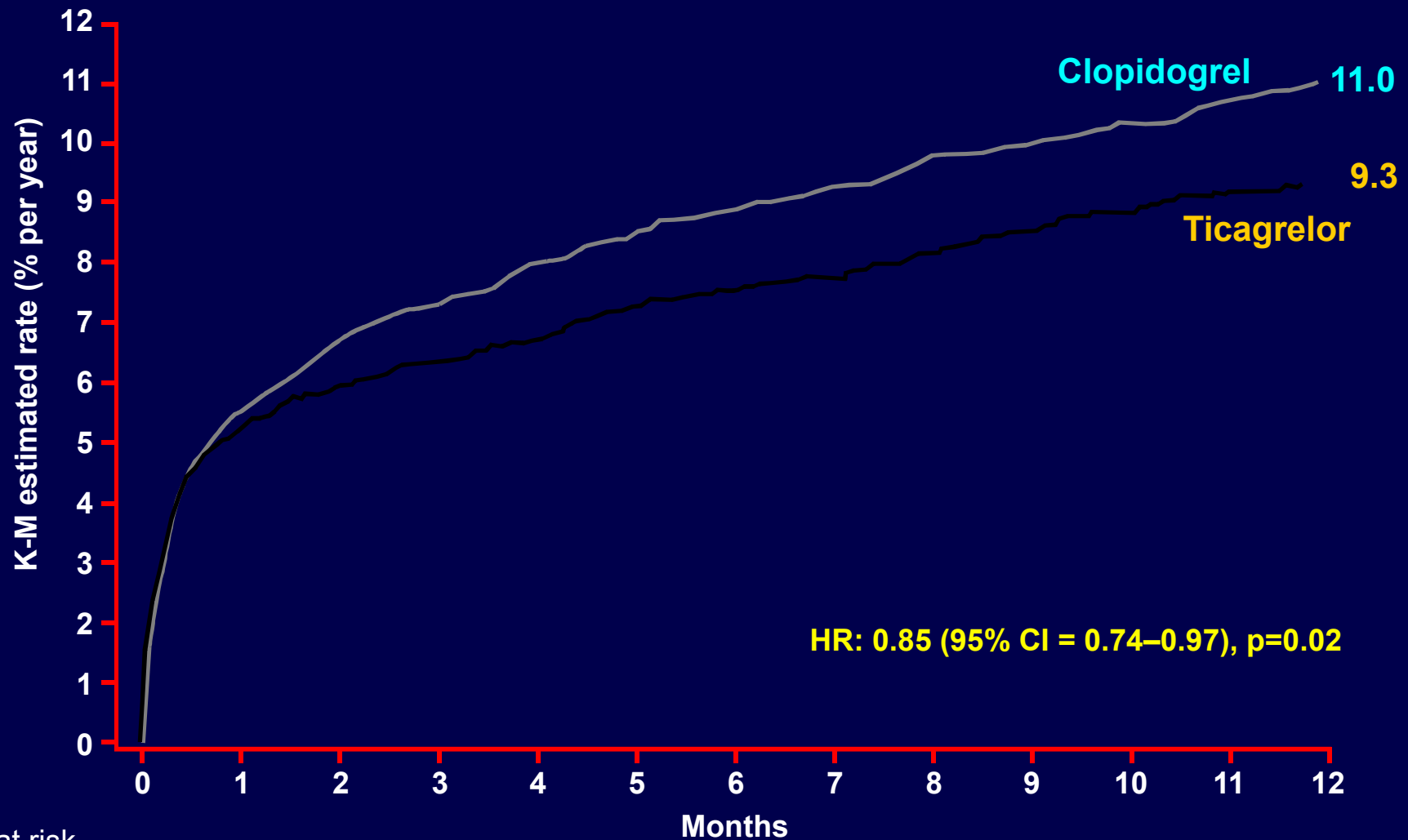
	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)
Start of randomized treatment		
Median time after start of chest pain, hours	5.6	5.8
Premature discontinuation of study drug, %	19.5	18.9
Invasive procedures at index hospitalization, %		
Coronary angiography	92.6	92.8
PCI during index hospitalization	80.6	80.0
CABG during index hospitalization	2.2	2.9
Received at least one stent, %	74.3	74.2
Bare metal stent only	57.9	57.6
Drug-eluting stent (at least one)	16.1	16.3
Open-label clopidogrel pre-randomization, %		
None	56.5	55.5
75 mg	4.8	5.1
300 mg	18.1	18.6
600 mg	20.7	20.8
Total clopidogrel (OL + IP)* pre-randomization to 24 h, %		
300 mg	65.2	65.4
600 mg	34.8	34.6

* Includes placebo in the Ticagrelor arm

Co-medication

Medication	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)
Anti-thrombotic treatment in hospital, %		
Aspirin prior to index event	21.4	20.7
Aspirin from index event to discharge	99.0	98.8
Unfractionated heparin	66.3	65.8
Low molecular weight heparin	45.8	46.1
Fondaparinux	1.8	1.7
Bivalirudin	1.3	1.4
GPIIb/IIIa inhibitor from index event to randomization	34.7	35.2
Other medication in hospital or at discharge, %		
Beta-blockade	85.8	86.2
ACE inhibition and/or angiotensin-II receptor blocker	86.0	85.9
Cholesterol lowering (statin)	94.8	95.1
Calcium-channel blocker	17.1	17.1
Diuretic	36.2	35.4
Proton pump inhibitor	49.1	49.1

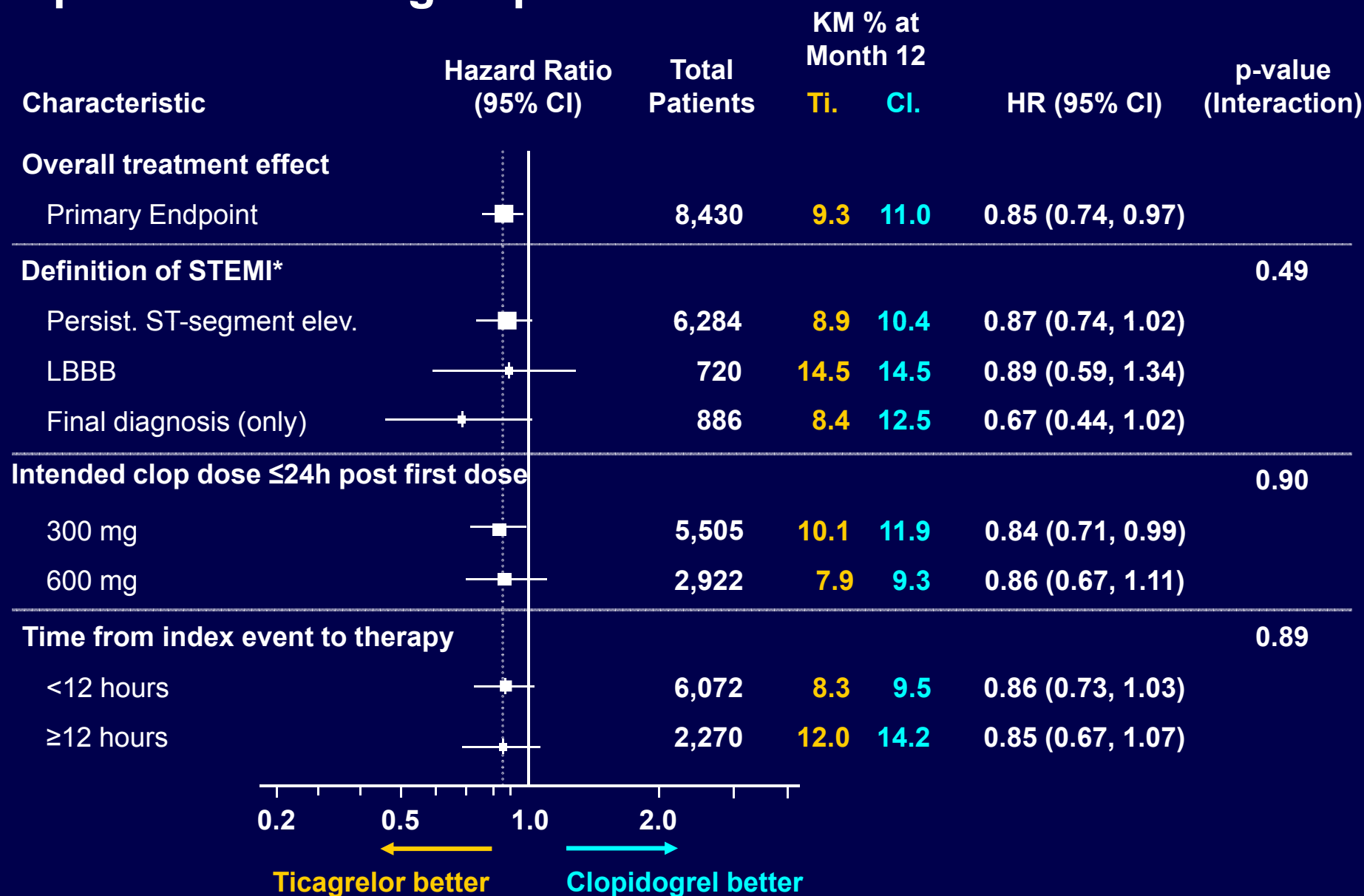
Primary endpoint: CV death, MI or stroke



No. at risk

Ticagrelor	4,201	3,887	3,834	3,732	3,011	2,297	1,891
Clopidogrel	4,229	3,892	3,823	3,730	3,022	2,333	1,868

Primary efficacy endpoint in **selected** pre-defined subgroups



*Patients with LBBB and ST-elevation were classified as LBBB

Hierarchical testing of major efficacy endpoints

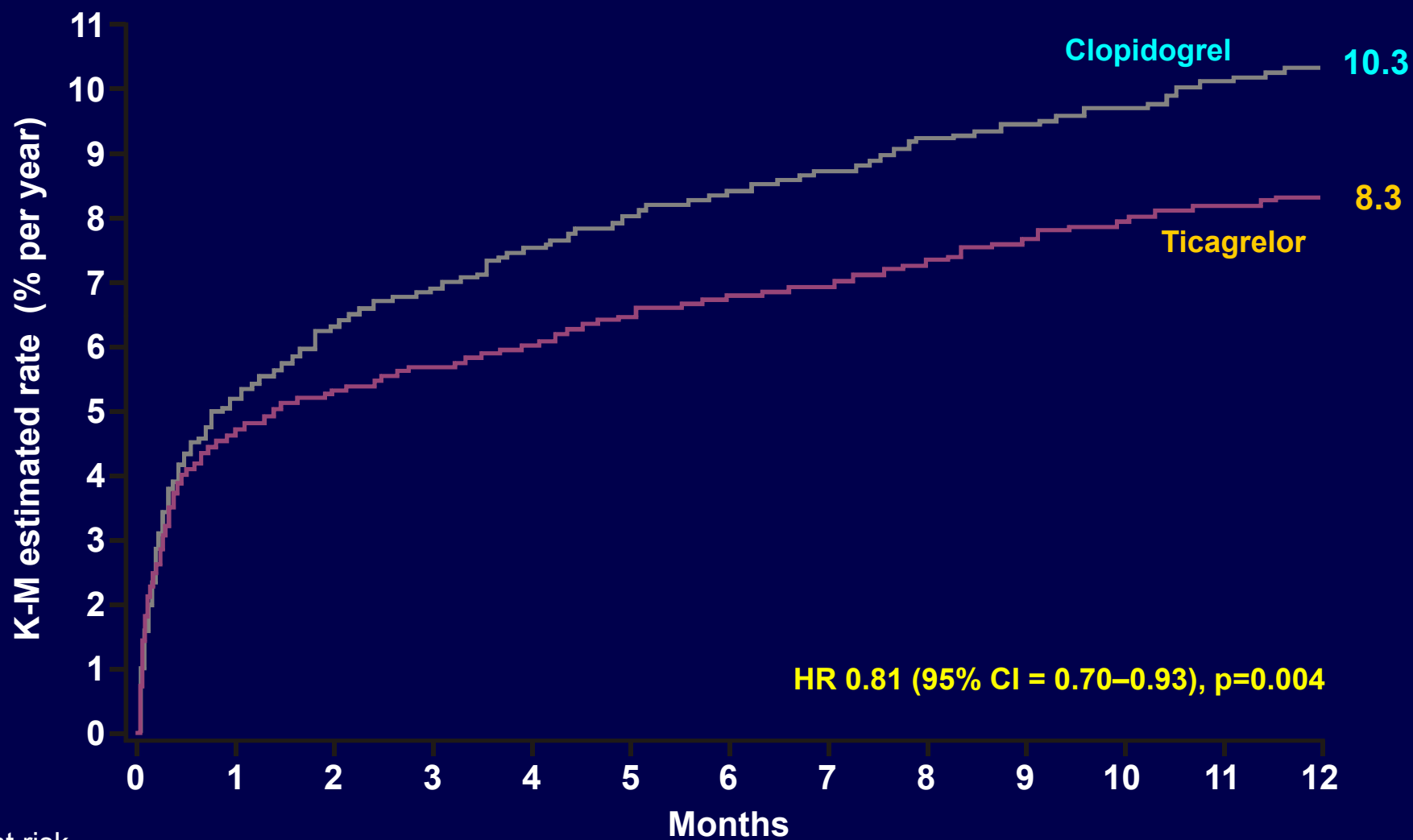


Endpoint*	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)	HR for ticagrelor (95% CI)	p-value†
Primary endpoint, %				
CV death + MI + stroke	9.3	11.0	0.85 (0.74–0.97)	0.02
Secondary endpoints, %				
Total death + MI + stroke	9.7	11.5	0.84 (0.73–0.96)	0.01
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	13.4	15.4	0.86 (0.76–0.96)	0.01
MI	4.7	6.1	0.77 (0.63–0.93)	0.01
CV death	4.5	5.4	0.84 (0.69–1.03)	0.09
Stroke	1.6	1.0	1.45 (0.98–2.17)	0.07
All-cause mortality	4.9	6.0	0.82 (0.68–0.99)	0.04

The percentages are K-M estimates of the rate of the endpoint at 12 months. Patients could have had more than one type of endpoint.

†By univariate Cox model

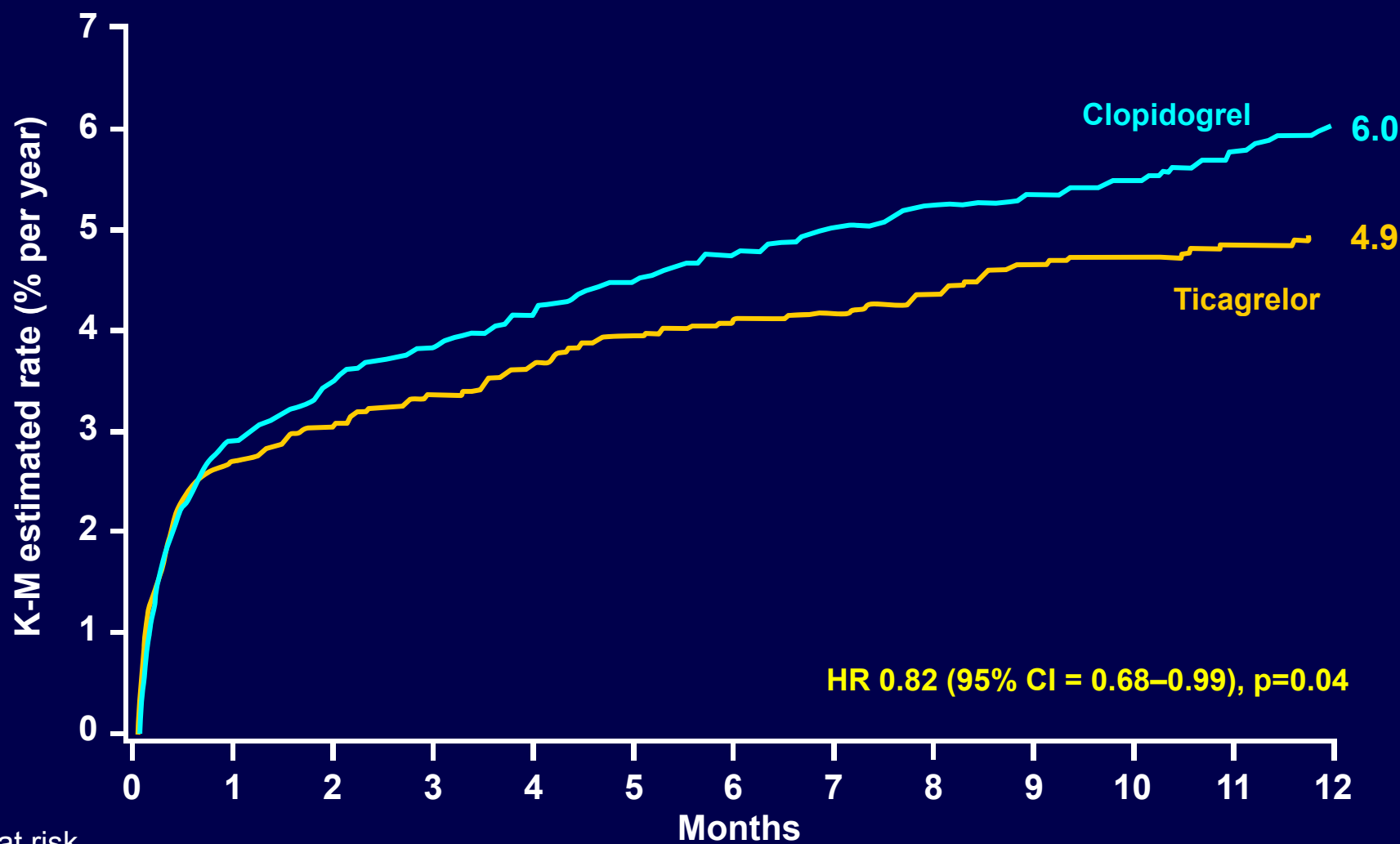
CV death/total MI



No. at risk

Ticagrelor	4,201	3,912	3,862	3,759	3,038	2,321	1,914
Clopidogrel	4,229	3,908	3,841	3,751	3,043	2,350	1,881

All cause mortality



No. at risk

Ticagrelor	4,201	4,005	3,962	3,876	3,150	2,413	1,993
Clopidogrel	4,229	4,029	3,989	3,912	3,195	2,471	1,980

Stent thrombosis (as per ARC definitions)*

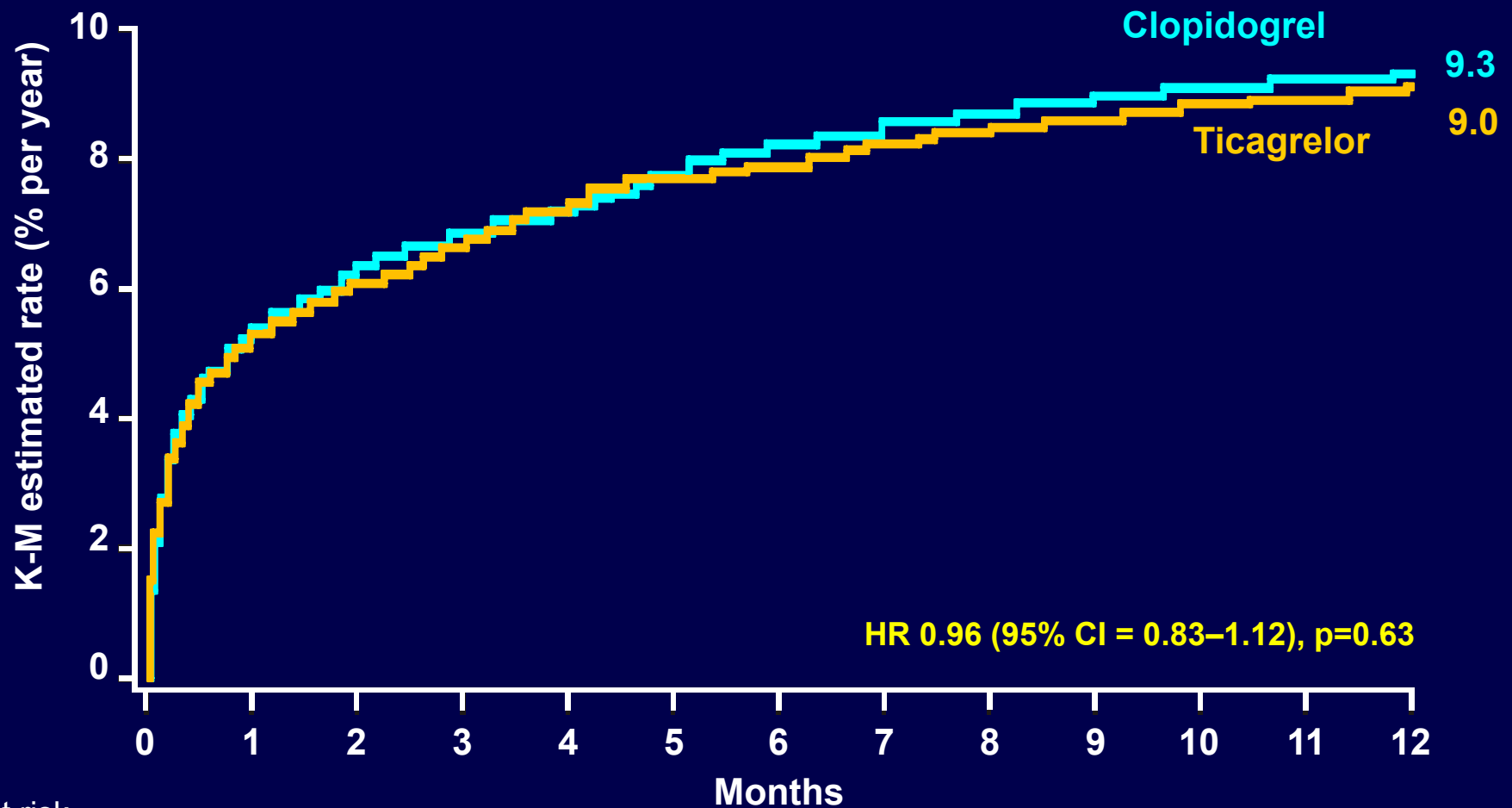
	Ticagrelor (n=4,201)	Clopidogrel (n=4,229)	HR for ticagrelor (95% CI)	p-value†
Definite	1.6	2.5	0.61 (0.42–0.87)	0.01
Probable or definite	2.5	3.6	0.69 (0.52–0.92)	0.01
Possible, probable, or definite	3.2	4.4	0.73 (0.56–0.94)	0.02

Time-at-risk is calculated from the date of first stent insertion in the study or date of randomization

*Cutlip et. al., Circulation. 2007;115:2344–2351

†By univariate Cox model

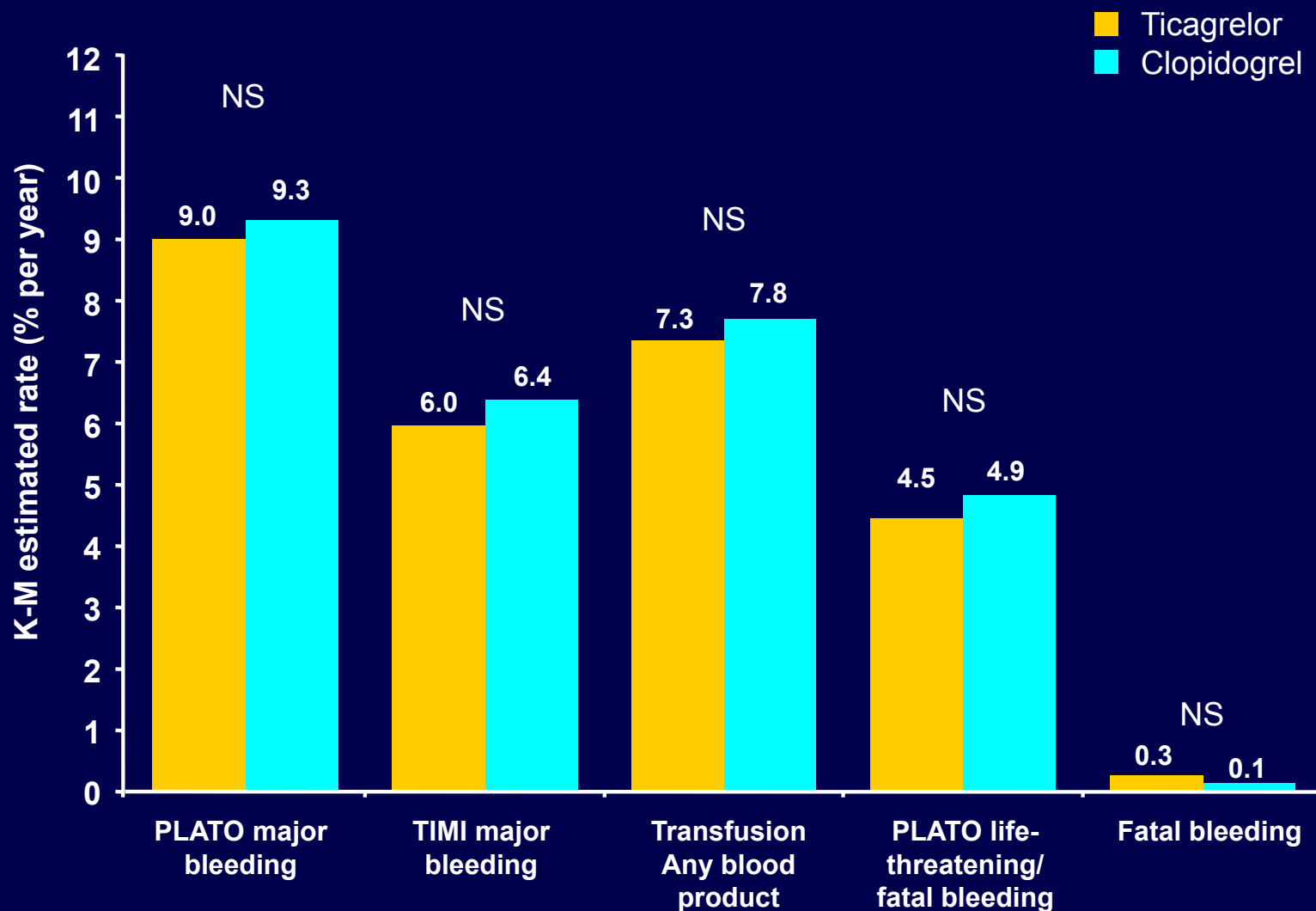
Primary safety event: major bleeding



No. at risk

Ticagrelor	4,165	3,431	3,254	3,137	2,440	1,786	1,640
Clopidogrel	4,181	3,430	3,297	3,159	2,441	1,804	1,635

Total major bleeding



Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. New Eng J Med. 2007;357:2001–15; NS = not significant

Other findings

All patients	Ticagrelor (n=4,165)	Clopidogrel (n=4,181)	p-value*
Dyspnoea, %			
Any	12.9	8.3	<0.0001
Requiring discontinuation of study treatment	0.5	0.1	0.0003
Bradycardia-related events, %			
Bradycardia	4.6	4.9	0.57
Pacemaker placement	1.2	1.0	0.35
Syncope	1.0	0.8	0.35
Heart block	1.0	0.9	0.82

* Fisher's exact test

Conclusions

- Reversible, more intense P2Y₁₂ receptor inhibition for one year with ticagrelor in comparison with clopidogrel in patients with STEMI intended for reperfusion with primary PCI provides
 - Reduction in composite of CV death, MI or stroke
 - Reduction in MI and stent thrombosis
 - Reduction in total mortality
 - No increase in the risk of major bleeding
- The NNT (number needed to treat) to avoid one primary endpoint (CV death, MI or stroke) is 59
- The mortality reduction is afforded on top of modern care

Ticagrelor may become a new standard of care for the management of patients with STEMI intended for primary PCI

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Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study



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Summary

Background Variation in and irreversibility of platelet inhibition with clopidogrel has led to controversy about its optimum dose and timing of administration in patients with acute coronary syndromes. We compared ticagrelor, a more potent reversible P2Y₁₂ inhibitor with clopidogrel in such patients.

Methods At randomisation, an invasive strategy was planned for 13 408 (72.0%) of 18 624 patients hospitalised for acute coronary syndromes (with or without ST elevation). In a double-blind, double-dummy study, patients were randomly assigned in a one-to-one ratio to ticagrelor and placebo (180 mg loading dose followed by 90 mg twice a day), or to clopidogrel and placebo (300–600 mg loading dose or continuation with maintenance dose followed by 75 mg per day) for 6–12 months. All patients were given aspirin. The primary composite endpoint was cardiovascular death, myocardial infarction, or stroke. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00391872.

Findings 6732 patients were assigned to ticagrelor and 6676 to clopidogrel. The primary composite endpoint occurred in fewer patients in the ticagrelor group than in the clopidogrel group (569 [event rate at 360 days 9.0%] vs 668 [10.7%], hazard ratio 0.84, 95% CI 0.75–0.94; $p=0.0025$). There was no difference between clopidogrel and ticagrelor groups in the rates of total major bleeding (691 [11.6%] vs 689 [11.5%], 0.99 [0.89–1.10]; $p=0.8803$) or severe bleeding, as defined according to the Global Use of Strategies To Open occluded coronary arteries, (198 [3.2%] vs 185 [2.9%], 0.91 [0.74–1.12]; $p=0.3785$).

Interpretation Ticagrelor seems to be a better option than clopidogrel for patients with acute coronary syndromes for whom an early invasive strategy is planned.

Funding AstraZeneca.

Introduction

Clopidogrel, a thienopyridine, in addition to aspirin is recommended for prevention of myocardial infarction and stent thrombosis in patients with acute coronary syndromes with or without ST elevation.^{1–4} It is a prodrug that undergoes hepatic conversion, therefore leading to delayed onset of action and substantial variability between individuals in levels of platelet inhibition. Up to a third of patients are low responders who have inadequate levels of inhibition.⁵ Prasugrel, another thienopyridine, is metabolised differently and results in higher levels of inhibition than does clopidogrel, without any low responders;⁶ the increased inhibition further reduces the risk of myocardial infarction and stent thrombosis when started at the time of percutaneous coronary intervention (PCI) in patients with acute coronary syndromes, albeit with an increased risk of bleeding.⁷ Because both thienopyridines are irreversible platelet inhibitors, patients need to produce new platelets to regain normal platelet function. To avoid the risk of severe bleeding, treatment has to be stopped for 5–7 days before coronary artery bypass graft (CABG) or other surgery can be

undertaken. Because of these properties, the early initiation of thienopyridines in patients with acute coronary syndromes is quite variable and controversial.⁸

Ticagrelor, a reversible and direct-acting oral P2Y₁₂-receptor antagonist, provides greater and more consistent platelet inhibition than does clopidogrel, with more rapid onset and offset of action.^{9–11} In the PLATelet inhibition and patient Outcomes (PLATO) trial, reversible long-term P2Y₁₂ inhibition with ticagrelor was better than that with clopidogrel for the prevention of cardiovascular and total death, myocardial infarction, and stent thrombosis, without an increase in the rates of major bleeding in a broad population of patients with acute coronary syndromes who were started on treatment as soon as possible after hospital admission.¹² We therefore compared ticagrelor with clopidogrel in patients with acute coronary syndromes who were planned to undergo an invasive strategy.

Methods

Patients

The details of the study design, patient population, and outcome definitions have been reported by James and

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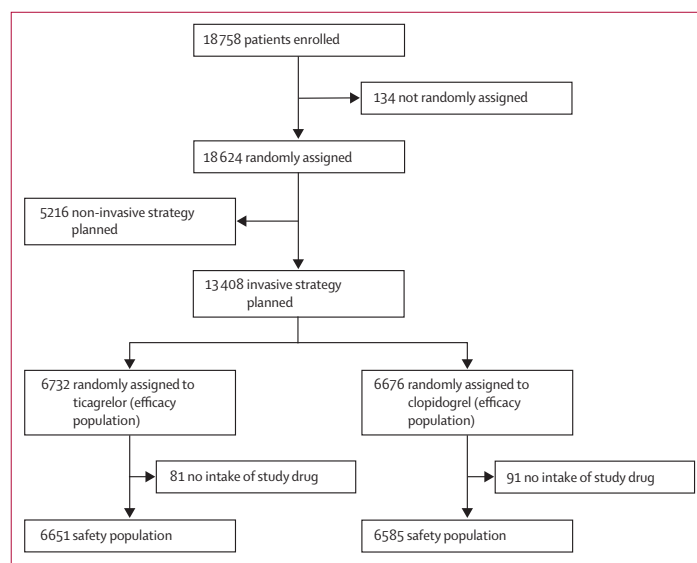


Figure 1: Trial profile

colleagues.¹³ PLATO was a prospective, randomised, double-blind, event-driven trial of patients hospitalised for acute coronary syndromes with or without ST-segment elevation, with an onset of symptoms in the previous 24 h. It was done in 862 centres in 43 countries. Inclusion criteria for patients with non-ST-elevation acute coronary syndromes were at least two of the following: ST-segment depression or transient elevation of at least 1 mm in two or more contiguous leads; positive biomarker indicating myocardial necrosis (ie, troponin I or T or creatine kinase-MB concentration greater than the upper limit of normal); or one of the following risk indicators: age ≥ 60 years; previous myocardial infarction or CABG; coronary artery disease with $\geq 50\%$ stenosis in at least two vessels; previous ischaemic stroke, hospital-based diagnosis of transient ischaemic attack, $\geq 50\%$ carotid stenosis, or cerebral revascularisation; diabetes mellitus; peripheral artery disease; or chronic renal dysfunction (creatinine clearance < 60 mL/min). Inclusion criteria for patients with ST-elevation myocardial infarction were persistent ST-segment elevation of at least 0.1 mV in two or more contiguous leads or new left bundle branch block, and the need for primary PCI.

The main exclusion criteria were contraindication to clopidogrel, treatment with fibrinolytic drugs within 24 h before randomisation, need for oral anticoagulant drugs, an acute complication of PCI (index event), PCI done after the index event but before first dose of study drug, increased risk of bradycardic events, and concomitant use of strong CYP3A inhibitors or inducers. For all patients, the intention for early invasive management had to be indicated by the investigator before the patients

	Ticagrelor (n=6732)	Clopidogrel (n=6676)
Age (years; median, IQR)	61.0 (53–69)	61.0 (53–70)
Age ≥ 75 years	843 (12.5%)	927 (13.9%)
Women	1694 (25.2%)	1688 (25.3%)
Ethnic origin		
White	6138 (91.2%)	6056 (90.7%)
Black	90 (1.3%)	101 (1.5%)
Oriental	409 (6.1%)	428 (6.4%)
Other	94 (1.4%)	91 (1.4%)
History		
Myocardial infarction	1148 (17.1%)	1131 (16.9%)
PCI	947 (14.1%)	885 (13.3%)
Coronary artery bypass graft	357 (5.3%)	380 (5.7%)
Transient ischaemic attack	145 (2.2%)	143 (2.1%)
Non-haemorrhagic stroke	209 (3.1%)	218 (3.3%)
Diabetes mellitus	1530 (22.7%)	1579 (23.7%)
Acute coronary syndrome		
ST-elevation myocardial infarction	3278 (48.8%)	3297 (49.5%)
Non-ST-elevation myocardial infarction	2564 (38.2%)	2481 (37.2%)
Unstable angina or other	873 (13.0%)	887 (13.3%)
Antithrombotic drug during initial hospital admission		
Aspirin	6584 (97.9%)	6544 (98.2%)
Unfractionated heparin	4440 (66.0%)	4404 (66.1%)
Low-molecular-weight heparin	3185 (47.4%)	3133 (47.0%)
Fondaparinux	124 (1.8%)	129 (1.9%)
Bivalirudin	181 (2.7%)	175 (2.6%)
Glycoprotein IIb/IIIa inhibitor	2368 (35.2%)	2362 (35.4%)

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were randomly assigned in the interactive randomisation process.

The trial adhered to the ethical principles of the Declaration of Helsinki, specifications of the International Conference of Harmonisation, and Good Clinical Practice. The study protocol was approved by an independent ethics committee or institutional review board in every country. Patients provided written informed consent before they were randomly assigned to treatment.

Randomisation and masking

Patients were randomly assigned, using an interactive voice response system and a blocking size of four, to ticagrelor or clopidogrel in a one-to-one ratio in a double-blind, double-dummy design. The randomisation schedule was created by the AstraZeneca GRAND system. The creation and ownership of the schedule was handled by a separate group that had no direct involvement in the study. In the double-blind phase, patients in the ticagrelor group were given a loading dose of 180 mg orally, followed by a maintenance dose of 90 mg twice a day, and placebo tablets for clopidogrel. Those in the clopidogrel group were given a loading dose of 300 mg orally followed by a maintenance dose of 75 mg per day, and placebo tablets

	Ticagrelor (n=6732)	Clopidogrel (n=6676)
(Continued from previous page)		
Clopidogrel (OL before randomisation)		
<600 mg	5646 (83.9%)	5638 (84.5%)
≥600 mg	1085 (16.1%)	1037 (15.5%)
Total clopidogrel (OL+IP) before randomisation to 24 h after first dose of IP		
<600 mg	4889 (72.6%)	4882 (73.1%)
≥600 mg	1842 (27.4%)	1792 (26.8%)
Other drug from randomisation to end of study		
β blocker	5751 (85.5%)	5738 (86.1%)
Angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker	5851 (87.0%)	5786 (86.8%)
Cholesterol-lowering (statin)	6416 (95.4%)	6362 (95.5%)
Proton-pump inhibitor	3659 (54.4%)	3578 (53.7%)
Invasive procedures during initial hospital admission		
Coronary angiography	6511 (96.7%)	6476 (97.0%)
Primary PCI* for ST-elevation myocardial infarction	2986 (44.4%)	2984 (44.7%)
Other PCI† before discharge for first event	2173 (32.3%)	2155 (32.3%)
PCI (total)	5159 (76.6%)	5139 (77.0%)
Coronary bypass surgery before discharge	372 (5.5%)	410 (6.1%)

Data are number (%), unless otherwise indicated. PCI=percutaneous coronary intervention. OL=open label. IP=investigational product. *Any PCI during the first 24 h after randomisation. †Any PCI after first 24 h following randomisation in patients with ST-elevation myocardial infarction, or any PCI in patients with non-ST-elevation myocardial infarction.

Table 1: Baseline characteristics, treatments, and interventions

for ticagrelor. Patients who had already had a loading dose of open-label clopidogrel before randomisation, or who had been taking clopidogrel or ticlopidine every day for 5 days or more before randomisation, were not specified to be given the loading dose of masked clopidogrel. Patients undergoing PCI more than 24 h after they were randomly assigned were given an additional dose (90 mg) of masked ticagrelor study drug (active to those in the ticagrelor group, and placebo to those in the clopidogrel group) before PCI; those undergoing PCI at any time relative to randomisation were given, at the discretion of the investigator, an additional loading dose (300 mg) of masked clopidogrel before PCI (active clopidogrel to those randomly assigned to clopidogrel, and placebo to those in the ticagrelor group).

All patients were given aspirin 75–100 mg per day unless they were intolerant. For those not previously given aspirin, a loading dose of 325 mg was preferred (160–500 mg allowed). After stent placement, aspirin, up to 325 mg per day was allowed for up to 6 months. Treatment in the randomised phase lasted for 6–12 months. Study visits were scheduled at 1 month, 3 months, 6 months, 9 months, and 12 months after hospital admission for the first event, with a safety follow-up visit 1 month after the end-of-treatment visit.

	Ticagrelor (n=6732)	Clopidogrel (n=6676)	Hazard ratio (95% CI)	p value
Primary efficacy endpoint				
Cardiovascular death+myocardial infarction*+stroke	569 (9.0%)	668 (10.7%)	0.84 (0.75–0.94)	0.0025
Secondary efficacy endpoint				
All-cause death+myocardial infarction*+stroke	595 (9.4%)	701 (11.2%)	0.84 (0.75–0.94)	0.0016
Cardiovascular death+myocardial infarction+stroke+severe recurrent cardiac ischaemia+recurrent cardiac ischaemia+transient ischaemic attack+other arterial thrombotic event	830 (13.1%)	964 (15.3%)	0.85 (0.77–0.93)	0.0005
Myocardial infarction*	328 (5.3%)	406 (6.6%)	0.80 (0.69–0.92)	0.0023
Cardiovascular death	221 (3.4%)	269 (4.3%)	0.82 (0.68–0.98)	0.0250
Stroke	75 (1.2%)	69 (1.1%)	1.08 (0.78–1.50)	0.6460
Ischaemic†	59 (0.9%)	59 (0.9%)	..	1.0000
Haemorrhagic†	12 (0.2%)	9 (0.1%)	..	0.6634
Unknown†	5 (0.07%)	1 (0.01%)	..	0.2187
All-cause death	252 (3.9%)	311 (5.0%)	0.81 (0.68–0.95)	0.0103
Stent thrombosis (n)	4949	4928
Definite	62 (1.3%)	97 (2.0%)	0.64 (0.46–0.88)	0.0054
Patients with a drug-eluting stent	17 (1.3%)	25 (1.8%)	0.69 (0.37–1.27)	0.2304
Patients with a bare-metal stent	45 (1.4%)	72 (2.1%)	0.62 (0.43–0.90)	0.0115
Definite or probable	104 (2.2%)	142 (3.0%)	0.73 (0.57–0.94)	0.0142
Patients with a drug-eluting stent	32 (2.3%)	36 (2.5%)	0.90 (0.56–1.45)	0.6581
Patients with a bare-metal stent	72 (2.2%)	106 (3.1%)	0.67 (0.50–0.91)	0.0092
Total (definite, probable, or possible)	132 (2.8%)	179 (3.8%)	0.73 (0.59–0.92)	0.0068
Patients with a drug-eluting stent	41 (3.1%)	53 (3.8%)	0.78 (0.52–1.17)	0.2349
Patients with a bare-metal stent	91 (2.7%)	126 (3.8%)	0.71 (0.55–0.94)	0.0142

Data are number (Kaplan-Meier estimated % at 360 days), unless otherwise indicated. p values calculated by use of univariate Cox model, unless otherwise indicated. *Excludes silent myocardial infarction. †Data are number (%), and p values calculated with Fisher's exact test.

Table 2: Efficacy of ticagrelor versus clopidogrel

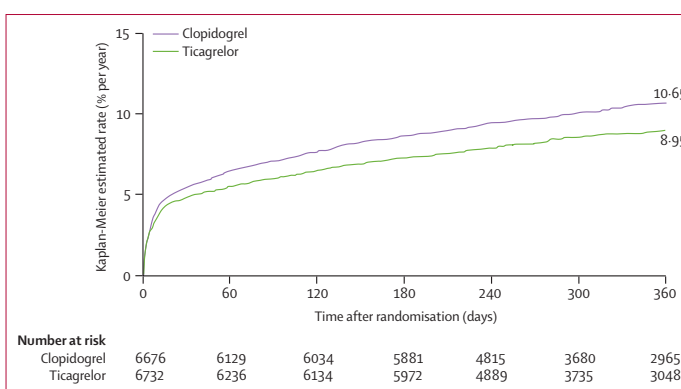


Figure 2: Cumulative Kaplan-Meier estimates of time to first primary efficacy endpoint in patients for whom an invasive strategy was planned

Endpoints

The primary efficacy endpoint was the composite of death from vascular causes, myocardial infarction, or stroke.^{12,13} Secondary endpoints were the composite of all-cause mortality, myocardial infarction, or stroke;

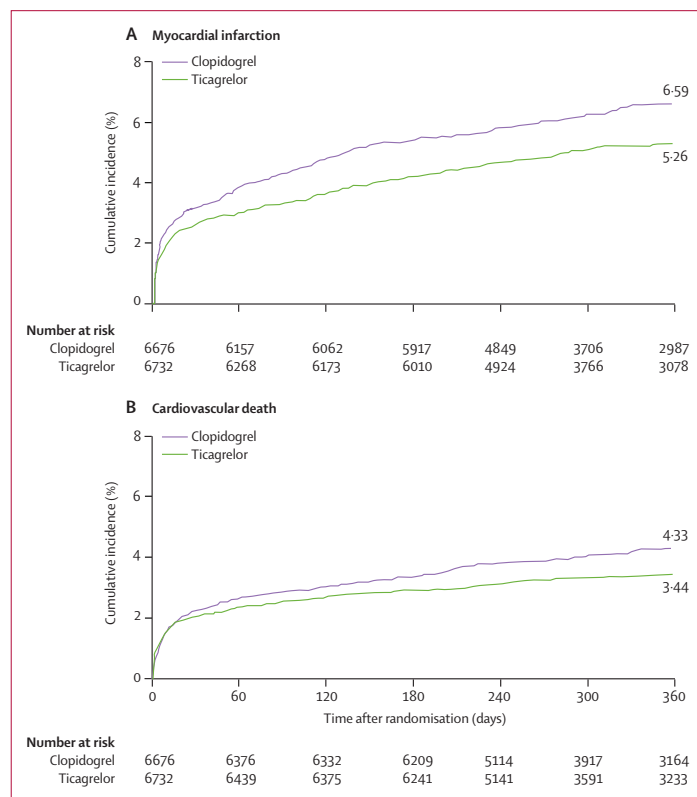


Figure 3: Cumulative Kaplan-Meier estimates of time to myocardial infarction (A) or cardiovascular death (B) in patients intended to undergo an invasive strategy

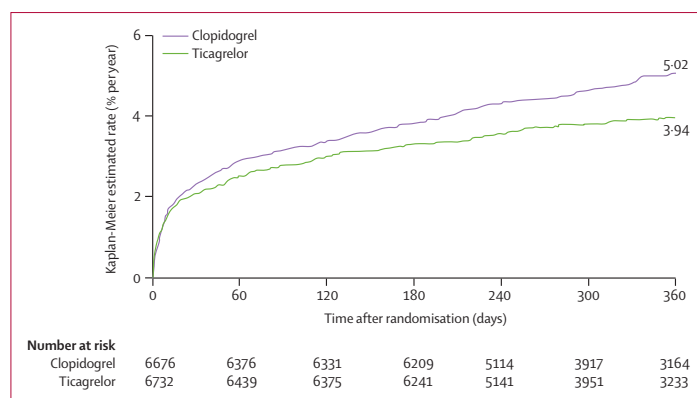


Figure 4: Cumulative Kaplan-Meier estimates of time to all-cause mortality in patients intended to undergo an invasive strategy

death from vascular causes, myocardial infarction, stroke, severe recurrent cardiac ischaemia, recurrent cardiac ischaemia, transient ischaemic attack, or other arterial thrombotic event; components of the primary

endpoint; all-cause mortality; and stent thrombosis. Deaths from vascular causes were those resulting from cardiovascular and cerebrovascular events, or any other death for which there was no clearly documented non-vascular cause. Myocardial infarction was defined in accordance with the universal definition.¹³ Stent thrombosis was established from medical records in accordance with the Academic Research Consortium criteria.¹⁴

The primary safety endpoint was PLATO-defined total major bleeding as previously described.^{12,13} An independent central adjudication committee, unaware of the group assignments, adjudicated all primary and secondary endpoints, and major and minor bleeding events. Major bleeding according to the Thrombolysis In Myocardial Infarction (TIMI) definition was recorded from the electronic case-report form, using a cutoff for haemoglobin of at least 50 g/L, but did not necessarily require clinical evidence of excessive bleeding after CABG. Severe bleeding, as defined according to the Global Use of Strategies To Open occluded coronary arteries (GUSTO),¹⁵ was also established from specific questions on the electronic case-report form, and was defined as fatal, intracranial, or intrapericardial bleeding with cardiac tamponade, or development of hypovolaemic shock or severe hypotension caused by bleeding and requiring pressor support or surgery. These events were specified by the investigators on a specific form for bleeding.

Statistical analysis

The analysis was a prespecified stratum of the whole trial, and based on the investigator's response in the interactive randomisation process, just before the patient was randomly assigned—ie, concerning this patient, do you intend to use an invasive strategy with coronary angiography followed by revascularisation based on the coronary anatomy, or a non-invasive strategy?

The outcome in relation to the clopidogrel loading dose was analysed according to the amount of open-label clopidogrel given to the patient 24 h before randomisation, allowing categorisation into subgroups that were given at least 600 mg or less than 600 mg. It was also analysed in comparison with the intended total amount of clopidogrel given to the patient before randomisation to 24 h after first dose of investigational product—ie, open-label clopidogrel before randomisation or as investigational product (active and placebo).

The Cox proportional hazards model was used to analyse the primary and secondary endpoints. The proportional hazards assumption was assessed with a model of time to event with randomised treatment. All analyses were by intention to treat, and were done with SAS (version 9.2). A p value of 0.05 was regarded as significant for the overall treatment differences.

Investigators were expected to indicate intention for an invasive strategy in about two-thirds of patients randomly

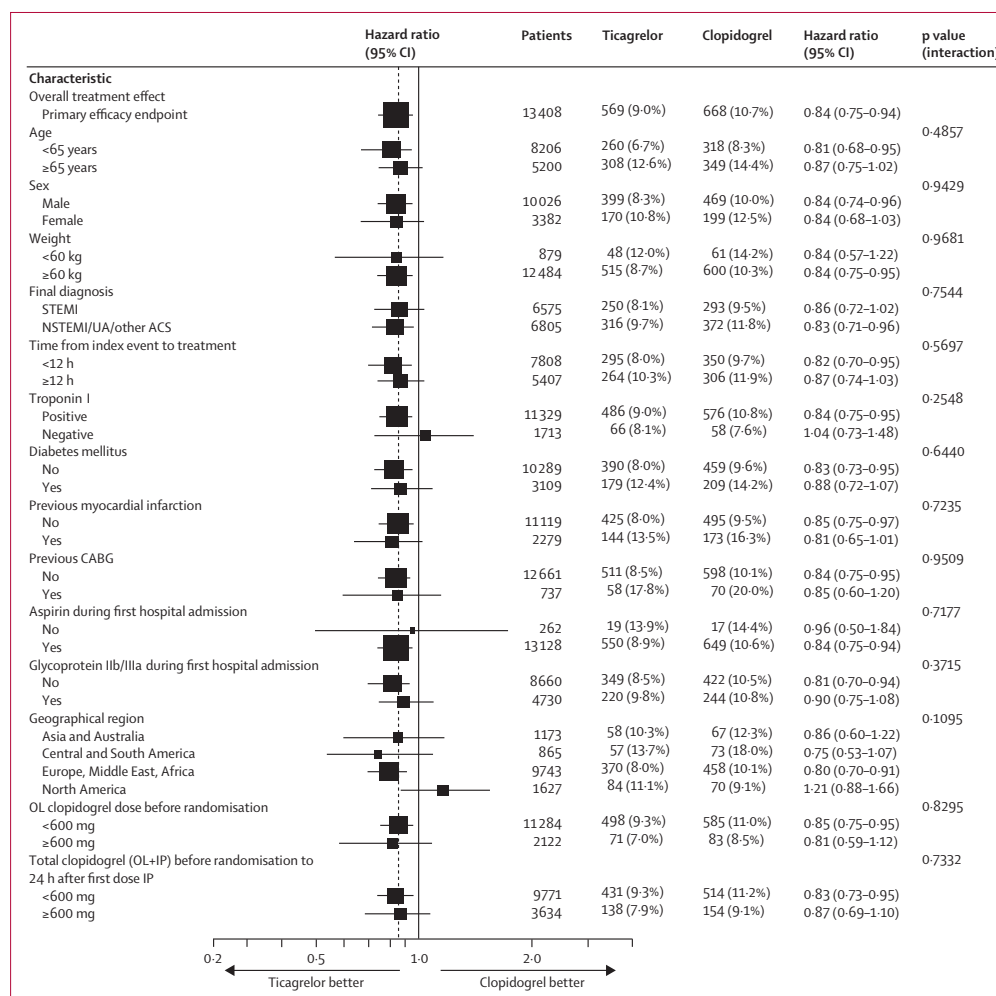


Figure 5: Hazard ratios of benefit with ticagrelor versus clopidogrel for primary efficacy endpoint according to patient subgroups, and clopidogrel dosing before randomisation and percutaneous coronary intervention
 Data are number (Kaplan-Meier estimated % at 360 days), unless otherwise indicated. Vertical dashed line represents the hazard ratio for the overall treatment effect. STEMI=ST-elevation myocardial infarction. NSTEMI=non-ST-elevation myocardial infarction. UA=unstable angina. ACS=acute coronary syndrome. CABG=coronary artery bypass graft. OL=open label. IP=investigational product.

assigned to treatment. A sample size of 13 500 patients was estimated to provide about 80% power to detect a target 15% reduction in relative risk with ticagrelor (13.5% after adjustment for dilution effect of patients discontinuing study drug) in the composite efficacy endpoint for the time to first occurrence of death from vascular causes, myocardial infarction, or stroke. This estimate was based on the same assumptions of sample size as those for the primary analysis at the 4.97% significance level. In accordance with the hierarchical statistical testing of the main secondary endpoints, this test was the first to be done after the primary endpoint.

This trial is registered with ClinicalTrials.gov, number NCT00391872.

Role of the funding source

The academic members of the executive committee designed the PLATO trial in collaboration with representatives from the sponsor. AstraZeneca coordinated data management. The statistical analyses for this report were done by the Duke Clinical Research Institute through which all coauthors had full access to all the data. The corresponding author prepared the first (and all subsequent) drafts of this report, which were

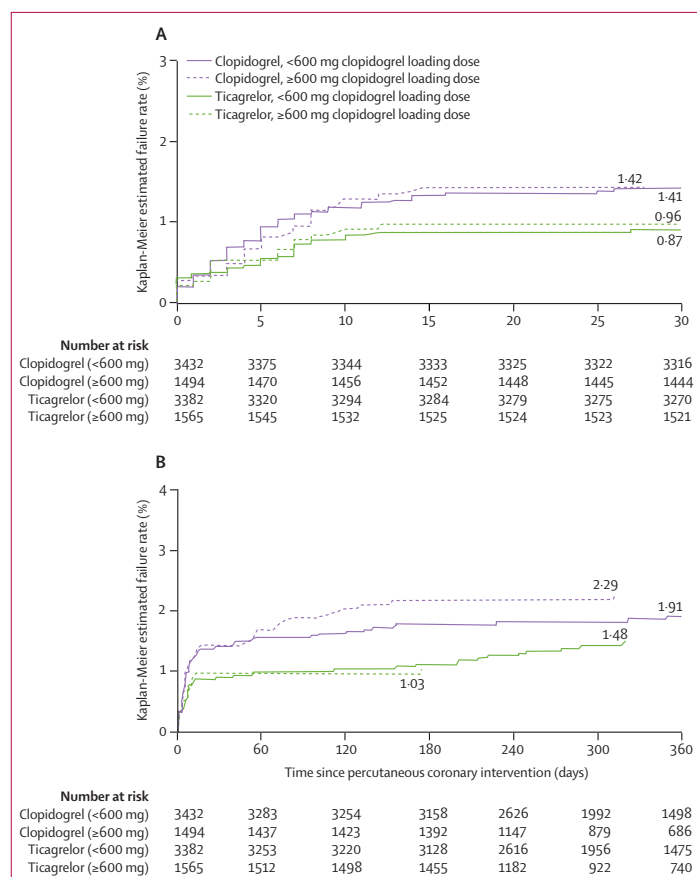


Figure 6: Kaplan-Meier estimates of definite (angiographically documented) stent thrombosis during 30 days (A) and 360 days (B) in patients given ticagrelor versus clopidogrel

then shared with the coauthors, executive and steering committee members, and sponsor for comments. The decision to submit the final version of the report was solely the responsibility of the executive committee.

Results

Figure 1 shows the trial profile. 18 624 patients with acute coronary syndromes (with or without ST elevation) were recruited into the PLATO trial between October 11, 2006, and July 18, 2008. 13 408 (72.0%) were specified by the investigator at the time of randomisation as planned to be managed with an invasive strategy. The baseline characteristics of the two groups were well balanced (table 1). 6575 (49.1%) patients for whom invasive strategy was planned had ST-elevation myocardial infarction, and 6805 (50.9%) had non-ST-elevation myocardial infarction, unstable angina, or other acute coronary syndrome. Coronary angiography was done in 12 987 (96.9%) patients during

the first admission to hospital a median of 0.6 h (IQR 0.1–3.6) after randomisation (table 1). PCI was done in 10 298 (76.8%) individuals, and CABG in 782 (5.8%) during first hospital admission (table 1). Median time to PCI was 2.4 h (0.8–20.1) after randomisation in patients with non-ST-elevation myocardial infarction or unstable angina, and 0.5 h (0.2–1.0) in those with ST-elevation myocardial infarction, whereas time to CABG was 6 days (3–10). No differences were noted in the timing of procedures between the two groups (data not shown).

Both groups started study drug at a median of 8.9 h (IQR 4.0–18.0) after the start of chest pain, and 2.4 h (IQR 0.8–11.4) after hospital admission. Onset of symptoms to start of study drug was 4.7 h (2.9–9.3) in patients with ST-elevation myocardial infarction, and 15.3 h (8.3–21.5) for those with non-ST-elevation myocardial infarction or unstable angina. 13 128 (97.9%) individuals were treated with aspirin; 12 020 (89.8%) were given a parenteral anticoagulant drug, including 8844 (66.1%) unfractionated heparin, 6318 (47.2%) low-molecular-weight heparin, 253 (1.9%) fondaparinux, and 356 (2.7%) bivalirudin; 4730 (35.3%) were treated with a glycoprotein IIb/IIIa inhibitor; and other guideline-recommended drugs were used at high rates (table 1). 644 (4.8%) had been receiving clopidogrel before the first acute coronary event, and 5914 (44.1%) were given clopidogrel on admission, before random assignment. When postrandomisation study drug (clopidogrel or placebo) was included, 3634 (27.1%) patients were given an intended loading dose of 600 mg or more. 1433 (21.8%) patients in the clopidogrel group and 1538 (23.1%) in the ticagrelor group prematurely discontinued the study drug; 404 (14.6%) patients in the clopidogrel group and 415 (14.0%) in the ticagrelor group switched to open-label clopidogrel after stopping the study drug. Reasons for discontinuation were unwillingness to continue the study drug (1268 [42.7%]), an adverse event (871 [29.4%]), and other reason (828 [27.9%]), without much difference between groups. The median exposure to study drug was 279 days (178–365) in the clopidogrel group, and 277 days (182–365) in the ticagrelor group.

The primary and secondary composite endpoints occurred in a smaller proportion of patients in the ticagrelor group than in the clopidogrel group (figure 2; table 2). Rates of deaths resulting from cardiovascular causes and of myocardial infarction were lower in the ticagrelor group than in the clopidogrel group, whereas rates of strokes did not differ between the groups (table 2; figure 3). Total mortality rate was significantly reduced in the ticagrelor group versus the clopidogrel group (figure 4; table 2).

The benefit of ticagrelor versus clopidogrel for the primary endpoint was similar across a wide range of subgroups (figure 5), irrespective of the loading dose of clopidogrel.

Rate of definite stent thrombosis was reduced in the ticagrelor group (table 2). Reductions in the rates of stent thrombosis were similar in patients with drug-eluting and bare-metal stents (table 2; for definite stent thrombosis p value for interaction=0.78). Rates of definite stent stenosis were lower in the ticagrelor group than in the clopidogrel group, including patients given a clopidogrel loading dose of 600 mg or more compared with those given a lower loading dose at 30 days (figure 6A) and 360 days (figure 6B). The pattern for rates of total stent thrombosis was similar to that for rates of definite stent thrombosis (figure 7A and B).

The rates of PLATO-defined total major bleeding, fatal or life-threatening bleeding, or other major bleeding did not differ in the clopidogrel and ticagrelor groups (figure 8; table 3). With a cutoff point specified on the TIMI scale for bleeding, there was no difference in the rates of total major bleeding between the two groups. Rates of total TIMI major or minor bleeding was similar in the two groups (table 3), whereas rates of non-CABG bleeding were non-significantly higher and those of CABG-related bleeding were non-significantly lower with ticagrelor (table 3). The overall rates of GUSTO-defined severe bleeding did not differ between groups (table 3). No difference was noted in the rates of non-CABG-related bleeding (table 3), but ticagrelor was associated with a non-significantly lower risk of CABG-related bleeding (figure 9; table 3). The rates of PLATO-defined major or minor bleeding were non-significantly higher in the ticagrelor group than in the clopidogrel group (table 3). No differences were noted between the groups in the proportion of patients needing transfusion of red blood cells or platelets (table 3).

Episodes of dyspnoea during 12 months were more common in the ticagrelor group than in the clopidogrel group (924 [event rate 13.9%] vs 527 [8.0%]; $p<0.0001$). However, only 51 (0.8%) patients in the ticagrelor group and ten (0.2%) in the clopidogrel group permanently discontinued the study drug because of this adverse event. The rates of deaths from non-cardiovascular causes in the ticagrelor and clopidogrel groups were not significantly different (31 [0.5%] vs 42 [0.6%]; $p=0.1979$).

Discussion

Patients given ticagrelor had significant and clinically relevant reductions in cardiovascular and total deaths, myocardial infarction, and stent thrombosis, without an increase in risk of major bleeding. The benefits with respect to clinical events and stent thrombosis were consistent whether or not patients were given standard or higher loading doses of clopidogrel, as advocated for patients undergoing invasive strategies.^{1,3,16} Thereby, ticagrelor has important advantages, and improves the early invasive and long-term management of patients with acute coronary syndromes.

Despite the present guidelines for early initiation of clopidogrel in patients with acute coronary syndromes,

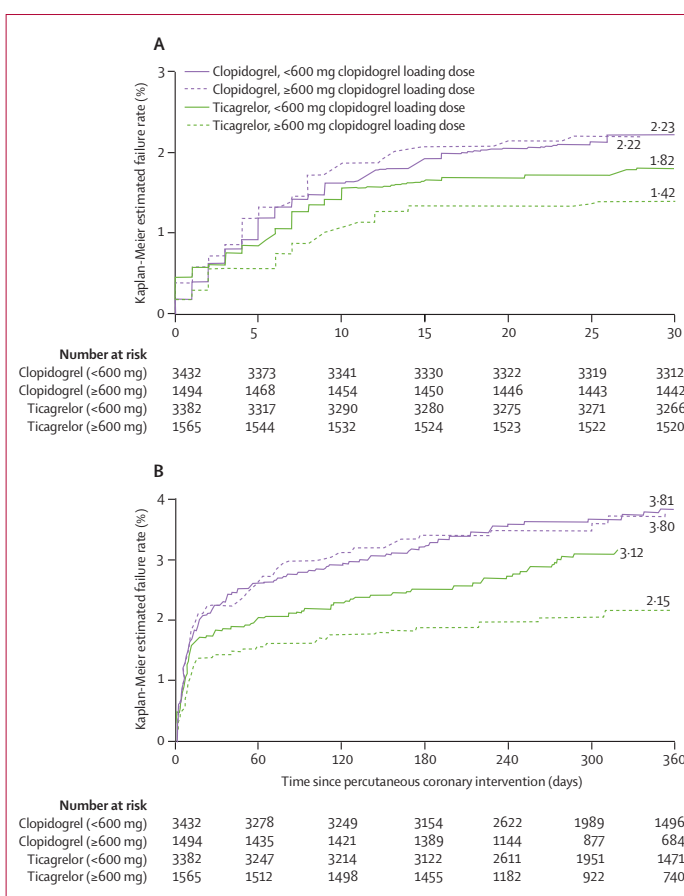


Figure 7: Kaplan-Meier estimates of total stent thrombosis during 30 days (A) and 360 days (B) in patients given ticagrelor versus clopidogrel

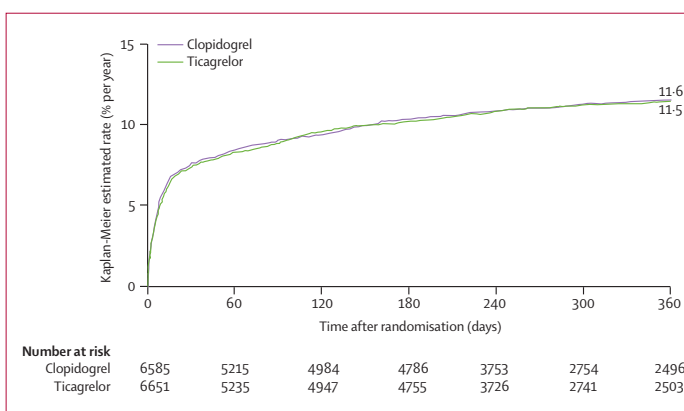


Figure 8: Cumulative Kaplan-Meier estimates of time to total major bleeding in patients intended to undergo an invasive strategy

	Ticagrelor (n=6651)	Clopidogrel (n=6585)	Hazard ratio (95% CI)	p value*
Primary safety endpoint				
Total major bleeding	689 (11.5)	691 (11.6%)	0.99 (0.89–1.10)	0.8803
Life-threatening or fatal bleeding	366 (6.0%)	351 (5.9%)	1.04 (0.90–1.20)	0.6095
Intracranial bleeding	15 (0.3%)	11 (0.2%)	1.36 (0.63–2.97)	0.4364
Other major bleeding	340 (5.9%)	360 (6.2%)	0.94 (0.81–1.09)	0.4030
Major bleeding events				
Non-CABG-related	272 (4.7%)	235 (4.0%)	1.16 (0.97–1.38)	0.1040
CABG-related	430 (7.1%)	480 (8.0%)	0.89 (0.78–1.01)	0.0745
Coronary-procedure-related	521 (8.5%)	554 (9.2%)	0.93 (0.83–1.05)	0.2573
Non-coronary-procedure-related	26 (0.5%)	30 (0.6%)	0.87 (0.51–1.46)	0.5911
Major or minor bleeding events				
Total	961 (16.0%)	883 (14.7%)	1.09 (0.99–1.19)	0.0700
Non-CABG-related	523 (8.9%)	416 (7.1%)	1.26 (1.11–1.43)	0.0004
CABG-related†	464 (7.7%)	516 (8.7%)	0.89 (0.79–1.01)	0.0710
Coronary-procedure-related	645 (10.5%)	652 (10.7%)	0.98 (0.88–1.10)	0.7768
Non-coronary-procedure-related	42 (0.7%)	50 (0.9%)	0.84 (0.56–1.26)	0.3998
Transfusion of blood products				
PRBCs or whole blood	531 (8.9%)	525 (8.7%)	1.01 (0.89–1.14)	0.9095
Platelets	98 (1.6%)	114 (1.9%)	0.85 (0.65–1.12)	0.2506
TIMI-defined cutoff point for major bleeding				
Total	476 (7.9%)	474 (7.9%)	1.00 (0.88–1.14)	1.0000
Non-CABG-related	160 (2.8%)	130 (2.2%)	1.23 (0.98–1.55)	0.0814
CABG-related†	322 (5.3%)	354 (5.9%)	0.90 (0.78–1.05)	0.1914
TIMI-defined cutoff point for minor bleeding				
Total	219 (3.8%)	220 (3.7%)	0.99 (0.82–1.19)	0.9218
Non-CABG-related	119 (2.1%)	101 (1.7%)	1.18 (0.90–1.53)	0.2329
CABG-related†	102 (1.8%)	122 (2.1%)	0.83 (0.64–1.08)	0.1665
TIMI-defined cutoff point for major or minor bleeding				
Total	675 (11.2%)	678 (11.3%)	0.99 (0.89–1.10)	0.8573
Non-CABG-related	270 (4.6%)	227 (3.9%)	1.19 (1.00–1.42)	0.0561
CABG-related†	424 (7.0%)	476 (8.0%)	0.88 (0.78–1.01)	0.0630
GUSTO-defined severe bleeding				
All	185 (2.9%)	198 (3.2%)	0.91 (0.74–1.12)	0.3785
Non-CABG-related	120 (2.0%)	103 (1.8%)	1.09 (0.83–1.43)	0.5227
CABG-related†	69 (1.1%)	97 (1.5%)	0.73 (0.53–1.00)	0.0520

Data are number (Kaplan-Meier estimated % at 360 days), unless otherwise indicated. CABG=coronary artery bypass graft. PRBCs=packed red blood cells. TIMI=Thrombolysis In Myocardial Infarction. GUSTO=Global Use of Strategies To Open occluded coronary arteries. *Calculated by use of univariate Cox model. †Percentages are of total population of patients with CABG-related bleeding. 906 (67.8%) of 1335 patients who had a CABG during the study had PLATElet inhibition and patient Outcomes-defined major bleeding, 673 (50.4%) had TIMI-defined major bleeding, and 165 (12.0%) had severe GUSTO-defined bleeding.

Table 3: Safety of ticagrelor versus clopidogrel in patients intended to undergo an invasive strategy

its use before coronary angiography varies. If clopidogrel is withheld early in the management of the patient, the risk of early ischaemic events is increased and there is no benefit of pretreatment for patients undergoing PCI,¹⁷ since even a loading dose of 600 mg requires 2–4 h before maximum platelet inhibition is achieved.¹¹ Within 30 min, a ticagrelor loading dose of 180 mg resulted in roughly the same level of inhibition of platelet aggregation as that achieved 8 h after a clopidogrel loading dose of 600 mg.¹¹

The advent of an oral reversible P2Y₁₂ inhibitor, with rapid onset of action and offset of antiplatelet effect within 2–3 days,¹¹ would allow great flexibility in the management of all types of patients with acute coronary syndromes. Results of this analysis show that use of such an inhibitor leads to improved outcomes with a reduction in the risk of death, myocardial infarction, and stent thrombosis, without an increase in the risk of bleeding. These findings show that, compared with the benefits noted with clopidogrel versus placebo,^{18–20} additional protection from ischaemic events can be achieved with ticagrelor. The benefits associated with ticagrelor were obtained in a broad patient population with acute coronary syndromes, including those already on clopidogrel at the start of the study. Ticagrelor was better than a strategy in which clopidogrel loading doses of 600 mg were allowed at the time of the procedures. These loading doses were part of the increased dose regimen of clopidogrel tested in OASIS 7-CURRENT.²¹

All-cause mortality was reduced in the ticagrelor group compared with the clopidogrel group, even in patients managed with an early invasive strategy, and who received high rates of guideline-recommended treatments, including, in many cases, a high loading dose of clopidogrel. The reduction in the rates of myocardial infarction and stent thrombosis as a result of the intense P2Y₁₂ inhibition by ticagrelor is in accord with the effects of prasugrel in the TRITON-TIMI 38 trial.⁷ However, by contrast with prasugrel or higher dose clopidogrel, ticagrelor reduced total mortality by 20% (1.1% absolute) compared with clopidogrel over 1 year in invasively managed patients (as was also noted in the trial as a whole).¹² Noteworthy is that the mortality curves showed continued separation throughout this period, whereas in invasively treated patients, the benefit might have been expected to be greater in the early months after acute coronary syndrome.

This mortality benefit compared with clopidogrel is similar in magnitude to other major advances, such as streptokinase or aspirin versus placebo,²² tissue plasminogen activator versus streptokinase,¹⁵ and primary PCI versus tissue plasminogen activator,²³ in care of patients with ST-elevation myocardial infarction. The mortality benefit was more notable in patients with non-ST-elevation acute coronary syndromes, when previous antithrombotic treatments were unsuccessful in improving survival by a reduction in ischaemic events. Thus, platelet inhibition with aspirin,²⁴ clopidogrel,¹⁸ prasugrel,⁷ glycoprotein IIb/IIIa inhibitors,²⁵ or treatment with unfractionated or low-molecular-weight heparins,²⁶ or an early invasive strategy²⁷ have not had any consistent effects on overall mortality in the setting of non-ST-elevation acute coronary syndromes.

The mechanisms of the mortality benefit cannot be defined from this analysis, but might relate to the reduction in ischaemic events without an increase in bleeding. The rate of late mortality was reduced without a difference in ischaemic events, but the risk of bleeding was

lower with fondaparinux than with low-molecular-weight heparin in patients with unstable angina or non-ST-elevation myocardial infarction,²⁸ and with bivalirudin than with unfractionated heparin in those with ST-elevation myocardial infarction.²⁹ A simultaneous reduction in ischaemic events and total mortality rate in invasively managed patients and in the entire trial, not only shows that reversible platelet inhibition with ticagrelor is better than that with clopidogrel in patients with acute coronary syndromes, but also supports the idea that reduction in the rate of ischaemic events, if not associated with increased risk of bleeding, can reduce the mortality rate.

The reduction in the rate of mortality might also be a factor associated with this novel drug class, and thus might be a pleiotropic effect.^{30,31} Ticagrelor blocks reuptake of adenosine by red blood cells,³² which might explain why some patients had bradycardia and dyspnoea. Inhibition of adenosine reuptake could also lead to cardiovascular benefit through reduction in blood pressure, improved coronary flow, or protection against reperfusion injury.³¹

Definitions of bleeding are not consistent between trials, and these differences need to be taken into consideration when differences in rates of bleeding are assessed. Thus, unlike double-dose clopidogrel in the OASIS 7 trial,²¹ and prasugrel in the TRITON-TIMI 38 trial,⁷ ticagrelor was neither associated with an increase in total major PLATO-defined life-threatening or fatal major bleeding, nor with an increase in PLATO-defined other major bleeding (table 3). CABG-related bleeding has been a great cause for concern with the use of clopidogrel, and potentially even more so with prasugrel, which resulted in a 4.7-fold increase in CABG-related bleeding in clopidogrel-naïve patients.⁷ Risk of non-CABG related major bleeding was non-significantly higher, and that of CABG-related bleeding was lower in the ticagrelor group than in the clopidogrel group. Thus, the reversibility of the effect of ticagrelor could help avoid major bleeding associated with surgical procedures.

Although this report is based on some of the patient population in the overall trial, the results should be statistically reliable because this stratum was specified before randomisation (ie, by intention-to-treat invasively). We designed this main secondary analysis to avoid the presentation of a PCI subgroup, which would have been determined after randomisation.^{21,33–35} This cohort is also the most clinically relevant group since it corresponds to the point of decision making that is now a clinical routine worldwide. These data also are more easily applied in practice than are currently available data for prasugrel, which was studied in the setting of no thienopyridine drug before angiography. Our results thus show that ticagrelor might be safely initiated at first presentation and does not need to be withheld until the coronary anatomy is defined. We did not compare ticagrelor with the exact regimen used in the OASIS-7 trial,²¹ but the benefit of ticagrelor versus clopidogrel continued with

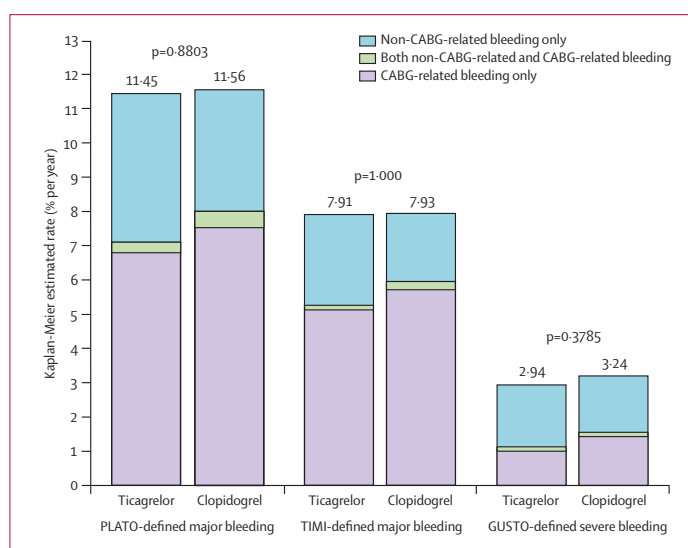


Figure 9: Rates of bleeding according to different definitions

CABG=coronary artery bypass graft. PLATO=PLATelet inhibition and patient Outcomes. TIMI=Thrombolysis In Myocardial Infarction. GUSTO=Global Use of Strategies To Open occluded coronary arteries.

time, and, as such, an additional 6 days of increased dose clopidogrel would be unlikely to have altered the overall findings.

We estimate that use of ticagrelor instead of clopidogrel for 1 year in 1000 patients with acute coronary syndromes and who are planned to undergo an invasive strategy at the start of drug treatment would lead to 11 fewer deaths, 13 fewer myocardial infarctions, and six fewer cases of stent thrombosis without an increase in the rates of major bleeding or transfusion. These results also support the idea that increased inhibition of platelet P2Y₁₂ receptors can achieve substantial reduction in the rate of mortality when not associated with an increase in the rate of major bleeding.

Contributors

CPC participated in study design, data gathering, analysis, and interpretation, writing the first draft, and all revisions of the report. RAH, SJ, RCB, SH, HK, PGS, RFS, and LW were involved in study design, data gathering, analysis, and interpretation, and revision of the report. MK, DA, FK, and BSL participated in data gathering and interpretation, and revision of the report. HE and NSK were involved in study design, data analysis, and critical review of the report. DW was involved in data analysis and revision of the report.

Conflicts of interest

CPC has received research or grant support from Accumetrics, AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis, GlaxoSmithKline, Merck, Intekrin Therapeutics, Novartis, and Takeda; and owns equity in Automedics Medical Systems. RAH has received consulting fees from Bristol-Myers Squibb, Sanofi-Aventis, Portola Pharmaceuticals, Schering-Plough, and AstraZeneca; lecture fees from Schering-Plough, Bristol-Myers Squibb, Sanofi-Aventis, and Eli Lilly; and grant support from Millennium Pharmaceuticals, Schering-Plough, The Medicines Company, Portola Pharmaceuticals, AstraZeneca, and Bristol-Myers Squibb. SJ has received research grants and advisory board fees from AstraZeneca; and honoraria from AstraZeneca, Bristol-Myers Squibb,

Schering-Plough, and Eli Lilly. DA has received research grants from AstraZeneca, Eli Lilly, Pfizer, and Boston Scientific; speaker's bureau payments and honoraria from GlaxoSmithKline, Boehringer-Ingelheim, Sanofi-Aventis, Pfizer, Eli Lilly, AstraZeneca, Schering-Plough, Daiichi Sankyo, Merck, and Boston Scientific; and advisory board fees from Sanofi-Aventis, Pfizer, Eli Lilly, AstraZeneca, Schering-Plough, Daiichi Sankyo, and Medtronic. RCB has received consulting fees from Regado Biosciences, AstraZeneca, Eli Lilly, and Bristol-Myers Squibb; and grant support from Momenta Pharmaceuticals, The Medicines Company, and Bristol-Myers Squibb. HE has been an employee of and owned equity in AstraZeneca. SH has received consulting fees from AstraZeneca, Sanofi-Aventis, and Eli Lilly; and lecture fees from AstraZeneca, Sanofi-Aventis, and Bristol-Myers Squibb. HK has received consulting and lecture fees from AstraZeneca, Bayer Healthcare, Abbott, Roche, and Menarini. MK has received consulting and lecture fees from AstraZeneca. NSK has been an employee of AstraZeneca. FK has received advisory board fees from AstraZeneca and Boehringer-Ingelheim; consulting fees from AstraZeneca, Boehringer-Ingelheim, and Sanofi-Aventis; grant support from Merck Sharp and Dohme, and Perseus Proteomics; and lecture fees from AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, Eli Lilly, Pfizer, and Sanofi-Aventis. BSL has received consulting fees from Bristol-Myers Squibb and Sanofi-Aventis; and grant support from AstraZeneca. PGS has received research grants from Sanofi-Aventis and Servier; lecture fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Menarini, Medtronic, Nycomed, Pierre Fabre, Sanofi-Aventis, Servier, and The Medicines Company; consulting or advisory board fees from Astellas, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Endotis, GlaxoSmithKline, Medtronic, Merck Sharp and Dohme, Nycomed, Sanofi-Aventis, Servier, and The Medicines Company; and has been a stockholder of Aterovax. RFS has received consulting fees from AstraZeneca, Eli Lilly, Daiichi Sankyo, Teva, and Schering-Plough; lecture fees from Eli Lilly, Daiichi Sankyo, and AstraZeneca; and grant support from AstraZeneca, Eli Lilly, Daiichi Sankyo, and Schering-Plough. DW declares that he has no conflicts of interest. LW has received consulting fees from Regado Biosciences and Athera Biotechnologies; lecture fees from Boehringer-Ingelheim, AstraZeneca, and Eli Lilly; and grant support from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Schering-Plough.

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Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO trial

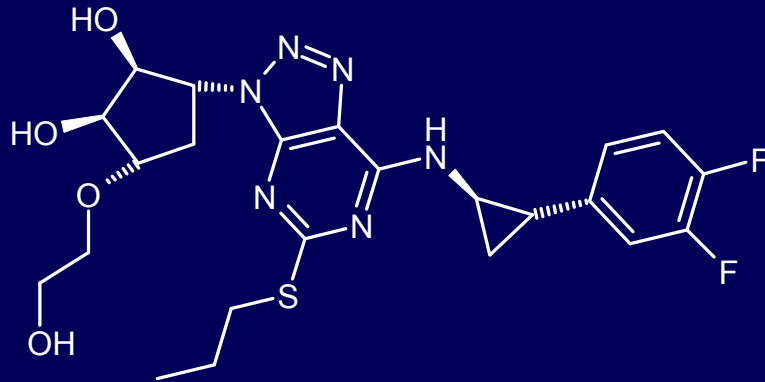
Claes Held, Jean-Pierre Bassand, Richard C. Becker, Christopher P. Cannon, Marc J. Claeys, Robert A. Harrington, Jay Horrow, Steen Husted, Stefan K. James, Kenneth W. Mahaffey, José C. Nicolau, Sylvia Olofsson, Benjamin M. Scirica, Robert F. Storey, Marius Vintila, Joseph Ycas and Lars Wallentin

Disclosures

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AstraZeneca, GlaxoSmithKline, Schering-Plough,
Sanofi-Aventis, Pfizer, Bristol-Myers Squibb

Ticagrelor (AZD 6140): an oral reversibly binding P2Y₁₂ antagonist



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
 - Not a pro-drug; does not require metabolic activation
 - Rapid onset of inhibitory effect on the P2Y₁₂ receptor
 - Greater inhibition of platelet aggregation than clopidogrel
- **Reversibly bound**
 - Degree of inhibition reflects plasma concentration
 - Faster offset of effect than clopidogrel
 - Functional recovery of circulating platelets within ~48 hours

Background

- In NSTEMI and STEMI ACS, guidelines recommend 12 months' treatment with aspirin and clopidogrel
- Clopidogrel is currently the standard of care but is hampered by
 - slow and variable transformation to the active metabolite
 - modest and variable platelet inhibition
 - risk of stent thrombosis and MI in poor responders
 - irreversible effect – increased risk of bleeding at urgent CABG
- Clopidogrel is recommended to be withdrawn 5 days prior to CABG but clinical reality often requires surgery earlier

PLATO = **PLA**telet inhibition and patient **Out**comes; NSTEMI = non-ST segment elevation; STEMI = ST segment elevation; ACS = acute coronary syndromes; MI = myocardial infarction; CABG = coronary artery bypass graft

Objectives

The objective of this pre-defined analysis was
to evaluate the efficacy and safety
of ticagrelor vs clopidogrel
in patients undergoing CABG
within 7 days of last intake of study drug

PLATO study design



NSTEMI ACS (moderate-to-high risk) or STEMI ACS (if primary PCI) (N=18,624)
Clopidogrel-treated or -naive; randomized <24 hours of index event

Clopidogrel

**If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre-PCI)**

Ticagrelor

**180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)**

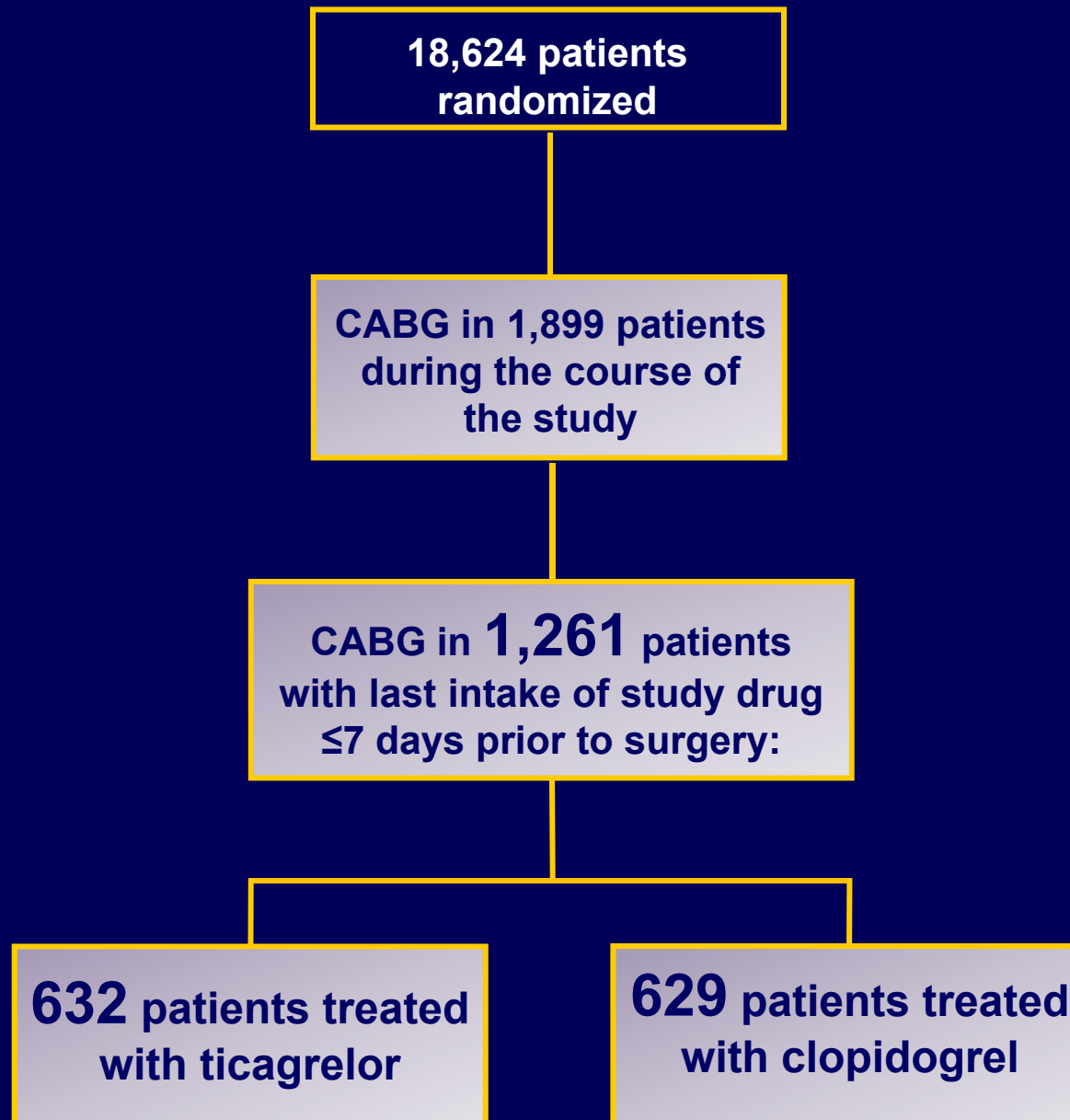
6–12 months treatment

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

Recommendations for patients undergoing CABG:

Study drugs withheld prior to surgery: 5 d for clopidogrel and 24–72 h for ticagrelor.
Study drug be restarted as soon as possible after surgery and prior to discharge

Patient disposition



Baseline CV risk and history

Characteristic	Ticagrelor (n=632)	Clopidogrel (n=629)
CV risk factors, %		
Smoker	32.9	29.4
Hypertension	68.5	67.1
Dyslipidemia	56.3	52.1
Diabetes	30.5	32.9
CV history, %		
Angina pectoris	54.4	52.0
MI	19.6	20.8
Congestive heart failure	4.7	3.5
PCI	9.2	11.6
CABG	0.8	2.2
Transient ischemic attack	3.3	2.9
Non-hemorrhagic stroke	3.8	4.0
Peripheral artery disease	6.8	8.4
Chronic renal disease	5.2	4.3

Evaluations and invasive procedures at study entry

Characteristic	Ticagrelor (n=632)	Clopidogrel (n=629)
Median age, %	64	64
Males, %	80.9	76.9
Age >75 years, %	13.6	15.7
Evaluations, %		
Killip class >2	1.4	1.8
ST-segment elevation >1mm/ LBBB	32.6	33.4
TIMI STEMI risk score >2	59.2	55.2
Invasive procedures in hospital, %		
Coronary angiography	89.2	90.1
PCI within 24 hours of randomization	17.7	20.0
Any PCI pre-discharge	20.6	21.5
<i>CABG pre-discharge</i>	55.7	58.5

LBBB = left bundle branch block; TIMI = thrombolysis in myocardial infarction

Study medication at study entry

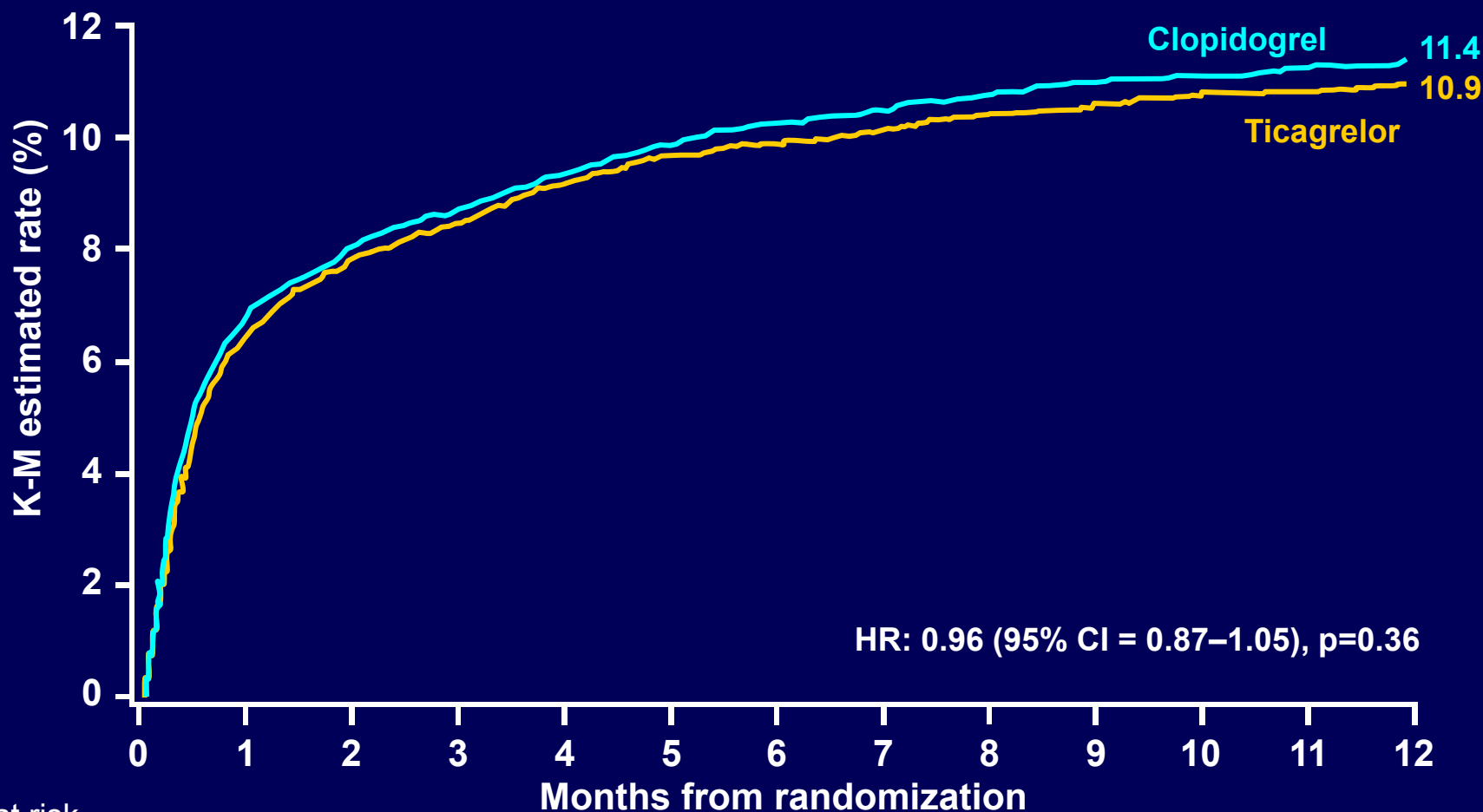
Medication	Ticagrelor (n=632)	Clopidogrel (n=629)
Median treatment duration, days (range)	226 (26–364)	223 (28–353)
Median delay from hospital admission, h	9.0	6.8
Total clopidogrel (OL + IP) pre-randomization to 24 h, %		
300 mg	83.4	81.2
600 mg	16.6	18.8
Open-label clopidogrel pre-randomization, %		
Any dose	46.5	44.2
75 mg (50–150 mg)	14.9	10.5
300 mg (151–449 mg)	22.5	21.5
600 mg (≥450 mg)	9.2	12.2

OL = open-label; IP = investigational product

Study medication pre- and post-CABG

	Ticagrelor (n=632)	Clopidogrel (n=629)
Days study drug stopped before CABG, %		
1 day	13.3	14.0
2 days	16.8	13.7
3 days	18.0	11.6
4 days	13.3	11.0
5 days	12.5	15.3
6 days	14.4	17.5
7 days	11.7	17.0
Patients not restarted on study drug/unknown	n=234	n=238
Time study drug restarted after CABG, %	(n=398)	(n=391)
<7 days	57.0	57.5
7–14 days	27.9	25.6
>14 days	15.1	16.9

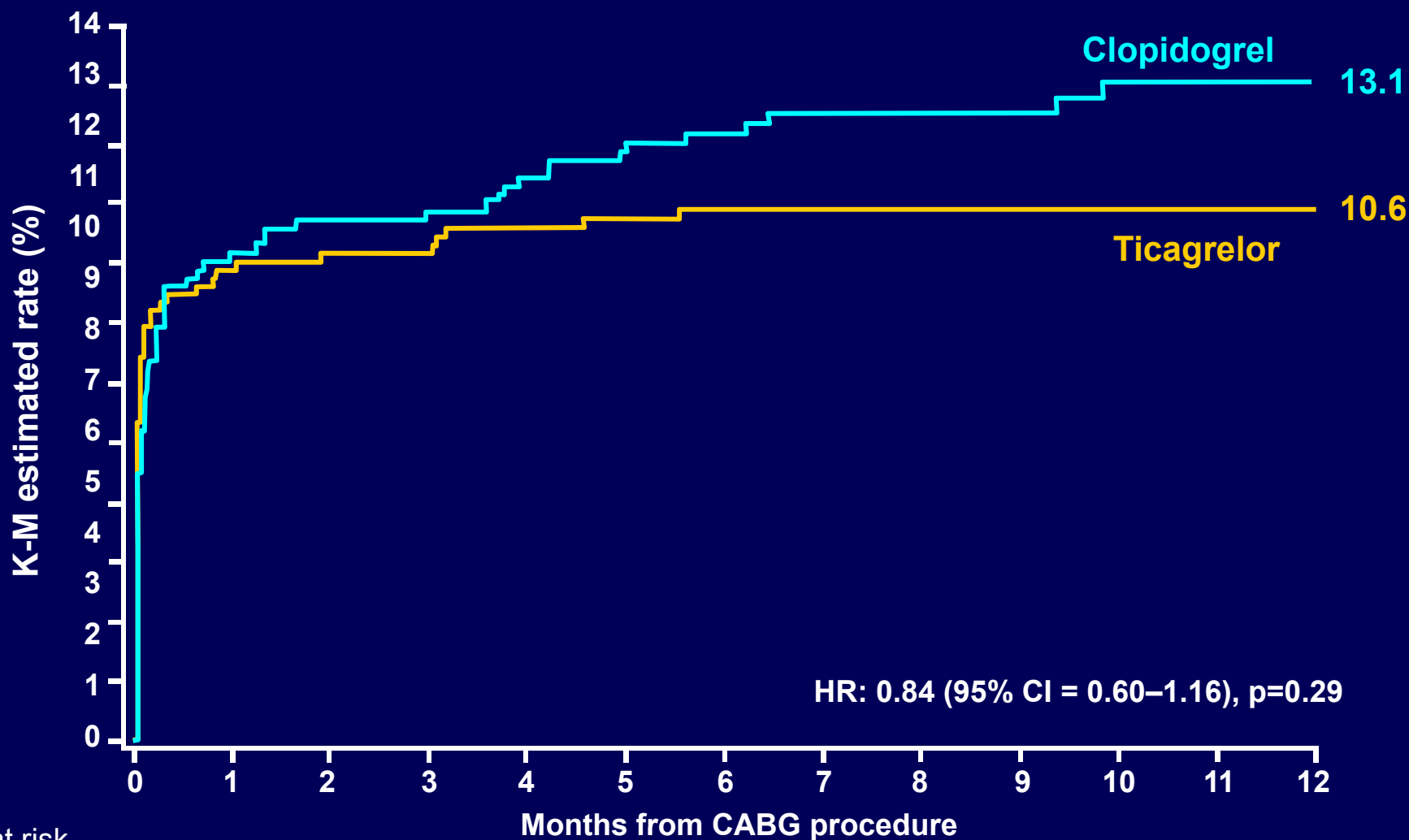
Time from study entry to first CABG surgery (total PLATO population)



No. at risk

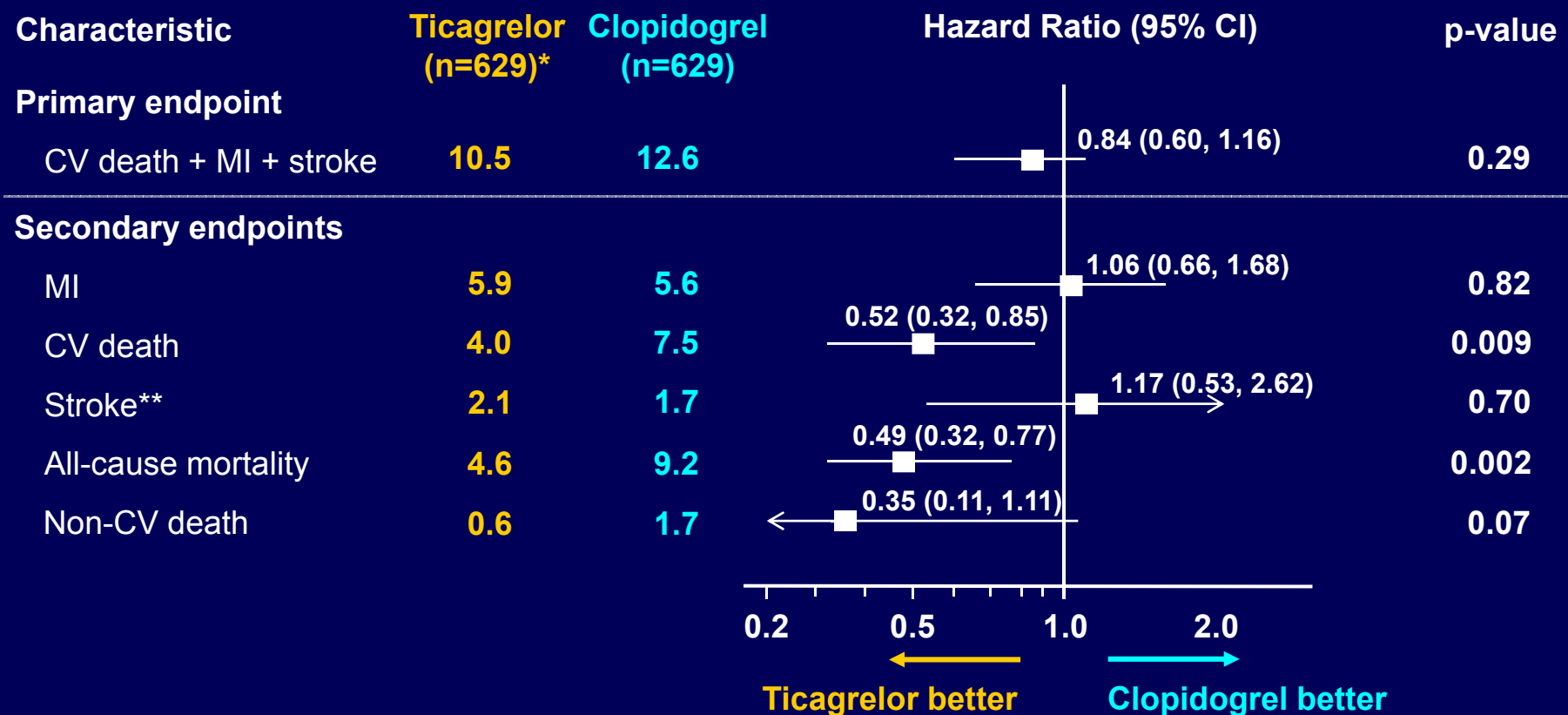
Ticagrelor	9,235	7,289	6,862	6,570	5,144	3,775	3,414
Clopidogrel	9,186	7,320	6,936	6,657	5,209	3,843	3,470

Time from CABG to primary endpoint: CV death, MI or stroke (CABG population)



No. at risk								
Ticagrelor	629	543	519	458	386	268	108	
Clopidogrel	629	541	516	448	386	255	125	

Primary and secondary efficacy endpoints from time of CABG

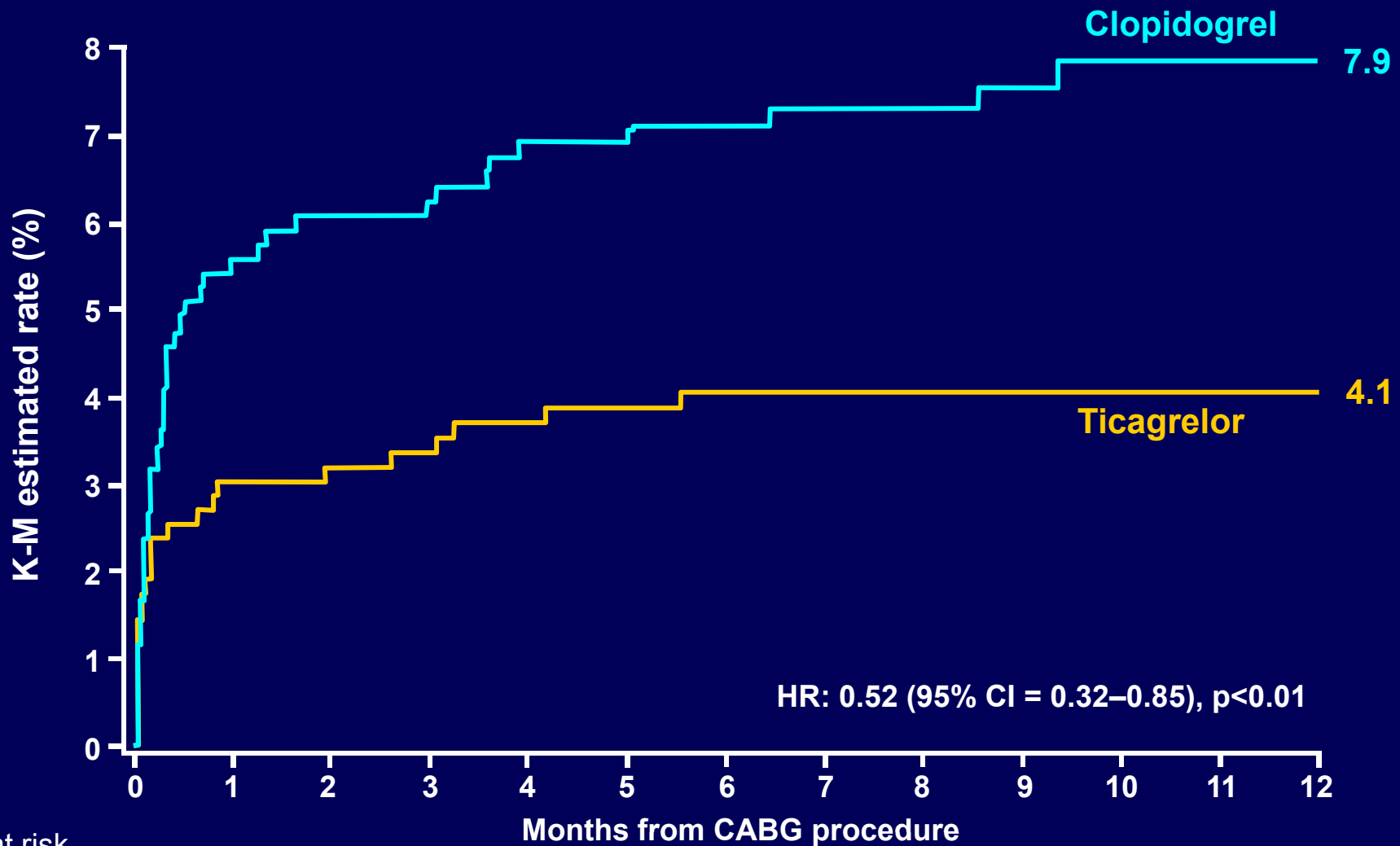


Patients could have had more than one type of endpoint. Values are incidences = number of events divided by n, not rates.

*Three patients had missing values for the efficacy endpoints due to CABG after the censoring date at 12 months

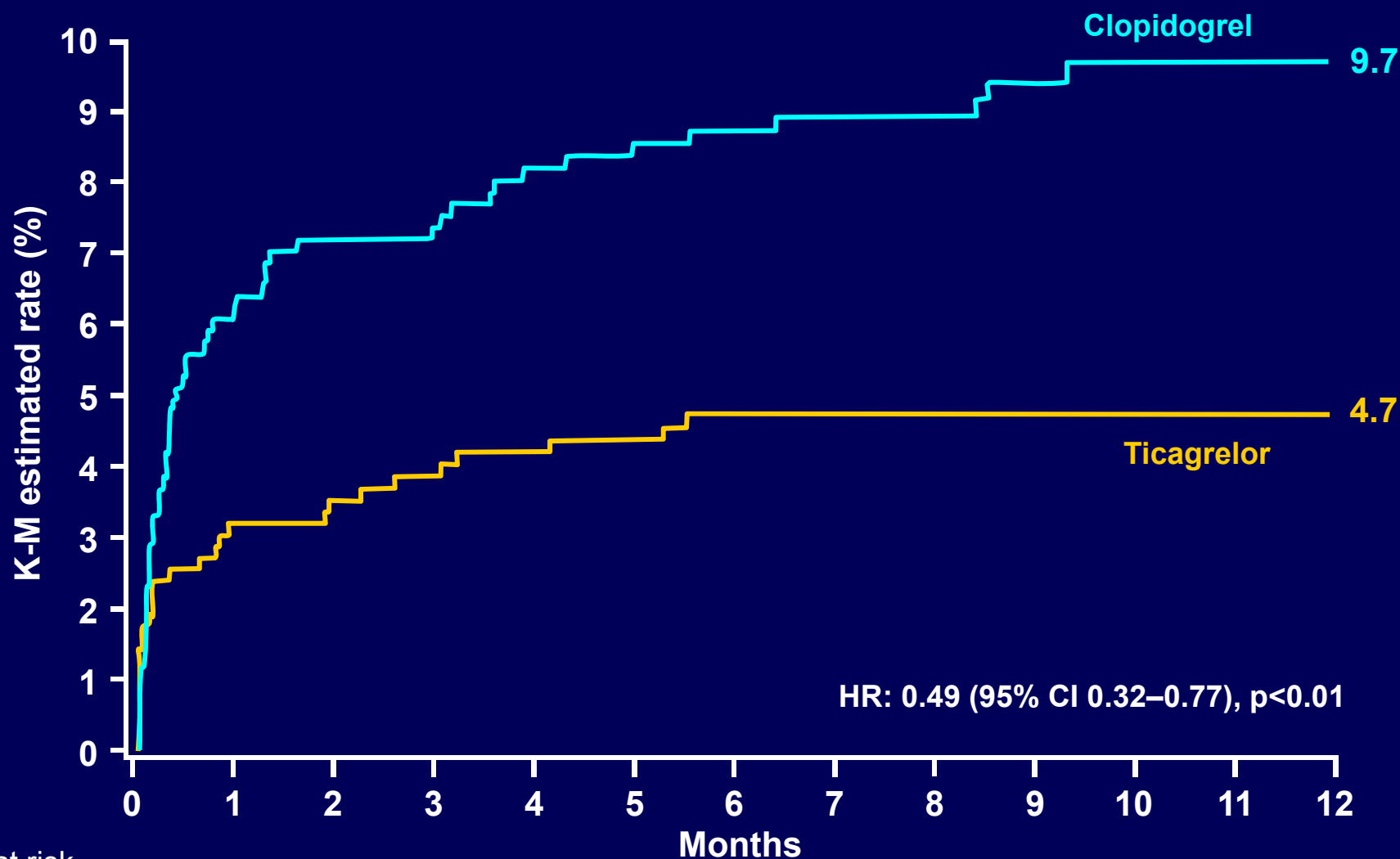
**Results for hemorrhagic stroke: 0.0% (ticagrelor) and 0.2% (clopidogrel); non-hemorrhagic stroke: 2.1% and 1.6%

Time from CABG to CV death (CABG population)



No. at risk									
Ticagrelor	629	583	557	491	415	291	119		
Clopidogrel	629	565	539	472	404	269	130		

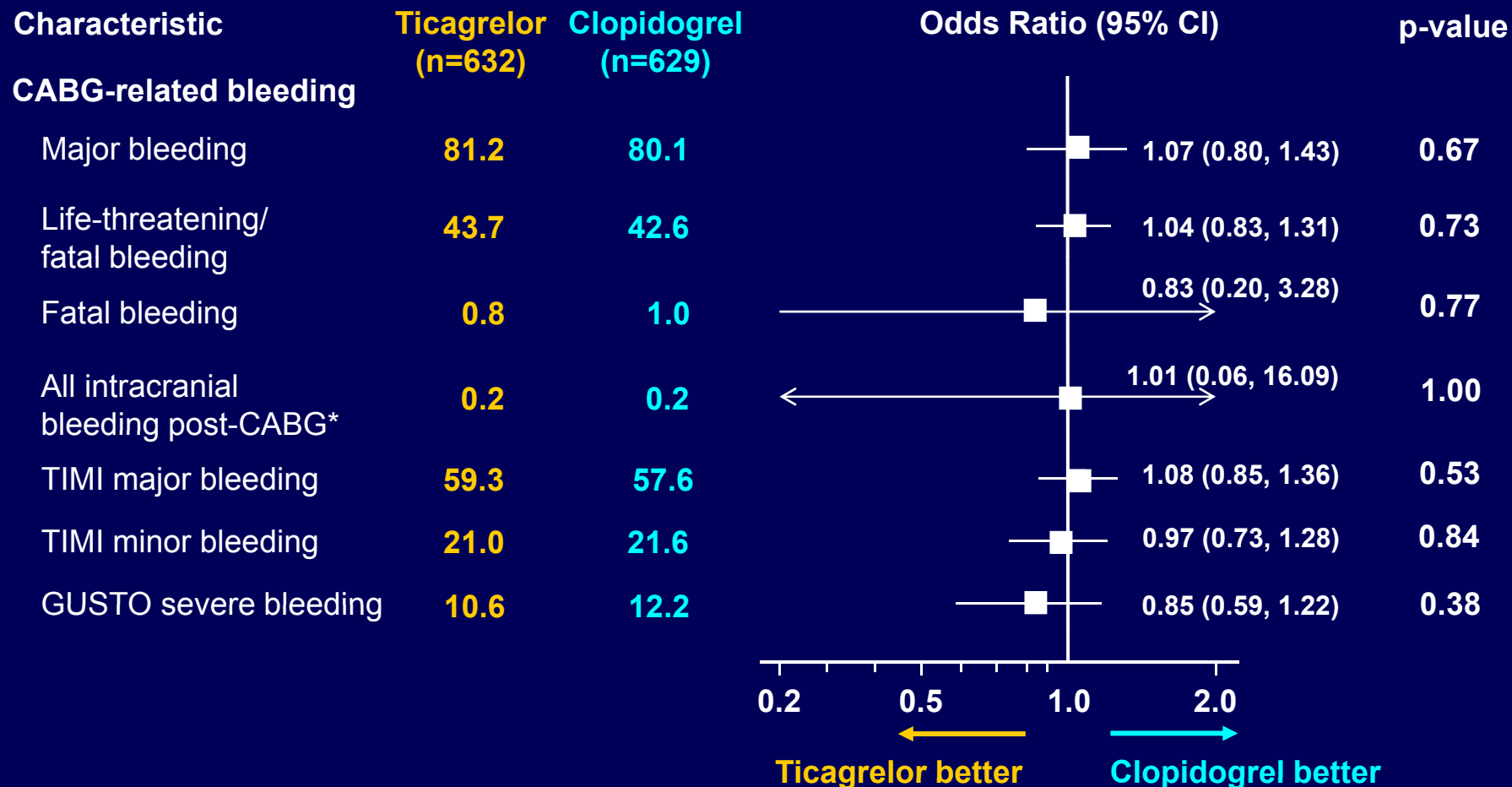
Time from CABG to any death (CABG population)



No. at risk

Ticagrelor	629	583	557	491	415	291	119
Clopidogrel	629	565	539	472	404	269	130

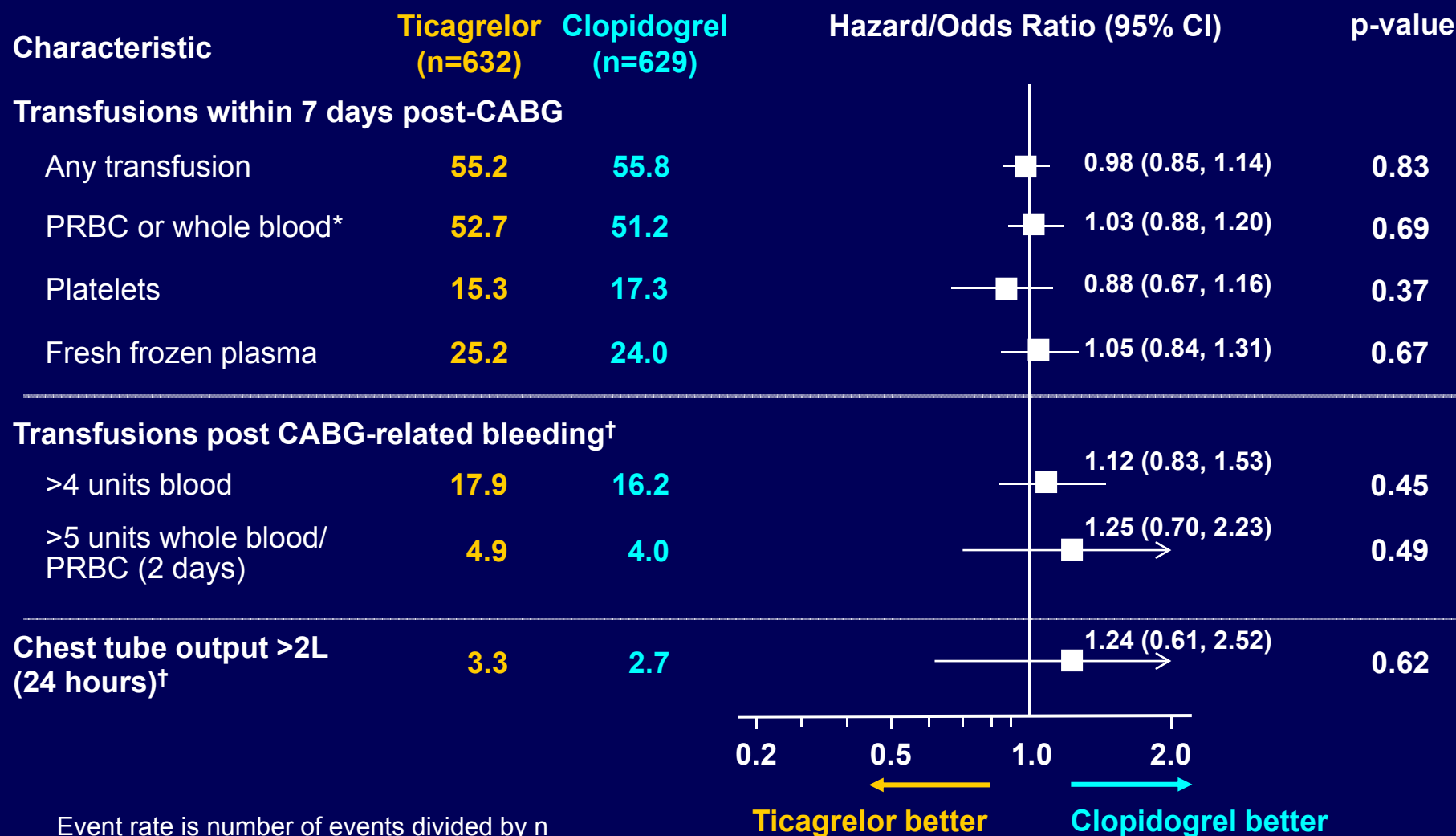
Bleeding from time of CABG



Values are incidences = number of events divided by n, not rates.

*Hazard ratio. Both CABG-related and non-related

Transfusions from time of CABG



Event rate is number of events divided by n

*Median (range) units transfused within 7 days post-CABG: tic 3.0 (2.0–4.0) vs. clop 3.0 (2.0–4.0); p=0.86

†Odds ratio and p-value from Fisher's exact test

Limitations

- **Retrospective analysis of a non-randomized subgroup of patients requiring CABG**
 - selection bias, survivor bias or other confounders
- **The formal adjudication of causes of deaths in the main trial separated death from vascular and non-vascular cause, but a further subcategorization was not performed**
 - a retrospective central review of the causes of post-CABG death is currently ongoing

Conclusions

- In ACS patients undergoing CABG within 7 days after stopping P2Y₁₂-inhibitor treatment, patients previously treated with ticagrelor as compared with clopidogrel have
 - **lower mortality after CABG – both total and CV**
 - **similar rate of CABG-related bleeding**
- The results are consistent with the main study outcomes

In ACS patients with a potential urgent need of CABG surgery, ticagrelor is a more effective alternative to clopidogrel for the prevention of cardiovascular and total death without an increase in major bleeding

REFERENCE

Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;120(25):2577-2585.

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**Randomized Double-Blind Assessment of the ONSET and OFFSET of the
Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable
Coronary Artery Disease: The ONSET/OFFSET Study**

Paul A. Gurbel, Kevin P. Bliden, Kathleen Butler, Udaya S. Tantry, Tania Gesheff,
Cheryl Wei, Renli Teng, Mark J. Antonino, Shankar B. Patil, Arun Karunakaran,
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Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Artery Disease The ONSET/OFFSET Study

Paul A. Gurbel, MD; Kevin P. Bliden, BS; Kathleen Butler, MD; Udaya S. Tantry, PhD;
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Shankar B. Patil, MD; Arun Karunakaran, MD; Dean J. Kereiakes, MD;
Cordell Parris, MD; Drew Purdy, MD; Vance Wilson, MD; Gary S. Ledley, MD; Robert F. Storey, MD

Background—Ticagrelor is the first reversibly binding oral P2Y₁₂ receptor antagonist. This is the first study to compare the onset and offset of platelet inhibition (IPA) with ticagrelor using the PLATO (PLATElet inhibition and patient Outcomes) trial loading dose (180 mg) with a high loading dose (600 mg) of clopidogrel.

Methods and Results—In a multicenter, randomized, double-blind study, 123 patients with stable coronary artery disease who were taking aspirin therapy (75 to 100 mg/d) received ticagrelor (180-mg load, 90-mg BID maintenance dose [n=57]), clopidogrel (600-mg load, 75-mg/d maintenance dose [n=54]), or placebo (n=12) for 6 weeks. Greater IPA (20 μ mol/L ADP, final extent) occurred with ticagrelor than with clopidogrel at 0.5, 1, 2, 4, 8, and 24 hours after loading and at 6 weeks ($P<0.0001$ for all); by 2 hours after loading, a greater proportion of patients achieved $>50\%$ IPA (98% versus 31%, $P<0.0001$) and $>70\%$ IPA (90% versus 16%, $P<0.0001$) in the ticagrelor group than in the clopidogrel group, respectively. A faster offset occurred with ticagrelor than with clopidogrel (4-to-72-hour slope [% IPA/h] -1.04 versus -0.48 , $P<0.0001$). At 24 hours after the last dose, mean IPA was 58% for ticagrelor versus 52% for clopidogrel ($P=NS$). IPA for ticagrelor on day 3 after the last dose was comparable to clopidogrel at day 5; IPA on day 5 for ticagrelor was similar to clopidogrel on day 7 and did not differ from placebo ($P=NS$).

Conclusions—Ticagrelor achieved more rapid and greater platelet inhibition than high-loading-dose clopidogrel; this was sustained during the maintenance phase and was faster in offset after drug discontinuation.

Clinical Trial Registration Information—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00528411. (*Circulation*. 2009;120:2577-2585.)

Key Words: platelets ■ ticagrelor ■ clopidogrel ■ antiplatelet agents

Platelet activation by ADP is central to the development of atherothrombosis. The importance of the ADP-P2Y₁₂ receptor interaction has been demonstrated by the clinical benefits associated with the addition of clopidogrel to aspirin therapy in patients with acute coronary syndromes and patients treated with stents.^{1,2}

Clinical Perspective on p 2585

The antiplatelet effect of clopidogrel is slow in onset, variable, and irreversible, and approximately 15% to 30% of patients have been reported to be nonresponsive.¹⁻³ A 75-mg/d clopidogrel maintenance dose required at least 5 days and a 600-mg loading dose of clopidogrel required up

to 8 hours to achieve $\approx 50\%$ steady state of inhibition of ADP-induced platelet aggregation.^{1,4,5} Moreover, translational research studies have established a relationship between nonresponsiveness to antiplatelet drugs, high on-treatment platelet reactivity, and the occurrence of ischemic events in percutaneous coronary intervention patients.⁶⁻⁸ In addition, the slow offset of the antiplatelet effect due to irreversible P2Y₁₂ binding by the active thienopyridine metabolite is potentially problematic in the management of patients who are treated before coronary angiography and then require coronary artery bypass graft surgery or who need other unanticipated surgical procedures.⁹

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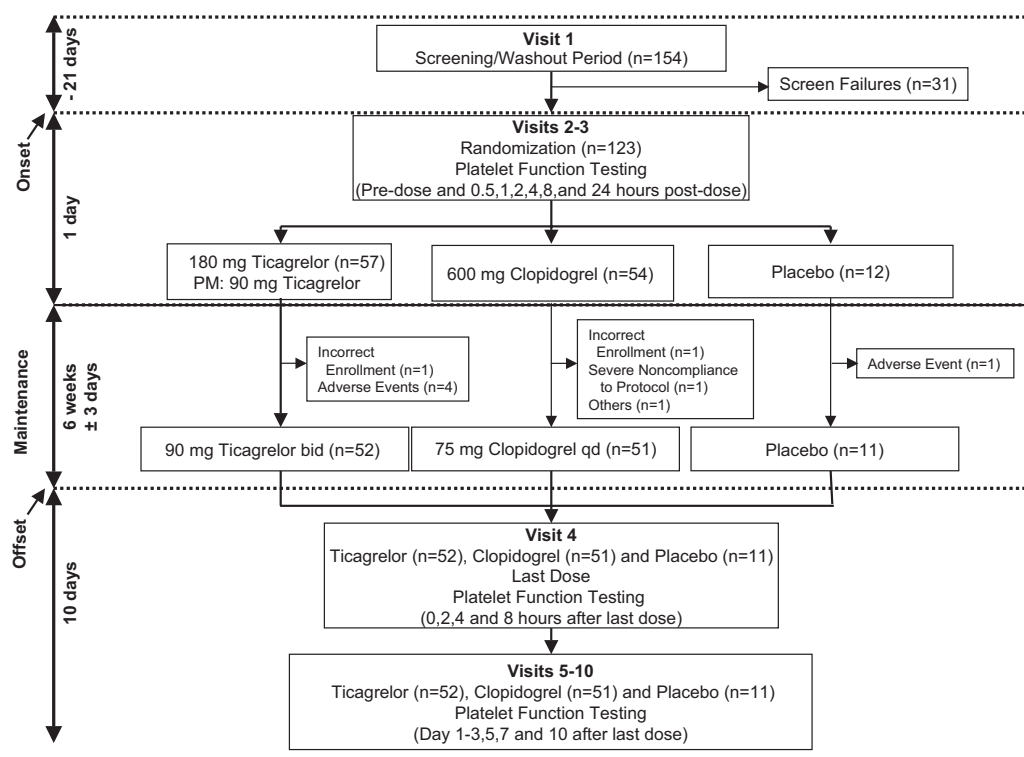


Figure 1. Study design. bid Indicates twice daily; qd, once daily.

Ticagrelor (formerly AZD6140) is the first reversibly binding oral, direct-acting P2Y₁₂ receptor antagonist. Clinical pharmacology and early dose-finding studies suggested a faster onset and greater inhibition of platelet aggregation (IPA) with ticagrelor than with clopidogrel.^{10–12} Although the clinical efficacy of ticagrelor has been studied extensively in PLATO (A Study of Platelet Inhibition and Patient Outcomes), a comprehensive characterization of its antiplatelet onset and offset effect profile in a statistically powered comparison with clopidogrel has not been conducted in patients with coronary artery disease (CAD).¹³ Moreover, ticagrelor has not been compared with high-loading-dose clopidogrel in patients. Therefore, the present study was designed to determine the onset and offset of the antiplatelet effect of ticagrelor with the PLATO trial dose compared with high-loading-dose clopidogrel and placebo in stable CAD patients given background aspirin therapy.

Methods

Study Design and Subjects

The ONSET/OFFSET study was a multicenter, randomized, double-blind, double-dummy, parallel-group study. The study was performed in accordance with standard ethical principles; written consent was obtained from all patients. Patients ≥18 years of age with documented stable CAD who were undergoing aspirin therapy (75 to 100 mg/d) were enrolled in 8 investigational sites in the United States and the United Kingdom between October 2007 and March 2009. Exclusion criteria were a history of acute coronary syndrome within 12 months of screening; any indication (eg, atrial fibrillation, prosthetic heart valve, or coronary stent) for antithrombotic therapy (eg, warfarin, clopidogrel, or aspirin dose other than 75 to 100 mg/d

during the study period); congestive heart failure; left ventricular ejection fraction <35%; forced expiratory volume in the first second or forced vital capacity below the lower limits of normal; bleeding diathesis or severe pulmonary disease; pregnancy; current smoking; concomitant therapy with moderate or strong cytochrome P450 3A inhibitors, substrates, or strong cytochrome P450 3A inducers; platelet count <100 000/mm³; hemoglobin <10 g/dL; hemoglobin A1c ≥10%; history of drug addiction or alcohol abuse in the past 2 years; need for nonsteroidal antiinflammatory drug; or creatinine clearance <30 mL/min.

The total duration of the study was ≈10 weeks (Figure 1). Randomization numbers were prepared by AstraZeneca (Wilmington, Del). After a screening period of up to 21 days (visit 1), patients were randomized at visit 2 in balanced blocks (6 patients in each block) to ensure 1:1:1 randomization to clopidogrel, ticagrelor, and placebo treatment. The goal was 50 patients per treatment group. After 12 placebo patients had been randomized, the remaining patients were randomized to ticagrelor or clopidogrel in a 1:1 ratio. Randomization numbers were assigned sequentially as patients became eligible. An initial loading dose of ticagrelor (180 mg), clopidogrel (600 mg), or placebo was given after randomization at visit 2 followed by a maintenance administration (90 mg of ticagrelor or placebo) in the evening with a 12-hour interval between dosing. Patients then received maintenance treatment for 6 weeks (ticagrelor 90 mg BID, clopidogrel 75 mg/d, or placebo), followed by a 10-day drug-offset period during which patients received a final dose of the study drug on the first day of the offset period (time ≈0 hours). To ensure blinding of the treatments, matching placebo ticagrelor tablets and placebo clopidogrel capsules were provided. Each treatment group consisted of the same combination of matching active and placebo tablets/capsules, so medications provided for each treatment group were identical in appearance.

Patients fasted ≥8 hours before all visits, and all patients received concomitant aspirin (75 to 100 mg/d). Eligible patients undergoing clopidogrel therapy before screening underwent a 14-day minimum washout period before randomization. Compliance was measured by

the amount of medication returned at the respective visits. Bleeding was defined according to the PLATO criteria.¹⁴ The frequency of patients with dyspnea was determined.

Blood Sampling for Platelet Function Testing

Samples for platelet function testing were taken at predosing (0 hour) and after the first dose of study drug on visit 2, then throughout the onset period (0.5 to 24 hours after the first loading dose), at the start of the offset period (0 hour, visit 4), and throughout the 10-day offset period (2 to 240 hours after the last dose; online-only Data Supplement Table II).

Blood was collected from the antecubital vein into Vacutainer tubes (Becton-Dickinson, Franklin Lakes, NJ) that contained 3.2% trisodium citrate for light-transmittance aggregometry and flow cytometry analyses and in 1 tube that contained 3.2% sodium citrate (Greiner Bio-One Vacutette North America, Inc, Monroe, NC) for VerifyNow measurements.

Light-Transmittance Aggregometry

Platelet aggregation induced by ADP (20 and 5 $\mu\text{mol/L}$), collagen 2 $\mu\text{g/mL}$, and arachidonic acid 2 mmol/L in platelet-rich plasma was assessed with a Chrono-log Optical Aggregometer (model 490-4D; Chrono-log Corporation, Havertown, Pa) as described previously.⁴ The assessment of 2 mmol/L arachidonic acid-induced aggregation was performed to evaluate the effects of aspirin.¹⁵ The final extent of aggregation, measured at 6 minutes after agonist addition, and the maximal extent of aggregation were expressed as the percent change in light transmittance from baseline, with platelet-poor plasma as a reference. IPA was calculated as follows, where PA is platelet aggregation, b is predosing, and t is postdosing:

$$\text{IPA}(\%) = 100\% \times \frac{\text{PA}_b - \text{PA}_t}{\text{PA}_b}$$

VerifyNow P2Y₁₂ Assay

VerifyNow is a turbidimetric-based system that measures platelet aggregation in whole blood.⁹ The instrument measures an optical signal, reported as P2Y₁₂ reaction units (PRU), and calculates the percent of inhibition based on iso-TRAP (thrombin receptor activating peptide)/protease-activated receptor (PAR)-4 activating peptide-induced aggregation as the baseline.

Vasodilator-Stimulated Phosphoprotein Phosphorylation Assay

The measurement of vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) is a method of quantifying P2Y₁₂ receptor reactivity and reflects the extent of P2Y₁₂ receptor blockade (Biocytex Inc, Marseille, France).⁸ The platelet reactivity index (PRI) is calculated after measurement of VASP-P levels (mean fluorescence intensity [MFI]) determined by monoclonal antibodies after stimulation with prostaglandin (PG) E₁ (MFI_{PGE1}) and PGE₁ plus ADP (MFI_{PGE1+ADP}): PRI (%) = [(MFI_{PGE1}) - (MFI_{PGE1+ADP}) / (MFI_{PGE1})] × 100%.

Glycoprotein IIb/IIIa and P-Selectin Expression

ADP-stimulated (5 $\mu\text{mol/L}$, final concentration) expression of glycoprotein IIb/IIIa receptors and P-selectin was measured as described previously.⁴ The percent inhibition of baseline stimulated receptor expression was determined.

Primary End Points for Onset and Offset of IPA

The primary end point for onset was IPA (20 $\mu\text{mol/L}$ ADP, final extent) at 2 hours after the first dose; for offset, it was the slope of IPA between 4 and 72 hours after the last dose of study drug. Secondary pharmacodynamic end points were IPA (final and maximal extent), measured by 5- and 20- $\mu\text{mol/L}$ ADP- and 2- $\mu\text{g/mL}$ collagen-induced light-transmittance aggregometry; PRI; ADP-induced glycoprotein IIb/IIIa and P-selectin expression; and PRU and percent inhibition, measured by the VerifyNow P2Y₁₂ assay.

Sample-Size Calculation

In the DISPERSE study (Dose confirmation Study assessing anti-Platelet Effects of AZD6140 versus clopidogrel in non-ST-segment Elevation myocardial infarction), the variability (ie, SD) of IPA values at 2 hours after an initial 200-mg dose of ticagrelor (old formulation, comparable to 180 mg under the new formulation) was 12.3% (n=36).¹⁰ In the DISPERSE-2 study, the corresponding variability was 20.8% (n=7).¹¹ These 2 estimates were combined to give a weighted estimate of 13.9%. No patient data were available from the previous studies after a 600-mg loading dose of clopidogrel; however, with 50 patients per treatment group, it was calculated that there would be at least 91% power to detect mean differences in IPA of at least 15% between the 2 groups, with the assumption that the variability for the clopidogrel group was no more than double that for ticagrelor (14% versus 28%). The calculation also assumed a 5% significance level (2-sided).

For offset, estimates of the expected intercepts and slopes for each treatment group were obtained from the DISPERSE study.¹⁰ IPA data were available up to 24 hours after the last dose. A random coefficients model was fitted to the 4-, 8-, 12-, and 24-hour values and included fixed effects for treatment group, hour (ie, relative to last dose), and the treatment group-by-hour interaction and random coefficients for the patient and patient-by-hour interaction. The power to detect a given difference in slopes was calculated by simulation. Individual patient profiles of IPA were generated with the above estimates. With 50 patients per treatment group, there would be $\approx 90\%$ power to show a difference in slopes of -0.45 IPA%/h between therapies. The calculations assumed that the linear relationship in IPA offset would continue to the 72-hour time point.

Statistical Analysis

Statistical analyses were performed by QDS (King of Prussia, Pa) with SAS (version 8.2). The analysis was an intention-to-treat analysis that included patients who were randomized to a treatment group, received at least 1 dose of study drug, and contributed interpretable postbaseline data. For all analyses, the primary comparison was made between the ticagrelor and clopidogrel treatments. Demographic data were compared between the 2 treatment groups with *t* test for numerical data or Fisher exact test for categorical data. The antiplatelet effect of ticagrelor compared with clopidogrel was analyzed by the Wilcoxon rank sum test (level of significance 0.05). The slopes of onset and offset were determined by a random coefficients model fitted to IPA values at 0.5, 1, and 2 hours after loading (onset) and 4, 8, 24, 48, and 72 hours after last dose (offset) and included fixed effects for treatment group, hour (relative to last dose or first dose), the treatment group-by-hour interaction, center, and center-by-treatment interaction, as well as random coefficients for the patient and patient-by-hour interaction. Difference of the slopes and 95% confidence intervals for primary comparisons of interest (ticagrelor versus clopidogrel) were calculated. The area under the effect curve from 0 to 8 hours after loading was determined for each treatment group. The mean time to maximum IPA was determined by the mean of each patient's time to reach his or her own maximum IPA.

The estimation for the time of IPA declining from 30% to 10% after the last dose was calculated with an IPA exponential decline-with-time model ($\text{IPA} = \text{IPA}_0 e^{-kt}$), where *t* is the time and *k* is the declining rate constant. Correlation analyses of IPA (20 $\mu\text{mol/L}$ ADP, final extent) versus IPA determined after stimulation by other agonists (final and maximal extent), PRI, the inhibition of stimulated glycoprotein IIb/IIIa and P-selectin expression, and percent inhibition and PRU as assessed by the VerifyNow test were performed with the Pearson product-moment correlation coefficient.

Results

Compliance, Demographics, and Baseline Characteristics

The number of patients enrolled at each center is listed in the online-only Data Supplement (Table I). Two centers, 1 in the

Table 1. Demographics

	Total Group (n=123)	Ticagrelor (n=57)	Clopidogrel (n=54)	Placebo (n=12)	Ticagrelor vs Clopidogrel, <i>P</i>
Demographics					
Age, y	64±9	62±9	65±8	64±8	0.07
Male, n (%)	93 (76)	43 (75)	40 (74)	10 (83)	0.24
Body mass index, kg/m ²	30±4	31±5	30±4	29±4	0.06
Ethnicity, n (%)					
White	108 (88)	51 (90)	48 (89)	9 (75)	0.92
Black	12 (10)	4 (7)	5 (9)	3 (25)	0.66
Other	3 (2)	2 (3)	1 (2)	0 (0)	0.59
Medical history, n (%)					
Family history of CAD	88 (72)	43 (75)	36 (67)	9 (75)	0.31
Hypertension	92 (75)	44 (77)	39 (72)	9 (75)	0.55
Hyperlipidemia	118 (96)	54 (95)	52 (96)	12 (100)	0.69
Diabetes mellitus					
HbA1c >6.0%	19 (15)	6 (11)	8 (15)	5 (42)	0.50
HbA1c ≤6.0%	8 (7)	6 (11)	2 (4)	0 (0)	0.15
Prior myocardial infarction	55 (45)	26 (46)	23 (43)	6 (50)	0.75
Prior coronary artery bypass graft	47 (38)	23 (40)	21 (39)	3 (25)	0.87
Prior percutaneous coronary intervention	93 (76)	41 (72)	41 (76)	11 (92)	0.63
Baseline medications, n (%)					
Statins	110 (89)	49 (86)	50 (93)	11 (92)	0.27
Angiotensin-converting enzyme inhibitors	20 (16)	10 (18)	8 (15)	2 (17)	0.70
β-blockers	90 (73)	39 (68)	42 (78)	9 (75)	0.27
Diuretics	42 (34)	20 (35)	18 (33)	4 (33)	0.84
Organic nitrates	18 (15)	6 (11)	12 (22)	0 (0)	0.10
Proton pump inhibitors	35 (29)	16 (28)	16 (30)	3 (25)	0.86
Calcium channel blockers	28 (23)	17 (30)	9 (17)	2 (17)	0.11
Baseline laboratory data					
White blood cells (×1000/mm ³)	6.5±1.6	6.6±1.8	6.4±1.4	6.6±1.5	0.52
Platelets (×1000/mm ³)	231±61	232±65	227±55	235±62	0.66
Hematocrit, %	42±4	42±3	42±4	42±4	1.0
Creatinine, μmol/L	91±22	91±24	89±21	88±26	0.82
LDL, mg/dL	68±48	72±55	63±45	81±31	0.35
HDL, mg/dL	34±25	32±26	32±25	44±25	1.0
Uric acid, μmol/L	382±83	381±83	377±82	406±88	0.80

HbA1c indicates hemoglobin A1c.

United States and 1 in the United Kingdom, enrolled most of the patients (n=43 and n=40, respectively). Fifty-two patients in the ticagrelor group, 51 in the clopidogrel group, and 11 in the placebo group completed the study. For the complete pharmacodynamic analysis set, there were 49 patients in the ticagrelor group, 44 in the clopidogrel group, and 10 in the placebo group. The overall compliance rate was >95% for each treatment group by drug count. The treatment code was not broken prematurely for any patient. The most common protocol deviations related to laboratory tests (18.5% for the ticagrelor group and 10.0% for the clopidogrel group), procedures/tests (14.8% and 12.0%, respectively), and informed consent issues (13.0% and 14.0%, respectively). Approximately 6% of patients in each group had treatment visits outside the

protocol window. The treatment groups were evenly balanced and consisted predominantly of white men between 41 and 83 years of age (Table 1).

Arachidonic Acid–Induced Aggregation

Overall, 96% and 98% of patients had baseline and end-of-study arachidonic acid–induced maximal platelet aggregation <20%, respectively.

Onset and Maintenance IPA

The primary end point for onset, IPA at 2 hours after loading (20 μmol/L ADP, final extent) was greater for ticagrelor than for clopidogrel (88% versus 38%, *P*<0.0001; Table 2). IPA was higher at 0.5 hours after loading with ticagrelor (41% versus 8%, *P*<0.0001) and at all times in the first 24 hours

Table 2. IPA (20 μ mol/L ADP) at 2 Hours After First Dose of Ticagrelor and Clopidogrel

	Ticagrelor (n=54)		Clopidogrel (n=50)		<i>P</i>	
	IPA, %	PA, %	IPA, %	PA, %	IPA, %	PA, %
Final extent	88 \pm 15	7 \pm 9	38 \pm 33	44 \pm 24	<0.0001	<0.0001
Maximum extent	65 \pm 17	23 \pm 10	25 \pm 23	55 \pm 18	<0.0001	<0.0001

PA indicates platelet aggregation.
Values are mean \pm SD.

after loading and in the maintenance phase ($P<0.0001$; Figure 2). Within 1 hour of ticagrelor loading, IPA was greater than the maximum IPA achieved after clopidogrel loading. In the ticagrelor group, IPA did not differ between 2 and 8 hours after loading, whereas in the clopidogrel group, IPA was greater at 8 hours than at 2 hours ($P=0.02$, repeated-measures ANCOVA model).

The mean time to maximum IPA in the ticagrelor group was 5.8 hours less and the area under the effect curve from 0 to 8 hours after loading (20 μ mol/L ADP, final extent) was higher than in the clopidogrel group (Table 3). The rate of onset (slope) of the antiplatelet effect curve as assessed by IPA (20 μ mol/L ADP, final extent) from 0 to 2 hours after the loading dose was greater in the ticagrelor group than in the clopidogrel group (43.57 versus 19.45 IPA %/h, $P<0.0001$; Table 4). By 2 hours after loading, a greater proportion of patients achieved $>50\%$ IPA (98% versus 31%, $P<0.0001$) and $>70\%$ IPA (90% versus 16%, $P<0.0001$) in the ticagrelor group than in the clopidogrel group, respectively. Concordant results were observed with the final and maximum extent of platelet aggregation (Table 2).

Offset of IPA

At the end of the 6 weeks of treatment, IPA (20 μ mol/L ADP, final extent) was significantly higher in the ticagrelor group

Table 3. IPA_{max}, TIPA_{max}, and AUEC₀₋₈ (20 μ mol/L ADP, Final Extent) at Onset

	Ticagrelor (n=54)	Clopidogrel (n=50)
IPA _{max} , %	93	58
TIPA _{max} , h	2.0	7.8
AUEC ₀₋₈ , % h	659	275

IPA_{max} indicates maximum IPA; TIPA_{max}, time to IPA_{max}; and AUEC₀₋₈, area under the effect curve from 0 to 8 hours after loading.

than in the clopidogrel group ($P<0.0001$; Figure 2); however, IPA did not differ between the groups at 24 and 48 hours after the last dose. The ticagrelor group had significantly lower IPA at 72 and 120 hours after the last dose ($P\leq 0.05$), and the IPA did not differ thereafter between the groups (Figure 2). The rate of offset (slope) of the antiplatelet effect curve as assessed by IPA (20 μ mol/L ADP, final extent) from 4 to 72 hours after the last dose, the primary end point for offset, was greater in the ticagrelor group than in the clopidogrel group (-1.04 versus -0.48 IPA %/h, $P<0.0001$; Table 4). The time required for IPA to decrease from 30% to 10% in the ticagrelor group was less than half that in the clopidogrel group (53.30 versus 116.20 hours, respectively; Table 5), and the time to reach 10% was nearly twice as long after clopidogrel discontinuation (109.19 versus 195.66 hours, respectively). IPA for ticagrelor on day 3 after the last dose was comparable to that for clopidogrel at day 5; IPA on day 5 for ticagrelor was similar to clopidogrel on day 7 and did not differ from placebo ($P=NS$).

VerifyNow P2Y₁₂ Assay

The greatest change in PRU from baseline in the ticagrelor group occurred within 2 hours after loading compared with 8 hours in the clopidogrel group (Figure 3). PRU was significantly lower in the ticagrelor group at all times in the first 24 hours after loading and during maintenance ($P<0.0001$). PRU was lower at 8 and 24 hours after the final dose in the

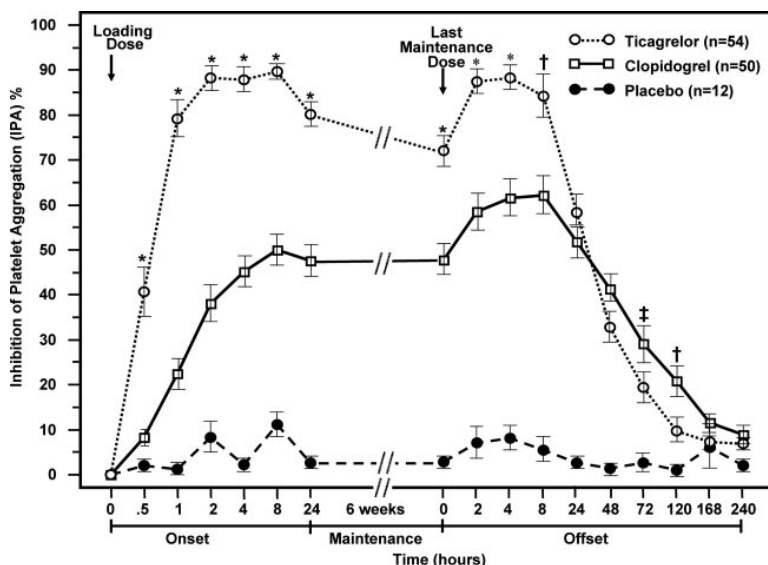


Figure 2. IPA (%; 20 μ mol/L ADP, final extent) by protocol time and treatment. Data are expressed as mean \pm SEM. * $P<0.0001$, † $P<0.005$, ‡ $P<0.05$, ticagrelor vs clopidogrel.

Table 4. Slope of Onset (0 to 2 Hours After Loading Dose) and Offset (4 to 72 Hours After Last Dose) Measured by IPA (20 μ mol/L ADP, Final Extent)

	Ticagrelor (n=54)		Clopidogrel (n=50)		Difference of Mean Slope (Ticagrelor—Clopidogrel)			
	Intercept	Slope (IPA %/h)	Intercept	Slope (IPA %/h)	Estimate (IPA %/h)	Lower 95% CI	Upper 95% CI	<i>P</i>
Onset								
Final extent	10.59	43.57	8.42	19.45	24.12	18.47	28.77	<0.0001
Maximum extent	6.75	31.44	5.56	11.98	19.47	15.34	23.59	<0.0001
Offset								
Final extent	94.00	−1.04	71.84	−0.48	−0.56	−0.71	−0.40	<0.0001
Maximum extent	59.78	−0.74	41.66	−0.29	−0.45	−0.60	−0.29	<0.0001

CI indicates confidence interval.

ticagrelor group ($P<0.0001$). At 48 hours and thereafter, PRU did not differ between groups.

Vasodilator-Stimulated Phosphoprotein Phosphorylation

The greatest change from baseline in PRI in the ticagrelor group occurred within 2 hours after loading compared with 8 hours in the clopidogrel group (Figure 4). PRI after the first loading dose and during maintenance was significantly lower, which indicates greater inhibition at all times in the ticagrelor group than in the clopidogrel group ($P<0.0001$). The PRI was lower at 8 and 24 hours after the final dose in the ticagrelor group ($P<0.005$ for both). At 48 hours and thereafter, there were no differences between the treatment groups.

Expression of Platelet Receptors

Platelet function, as measured by expression of glycoprotein IIb/IIIa and P-selectin receptors, demonstrated wide variability (Figures I and II in the online-only Data Supplement). The maximum antiplatelet effect of ticagrelor, as measured by both receptors, occurred within 2 hours of loading (2 versus 8 hours, $P=NS$) and was lower than in the clopidogrel group

at all times after loading and during maintenance ($P<0.05$). Receptor expression was more suppressed for ticagrelor at 0 and 24 hours after the final dose. At 48 hours and thereafter, there were no differences between treatment groups.

Correlation of IPA (20 μ mol/L ADP, Final Extent) With Other Pharmacodynamic Measurements

In both treatments groups, IPA (20 μ mol/L ADP, final extent) significantly correlated with other pharmacodynamic parameters ($P<0.0001$; Table III in the online-only Data Supplement). The strongest correlations for ticagrelor were with IPA (maximal extent) irrespective of the ADP concentration, inhibition (%), and PRU as measured by the Veri-fyNow P2Y₁₂ assay and PRI.

Clinical Outcomes

Bleeding-related events occurred more frequently in the ticagrelor group (28.1%) than in the clopidogrel (13.0%) and placebo (8.3%) groups. There was 1 clinically relevant minor bleeding event in the placebo group; the remaining events were classified as minor (1 event in the ticagrelor group) or minimal. There were no major bleeding events. Five patients discontinued study treatment owing to an adverse event (4 treated with ticagrelor and 1 in the placebo group). Dyspnea judged by the investigator to be likely or possibly due to the study drug occurred in 25%, 4%, and 0% of patients in the ticagrelor, clopidogrel, and placebo groups, respectively (ticagrelor versus clopidogrel $P<0.01$). Three patients in the ticagrelor group stopped the study drug owing to dyspnea.

Discussion

This is the first study to comprehensively characterize the onset and offset of the antiplatelet effect of ticagrelor in a statistically powered comparison with clopidogrel, and it is the first comparison of ticagrelor with high-dose clopidogrel (600 mg) in stable CAD patients. The 3 major findings of the present study are as follows: (1) The onset of the antiplatelet effect of ticagrelor with the PLATO dosing regimen was rapid (a significant antiplatelet effect was observed within 30 minutes of loading) and markedly greater than with high-loading-dose clopidogrel; (2) the greater antiplatelet effect of ticagrelor was sustained during maintenance therapy; and (3) the offset effect for ticagrelor as determined by the rate of offset (slope) measured by aggregometry was significantly

Table 5. Time for IPA (20 μ mol/L ADP) to Decrease From 30% to 10%

	Ticagrelor (n=54)	Clopidogrel (n=50)
Final extent		
IPA ₀	94.92±2.01	63.71±2.07
Declining rate constant	0.021±0.00096	0.009±0.00084
Time when IPA=30%, h	55.88	79.66
Time when IPA=10%, h	109.19	195.66
Average time, h	53.30	116.20
Maximal extent		
IPA ₀	67.83±1.72	37.44±1.51
Declining rate constant	0.023±0.0012	0.008±0.00096
Time when IPA=30%, h	36.13	26.12
Time when IPA=10%, h	84.80	155.73
Average time, h	48.66	129.61

IPA₀ indicates IPA at beginning of offset; average time, time when IPA=30%–time when IPA=10%.

Data are presented as mean±SE. IPA data from 2 to 240 hours after last dose were used to fit the model.

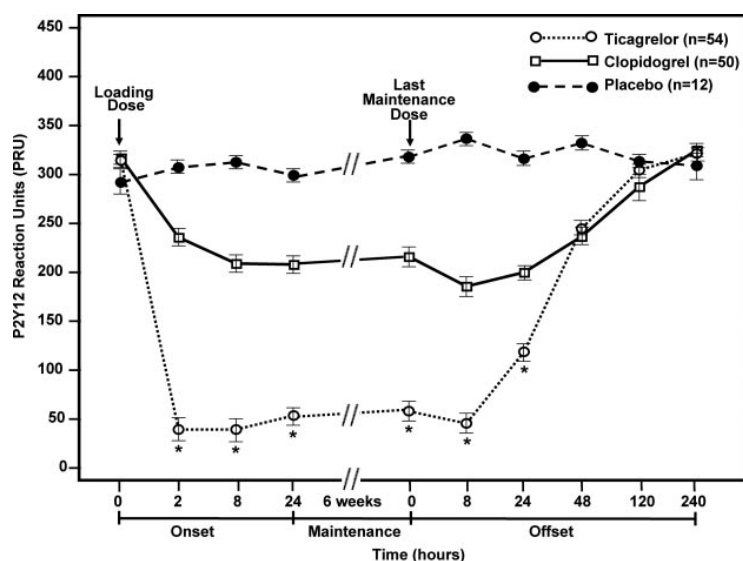


Figure 3. P2Y₁₂ reaction units (PRU) as assessed by the VerifyNow P2Y₁₂ assay by protocol time and treatment. Data are expressed as mean \pm SEM. * $P < 0.0001$, ticagrelor vs clopidogrel.

faster than clopidogrel, and the residual antiplatelet effect of ticagrelor returned to baseline faster than clopidogrel.

Onset Pharmacodynamics

The pharmacodynamic response to the ticagrelor loading dose in the present study is consistent with the results of the DISPERSE and DISPERSE-2 studies.^{10,11} In those studies, the earliest platelet function assessment was at 2 hours after loading, and at that time, a maximal antiplatelet effect occurred. However, in the ONSET/OFFSET study, platelet aggregation was measured earlier after the loading dose (0.5- and 1-hour measurements), and within 1 hour, we observed a near-maximal response ($\approx 80\%$ inhibition). At 1 hour after loading, platelet inhibition induced by ticagrelor was ≈ 1.6 times greater than the maximal platelet inhibition induced by clopidogrel that occurred at 8 hours after loading. The significant antiplatelet effect observed within 30 minutes of loading indicates that ticagrelor may have

particular utility in the setting of ad hoc percutaneous coronary intervention, for which immediate inhibition is desired. The rapid onset of IPA after ticagrelor loading is consistent with the properties of a direct-acting P2Y₁₂ inhibitor, for which IPA is dependent on plasma drug concentrations.¹⁰

The present results are also concordant with the CLEAR PLATELETS (Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets) and CLEAR PLATELETS-2 studies that examined the pharmacodynamic response to a 600-mg clopidogrel loading dose administered at the time of elective coronary artery stenting.^{5,6} The maximum antiplatelet effect from a 600-mg clopidogrel load on a background of aspirin therapy occurred at 6 to 8 hours after dosing, similar to the ONSET/OFFSET study. Overall, the pharmacodynamics measured by light-transmittance aggregometry were largely consistent with the results of VerifyNow and flow cytometry measuring VASP-P. The ONSET/OFFSET study

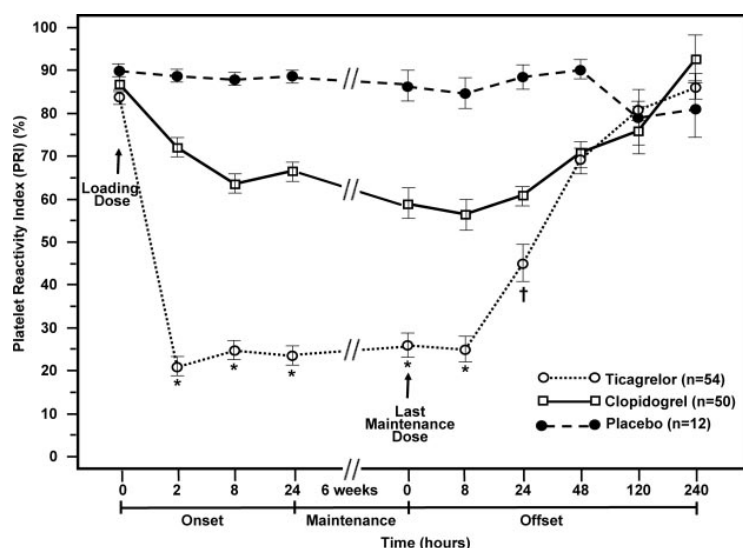


Figure 4. Platelet reactivity index (PRI, %) as assessed by VASP-P by protocol time and treatment. Data are expressed as mean \pm SEM. * $P < 0.0001$, † $P < 0.005$, ticagrelor vs clopidogrel.

was also the first prospective study to use the VASP-P and VerifyNow P2Y₁₂ assays to detect the antiplatelet properties of a direct-acting P2Y₁₂ inhibitor.

Offset Pharmacodynamics

Despite the greater antiplatelet effect of ticagrelor, IPA at 24 hours after the last dose was equivalent in ticagrelor- and clopidogrel-treated patients, which is indicative of a faster immediate offset of effect. These data suggest that patients who miss 1 dose of ticagrelor will have a level of platelet inhibition at 24 hours after the last dose that is equivalent to patients undergoing maintenance clopidogrel therapy. Platelet inhibition in the ticagrelor group was numerically less at 48 hours after the last dose and was significantly less at 72 and 120 hours. Thereafter, platelet inhibition was equivalent. However, the VASP-P and VerifyNow measurements demonstrated equivalent antiplatelet effects at 48 hours that persisted for 240 hours. Price et al⁹ measured the onset and offset of platelet inhibition by clopidogrel in healthy volunteers with the VerifyNow P2Y₁₂ assay. They demonstrated low platelet inhibition (median 12%) at day 5 of offset in the majority of subjects.⁹ The latter results are consistent with the present observations.

On the basis of the present IPA data, bleeding risk may be less in patients taken to surgery between 48 and 120 hours after cessation of ticagrelor therapy compared with clopidogrel therapy. Moreover, in support of the offset data in the present study, in the PLATO trial, coronary artery bypass graft–related bleeding was numerically lower in ticagrelor-treated patients than in clopidogrel-treated patients despite the recommendation that the study drug be withheld for 5 days in the clopidogrel group and for 24 to 72 hours in the ticagrelor group.¹³ The primary safety end points in PLATO did not differ between groups, but non–coronary artery bypass graft–related major bleeding by PLATO and TIMI (Thrombolysis In Myocardial Infarction) criteria were greater in the ticagrelor group. However, the lower number of coronary artery bypass graft bleeding events in the ticagrelor group appeared to counterbalance the increased non–coronary artery bypass graft–related major bleeding and drove the primary end point of major bleeding to be no different between groups. It is clear that further prospective studies are required to demonstrate the relation of bleeding to platelet function in patients treated with reversible versus irreversible P2Y₁₂ inhibitors, and at this time, the optimal ex vivo measurements to determine safety and efficacy remain uncertain.

Ticagrelor inhibits the P2Y₁₂ receptor by a noncompetitive mechanism toward ADP.¹⁶ With noncompetitive binding, the agonist cannot displace the drug from the receptor. Theoretically, increasing concentrations of ADP should not significantly alter the antiplatelet effect of ticagrelor.¹⁶ Moreover, direct P2Y₁₂ inhibitors may inhibit the externalized internal pool of P2Y₁₂ receptors that are not accessible during transient exposure to active thienopyridine metabolites.¹⁷ In addition to overall greater platelet inhibition, the latter mechanisms may also explain the lower occurrence of ischemic events associated with ticagrelor than with clopidogrel therapy in the PLATO trial.

Study Limitations

The present study was neither sized adequately nor of sufficient duration to examine the relation of clinical outcomes to platelet function. The patient population had stable CAD, and similar findings may not occur in the analysis of platelet function in patients with unstable CAD or patients undergoing coronary stent implantation.

Conclusions

Ticagrelor achieved more rapid and greater platelet inhibition than high-loading-dose clopidogrel in patients with stable CAD. This inhibition was sustained during the maintenance phase and was faster in offset than clopidogrel. These effects may explain why ticagrelor treatment in the PLATO trial was associated with a lower occurrence of the primary end point than seen with clopidogrel therapy, whereas no difference in coronary artery bypass graft–related bleeding occurred between the 2 groups.

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CLINICAL PERSPECTIVE

In the present study, ticagrelor compared with high-loading-dose clopidogrel achieved more rapid and greater platelet inhibition in patients with stable coronary artery disease. Greater inhibition was also sustained during the maintenance phase, and the offset of action was faster with ticagrelor therapy than with clopidogrel. These pharmacodynamic effects may explain why ticagrelor treatment was associated with a lower occurrence of the primary end point (myocardial infarction, stroke, or cardiovascular death), similar coronary artery bypass graft–related bleeding, and no overall difference in major bleeding compared with clopidogrel therapy in the PLATO (PLATElet inhibition and patient Outcomes) trial.

SUPPLEMENTAL MATERIAL

Supplemental Tables

Table S1. Patient Enrollment in Each Center

Region	Center	Randomized Patients
United States	1	43
United Kingdom	2	40
United States	3	7
United States	5	4
United States	7	3
United States	8	12
United States	9	4
United States	10	10

Table S2. Platelet Function Testing Schedule

Measurement	Time in Onset and Offset Phases
2 mM arachidonic acid- induced platelet aggregation by light transmittance aggregometry	<ul style="list-style-type: none"> 0 h (pre-dose), on visit 2 and visit 4.
5 and 20 μ M ADP-, and 2 μ g/ml collagen- induced platelet aggregation by light transmittance aggregometry	<ul style="list-style-type: none"> Onset: 0 (pre-dose), 0.5, 1, 2, 4, 8 and 24 h after first dose Offset: 0 (pre-dose), 2, 4, 8, 24, 48, 72, 120, 168 and 240 h after last dose
VASP-Phosphorylation and Platelet receptors (GPIIb/IIIa and P-selectin) VerifyNow™ P2Y ₁₂ assay	<ul style="list-style-type: none"> Onset: 0 (pre-dose), 2, 8 and 24 h after first dose Offset: 0 (pre-dose), 8, 24, 48, 120, and 240 h after last dose

**Table S3. Correlation of Inhibition of Platelet Aggregation
(final extent, 20μM ADP) Versus Other Pharmacodynamic Measurements**

	Ticagrelor (n=54)		Clopidogrel (n=50)		Placebo (n=12)	
	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
IPA (%)						
5μM ADP (maximum)	0.9099	<0.0001	0.8805	<0.0001	0.6149	<0.0001
5μM ADP (final)	0.9257	<0.0001	0.9067	<0.0001	0.5698	<0.0001
20μM ADP (maximum)	0.9290	<0.0001	0.9396	<0.0001	0.9400	<0.0001
2ug/mL Collagen (maximum)	0.6249	<0.0001	0.4471	<0.0001	0.3909	<0.0001
2ug/mL Collagen (final)	0.6640	<0.0001	0.4298	<0.0001	0.3689	<0.0001
Flow Cytometry						
PRI (%)	0.7463	<0.0001	0.3973	<0.0001	-0.1310	0.1707
Inhibition of Stimulated P- Selectin Expression	0.4731	<0.0001	0.3586	<0.0001	-0.3561	0.0002
Inhibition of Stimulated GPIIb/IIIa Expression	0.3584	<0.0001	0.2934	<0.0001	-0.2343	0.0129
VerifyNow P2Y12 Assay						
Inhibition (%)	0.8483	<0.0001	0.7408	<0.0001	0.0054	0.9567
PRU	-0.8631	<0.0001	-0.5921	<0.0001	-0.1264	0.2640

ADP indicates adenosine diphosphate; IPA, inhibition of platelet aggregation; PRI, platelet reactivity index; PRU, Platelet Reactivity Units

Supplemental Legends

Figure S1. Adenosine diphosphate- stimulated p-selectin expression by protocol time and treatment. Data expressed as mean \pm SE.

* $P < 0.0001$, $^{\dagger}P < 0.005$, $^{\ddagger}P < 0.05$, Ticagrelor vs Clopidogrel

Figure S2. Adenosine Diphosphate- Stimulated GPIIb/IIIa Expression by Protocol Time and Treatment. Data are expressed as mean \pm standard error.

* $P < 0.0001$, $^{\dagger}P < 0.05$, Ticagrelor vs Clopidogrel

Supplemental Figures

Figure S1.

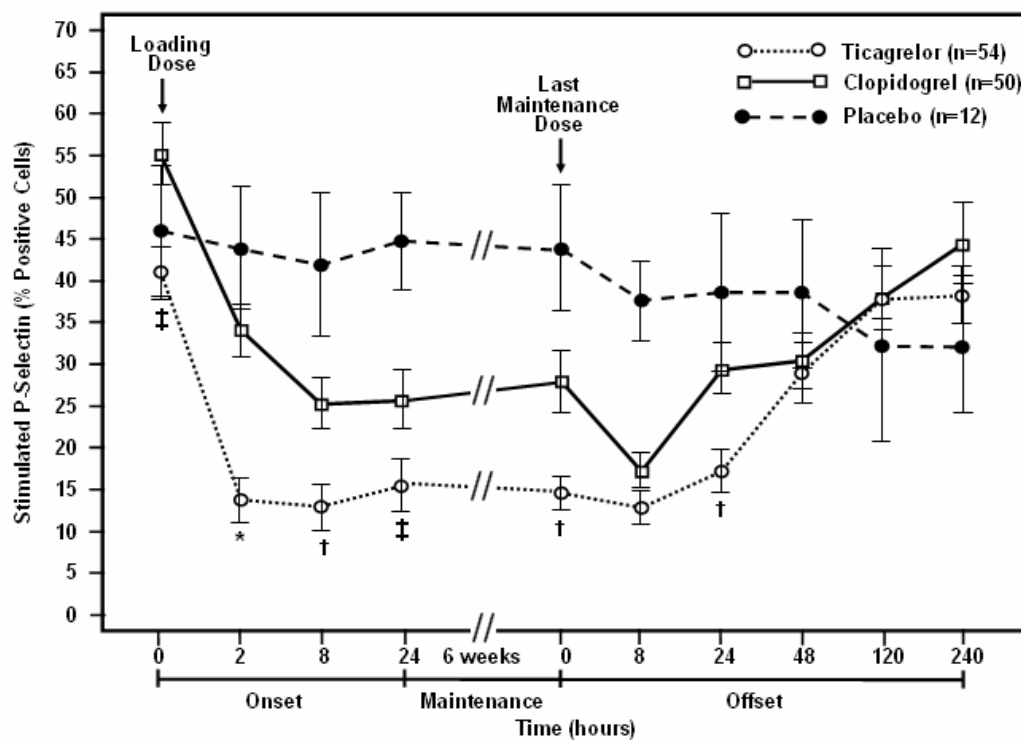
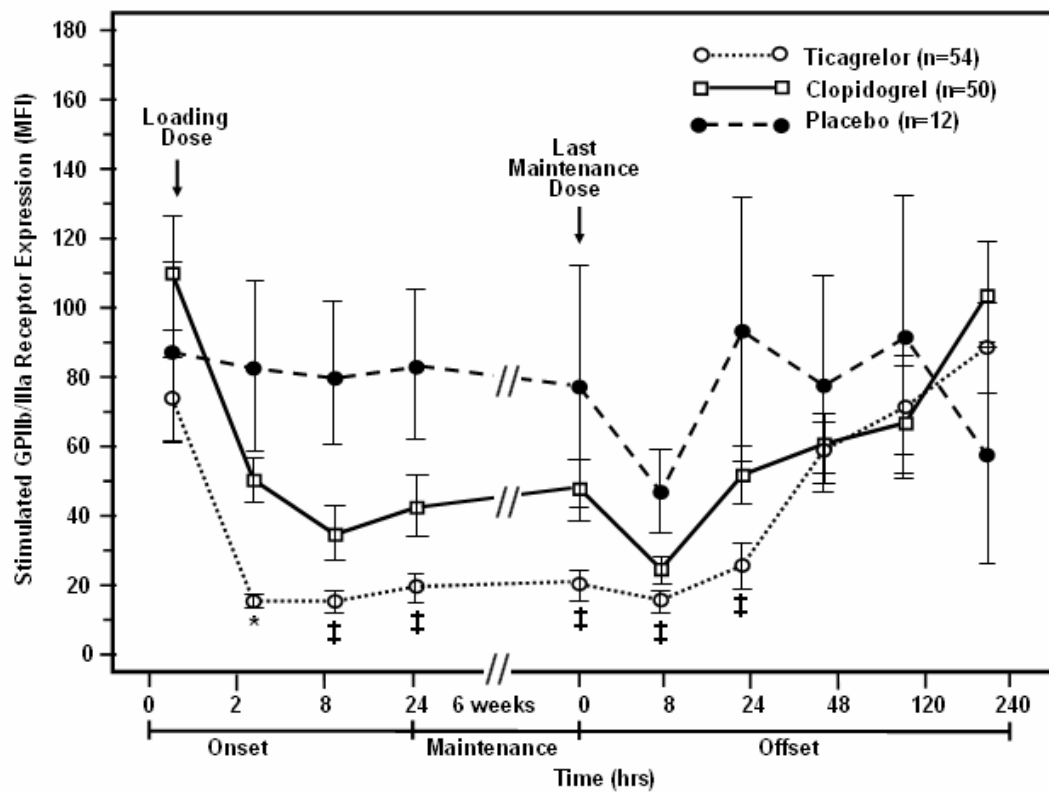


Figure S2.



REFERENCE

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Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies

The RESPOND Study

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Background—The antiplatelet effects of the Platelet Inhibition and Patient Outcomes (PLATO) trial dose of ticagrelor in patients nonresponsive to clopidogrel and after they switch agents are unknown.

Methods and Results—Patients with stable coronary artery disease on aspirin therapy received a 300-mg clopidogrel load; nonresponders were identified by light transmittance aggregometry. In a 2-way crossover design, nonresponders (n=41) and responders (n=57) randomly received clopidogrel (600 mg/75 mg once daily) or ticagrelor (180 mg/90 mg twice daily) for 14 days during period 1. In period 2, all nonresponders switched treatment; half of the responders continued the same treatment, whereas the others switched treatment. Inhibition of platelet aggregation was higher in nonresponders treated with ticagrelor compared with clopidogrel ($P<0.05$). Treatment with ticagrelor among nonresponders resulted in a $>10\%$, $>30\%$, and $>50\%$ decrease in platelet aggregation from baseline in 100%, 75%, and 13% of patients, respectively. Platelet aggregation fell from $59\pm 9\%$ to $35\pm 11\%$ in patients switched from clopidogrel to ticagrelor and increased from $36\pm 14\%$ to $56\pm 9\%$ in patients switched from ticagrelor to clopidogrel ($P<0.0001$ for both). Platelet reactivity was below the cut points previously associated with ischemic risk measured by light transmittance aggregometry, VerifyNow P2Y₁₂ assay, and vasodilator-stimulated phosphoprotein phosphorylation in 98% to 100% of patients after ticagrelor therapy versus 44% to 76% of patients after clopidogrel therapy.

Conclusions—Ticagrelor therapy overcomes nonresponsiveness to clopidogrel, and its antiplatelet effect is the same in responders and nonresponders. Nearly all clopidogrel nonresponders and responders treated with ticagrelor will have platelet reactivity below the cut points associated with ischemic risk.

Clinical Trial Registration—<http://www.clinicaltrials.gov>. Unique Identifier: NCT00642811. (Circulation. 2010;121:1188-1199.)

Key Words: antiplatelet agents ■ clopidogrel ■ platelet aggregation inhibitors ■ ticagrelor

Inhibition of P2Y₁₂ receptors by thienopyridines combined with aspirin therapy improved the outcome of patients with acute coronary syndromes and patients treated with stents compared with aspirin monotherapy.^{1–3} However, the antiplatelet effect of the most widely used thienopyridine, clopidogrel, is irreversible and variable.⁴ Patients treated with percutaneous coronary intervention who have high platelet reactivity (HPR) during clopidogrel and aspirin therapy or who are nonresponsive to clopidogrel have higher rates of ischemic events than responders.^{5–7} The latter observations are the rationale for new P2Y₁₂ receptor inhibitors.

Editorial see p 1169 Clinical Perspective on p 1199

Ticagrelor (formerly AZD6140), an oral, direct-acting, reversible, P2Y₁₂ receptor antagonist, was associated with less ischemic event occurrence than clopidogrel in patients with acute coronary syndromes in the Platelet Inhibition and Patient Outcomes (PLATO) trial. This beneficial effect may be related to more uniform and greater platelet inhibition.⁸ However, the antiplatelet effect of ticagrelor in patients who are nonresponsive to clopidogrel is unknown. In addition, the

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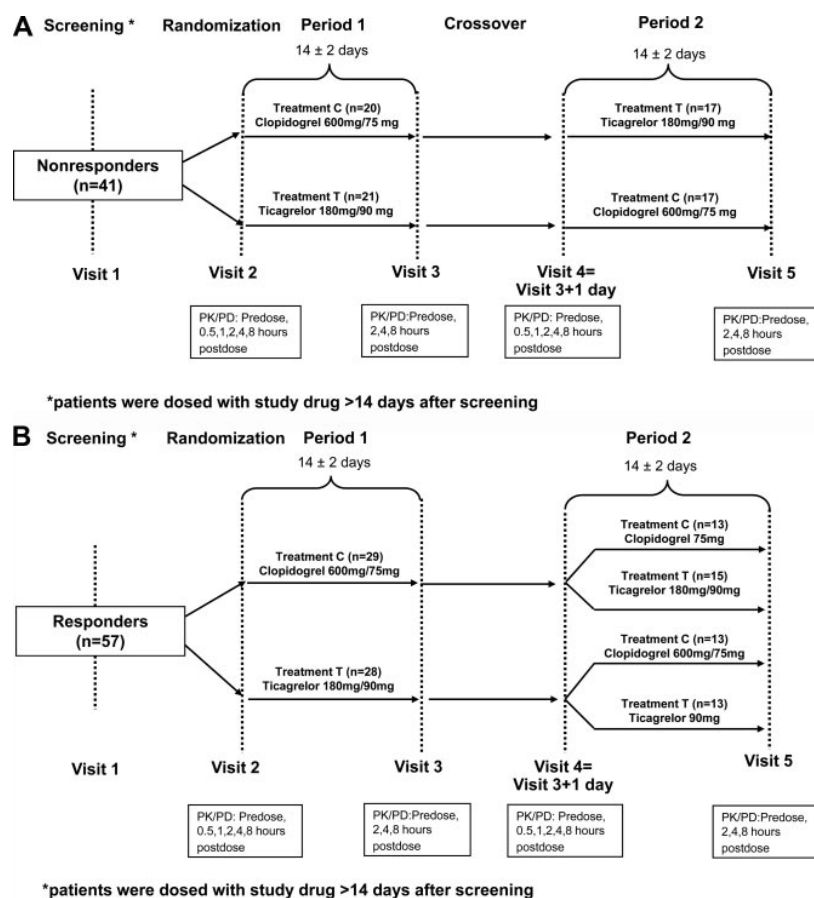


Figure 1. Study flow diagram demonstrating treatment in A, nonresponders and B, responders. PK/PD indicates pharmacokinetic/pharmacodynamic.

antiplatelet effect of switching from ticagrelor to clopidogrel therapy and vice versa is also unknown. Therefore, the aim of the present study was 2-fold: (1) to investigate the antiplatelet effect of ticagrelor dosed according to the PLATO trial in clopidogrel nonresponders and (2) to study platelet function during switching from clopidogrel to ticagrelor therapy and vice versa.

Methods

This study was a randomized, double-blind, double-dummy crossover investigation comparing the antiplatelet effects of ticagrelor with clopidogrel in patients with stable coronary artery disease identified as nonresponders or responders to a prior dose of clopidogrel. There were 10 study sites in North America and Europe. The methods and equipment were standardized across participating centers. The investigational review boards approved the study, and patients provided written informed consent.

Patients

Patients aged ≥ 18 years with documented stable coronary artery disease who were on aspirin therapy (75 to 100 mg once daily) were enrolled. Exclusion criteria were as follows: a history of acute coronary syndrome within 12 months of screening, a history of bleeding diathesis or severe pulmonary disease, pregnancy, current smoking (>1 pack per day), concomitant therapy with moderate or strong cytochrome P450 3A inhibitors or strong cytochrome P450 3A inducers within 14 days of the study, concomitant antithrombotic treatment other than aspirin within 14 days of the study, platelet count $<100\,000\text{ mm}^3$ or hemoglobin $<10\text{ g/dL}$, diabetic patients with hemoglobin $A_{1c} \geq 10\%$, history of drug addiction or alcohol

abuse in the past 2 years, nonsteroidal antiinflammatory drug use, and creatinine clearance $<30\text{ mL/min}$.

Definitions

To assess clopidogrel responsiveness, patients received a single 300-mg clopidogrel load. Responsiveness was based on $20\text{ }\mu\text{mol/L}$ ADP-induced platelet aggregation determined before the dose and at 6 to 8 hours after the dose.^{9,10} Patients were defined as nonresponders when the absolute change in platelet aggregation (maximum extent) was $\leq 10\%$, whereas patients with an absolute change of $>10\%$ were categorized as clopidogrel responders. Response status was confirmed 2 to 4 weeks before the first dose of study drug was received. Inhibition of platelet aggregation (IPA) was defined as follows:

$$\frac{(\text{Predose Aggregation} - \text{Postdose Aggregation})}{\text{Predose Aggregation}} \times 100\%$$

Study Design

The study design is shown in Figure 1A and 1B. Nonresponders and responders were randomly treated with either a 600-mg clopidogrel load followed by 14 ± 2 days of 75-mg daily maintenance therapy or a 180-mg ticagrelor load followed by 14 ± 2 days of 90-mg twice daily maintenance therapy (period 1). The last dose of study drug in period 1 was administered in the morning. All treatments were administered in a double-blind, double-dummy design, with matching placebo ticagrelor tablets and clopidogrel capsules administered (ie, all patients received both tablets and capsules daily). Randomization schedules for responder and nonresponder treatment regimens were independently generated in blocks (Global Randomization System, AstraZeneca).

In period 2, all nonresponders switched treatment, whereas half of the responders continued the same treatment, and the other half of the responders switched to the other treatment. Patients received treatments again for 14 ± 2 days. Patients who switched drugs received the other drug (patients treated with ticagrelor in period 1 received a 600-mg clopidogrel load followed by 75-mg daily maintenance therapy; patients treated with clopidogrel in period 1 received a 180-mg ticagrelor load followed by 90-mg twice daily maintenance therapy). Patients continuing on the same treatments in both study periods did not receive loading doses of study drug during period 2. In addition to study drug, all patients received concomitant aspirin therapy (75 to 100 mg once daily).

Blood Sampling

Blood samples were collected from the antecubital vein into 3 Vacutainer tubes (Becton-Dickinson, Franklin Lakes, NJ) containing 3.2% trisodium citrate for light transmittance aggregometry and flow cytometry measurements (Figure 1A and 1B). In addition, blood was collected in 1 tube containing 3.2% sodium citrate (Greiner Bio-One Vacuette, North America, Inc, Monroe, NC) for VerifyNow measurements. After the first 3 mL of free-flowing blood was discarded, the tubes were filled to capacity and gently inverted 3 to 5 times to ensure complete mixing of the anticoagulant.

Platelet Function Measurements

Light Transmittance Aggregometry

Platelet aggregation (5 and 20 $\mu\text{mol/L}$ ADP and 2 $\mu\text{g/mL}$ collagen) in platelet-rich plasma was assessed with the use of a Chronolog Optical Aggregometer (model 490–4D) as described previously.⁹ Maximum aggregation was determined and expressed as the maximum percent change in light transmittance from baseline, with platelet-poor plasma used as a reference.

VerifyNow P2Y₁₂ Assay

The VerifyNow P2Y₁₂ assay, a turbidimetric-based optical detection system, was used according to the manufacturer's instructions. An optical signal, reported as P2Y₁₂ reaction units (PRU), was recorded.¹¹

Vasodilator-Stimulated Phosphoprotein Phosphorylation

Vasodilator-stimulated phosphoprotein (VASP) phosphorylation, a measure of P2Y₁₂ receptor reactivity, was determined by flow cytometry with the use of the Platelet VASP-FCM kit (Biocytex Inc, Marseille, France) and recorded as the platelet reactivity index (PRI), as described previously.¹²

Glycoprotein IIb/IIIa and P-Selectin Expression

Nonstimulated and ADP-stimulated expression levels of glycoprotein IIb/IIIa and P-selectin were determined by whole blood flow cytometry with a multicolor analysis method as described previously.⁹ The differences in mean fluorescence intensity and percent positive cells between stimulated and nonstimulated cells were determined for activated glycoprotein IIb/IIIa and P-selectin expression, respectively.

Primary Analysis

The primary outcome variable was the estimation of the proportion of clopidogrel nonresponders who responded to ticagrelor after steady state dosing based on the platelet aggregation measurements taken 4 hours after the last dose. A patient was defined as a responder by the same definition used at screening. The proportion of patients who responded (P_{resp}) was determined by the following equation:

$$P_{\text{resp}} = 100\% \times (N_{\text{resp}}/N_{\text{total}})$$

where N_{resp} was the number of patients whose platelet aggregation (20 $\mu\text{mol/L}$ ADP, maximum extent) was $>10\%$, and N_{total} was the total number of dosed patients.

Table 1. Patient Demographics, Medical History, Concomitant Medications, and Baseline Laboratory Data

	Total Group (n=98)	Nonresponders (n=41)	Responders (n=57)	P
Demographics				
Age, y	65 \pm 8	66 \pm 7	64 \pm 9	0.24
Male, n (%)	76 (78)	28 (68)	48 (84)	0.07
BMI, kg/m ²	31 \pm 7	30 \pm 10	29 \pm 5	0.60
Ethnicity, n (%)				
White	87 (89)	38 (93)	49 (86)	0.30
Black	8 (8)	3 (7)	5 (9)	0.79
Other	3 (3)	0 (0)	3 (5)	0.14
Medical history, n (%)				
Smoking (current)	17 (17)	2 (5)	15 (26)	0.007
Family history of CAD	61 (62)	24 (59)	37 (65)	0.52
Hypertension	79 (81)	33 (81)	46 (81)	0.98
Hyperlipidemia	92 (94)	38 (93)	54 (95)	0.69
Diabetes mellitus	25 (26)	9 (22)	16 (28)	0.50
HbA _{1c} >6.0%	20 (21)	6 (15)	14 (25)	0.23
HbA _{1c} \leq 6.0%	2 (2)	1 (2)	1 (2)	0.84
Prior MI	56 (57)	22 (54)	34 (60)	0.57
Prior CABG	36 (37)	18 (44)	18 (32)	0.22
Prior PCI	47 (48)	21 (51)	36 (63)	0.24
Baseline medications n, (%)				
Statins	88 (90)	35 (85)	53 (93)	0.23
ACE inhibitors	20 (20)	10 (24)	10 (18)	0.41
β -Blockers	69 (70)	29 (71)	40 (70)	0.96
Diuretics	34 (35)	15 (37)	19 (33)	0.74
Organic nitrates	15 (15)	8 (20)	7 (12)	0.34
PPI	21 (22)	10 (24)	11 (19)	0.55
Calcium channel blockers	24 (25)	8 (20)	16 (28)	0.34
Baseline laboratory data				
WBC, $\times 1000/\text{mm}^3$	6.9 \pm 2.0	6.8 \pm 1.9	6.9 \pm 2.0	0.81
Platelets, $\times 1000/\text{mm}^3$	221 \pm 58	225 \pm 60	218 \pm 57	0.56
Hematocrit, %	42 \pm 4	42 \pm 4	42 \pm 4	1.0
Creatinine, $\mu\text{mol/L}$	90 \pm 21	93 \pm 26	88 \pm 18	0.27
LDL, mg/dL	97 \pm 35	105 \pm 28	91 \pm 40	0.06
HDL, mg/dL	48 \pm 12	48 \pm 12	48 \pm 12	1.0
Uric acid, $\mu\text{mol/L}$	372 \pm 88	363 \pm 89	378 \pm 87	0.41

BMI indicates body mass index; CAD, coronary artery disease; Hb, hemoglobin; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme; PPI, proton pump inhibitor; WBC, white blood cells; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

Other Analyses

Other analyses included the following: (1) comparison of IPA, PRU, and PRI during clopidogrel versus ticagrelor therapy in responders and nonresponders measured at the same time points; (2) comparison of the effect of ticagrelor versus clopidogrel therapy on platelet receptor expression, and IPA stimulated by 2 $\mu\text{g/L}$ collagen and 5 $\mu\text{mol/L}$ ADP; (3) comparison of the effect of clopidogrel versus ticagrelor in reducing platelet reactivity below cut points associated with ischemic risk; and (4) comparison of the antiplatelet effects of ticagrelor and clopidogrel in responders versus nonresponders.

Table 2. Proportion of Patients Who Responded to Ticagrelor vs Clopidogrel Based on the Primary Analysis (20 μ mol/L ADP, Maximum Extent Platelet Aggregation, Responsiveness at 4 Hours After Last Maintenance Dose) in the Nonresponder Cohort

Platelet Aggregation (20 μ mol/L ADP, Maximum Extent)	Ticagrelor		Clopidogrel		Ticagrelor vs Clopidogrel		McNemar Test <i>P</i>
	Patients, %	95% CI	Patients, %	95% CI	Difference, %	95% CI	
Decrease from baseline >10%	100	89–100	75	57–89	25	8–41	0.005
Decrease from baseline >30%	75	57–89	13	4–29	62	42–79	<0.001
Decrease from baseline >50%	13	4–29	0	0–11	13	1–23	0.046

Decrease from baseline=pretreatment aggregation (%) minus posttreatment aggregation (%). CI indicates confidence interval.

Other Assessments

The safety and tolerability of clopidogrel and ticagrelor were assessed. Bleeding events were classified according to PLATO trial definitions.⁸ Compliance was measured at visits 3 and 5 by the number of medication tablets returned by the patient.

Statistical Methods

Sample Size

On the basis of a previous study, we expected that ticagrelor therapy will result in an absolute increase in IPA of 25% compared with clopidogrel therapy.¹³ With the assumption of SD of 12 and an intrapatient correlation of 0.5, a sample size of ≈ 26 patients will be required to achieve at least 95% power to find this difference with an $\alpha=5\%$ on the basis of a 2-sided *t* test.¹⁴ Twenty-six patients will also yield 86% power to detect a difference of 50% in the proportions of subjects responding to antiplatelet therapy with the use of a 2-sided 0.05 level McNemar test if it is assumed that the proportion of discordant pairs is 80%. When the proportion of discordant pairs is 90%, the same difference in proportions can be detected with 80% power. If a potential dropout rate of 20% is considered, the study will enroll 32 patients into the nonresponder cohort of the study and 48 patients into the responder cohort of the study. In the case of the responder cohort, with the same sample size, type I error, testing assumptions, and an assumed variability of 14%, an absolute difference of 19% in 20 μ mol/L ADP final extent IPA can be detected with at least 91% power.¹⁴

Primary and Secondary Analyses

An intention-to-treat analysis model was used. The primary analysis was conducted with the McNemar test, and each patient was treated as a matching pair for clopidogrel and ticagrelor treatment. The proportion (with 95% confidence intervals) of patients who re-

sponded to treatment was determined, and the differences between the treatments were recorded. To analyze the pharmacodynamic parameters with repeated assessments, a repeated-measures mixed effect model was applied. The mixed effect model was used to compare the pharmacodynamic assessments between responders and nonresponders for ticagrelor and clopidogrel. The mixed effect model included fixed factors of treatment, cohort, cohort and treatment interaction, center, period, and treatment sequence and a random effect of patient within sequence. Treatment level means were estimated by least squares means and 2-sided 95% confidence intervals. The primary contrast (least squares mean difference between ticagrelor and clopidogrel) was also estimated with the use of least squares means and 2-sided 95% confidence intervals.

The McNemar test was used to assess the potential clinical efficacy of ticagrelor compared with clopidogrel. We used the following previously defined cut points of on-treatment HPR associated with long-term ischemic event occurrence: $>59\%$ 20 μ mol/L ADP-induced maximal platelet aggregation,⁷ ≥ 235 PRU based on the VerifyNow P2Y₁₂ assay,¹¹ and $>50\%$ PRI based on the VASP phosphorylation assay.¹² We determined the frequency of patients with HPR during both treatments on the basis of measurements taken at 4 hours after the last dose. Statistical analysis was performed by QDS, King of Prussia, Pa, with the use of SAS (version 8.2, SAS Institute Inc, Cary, NC). All statistical tests were 2-sided with a statistical significance level of 5% (ie, $\alpha=0.05$).

Results

Patients

Between May 19, 2008, and March 25, 2009, 144 patients satisfying the inclusion and exclusion criteria were screened for clopidogrel responsiveness. Patients were excluded from

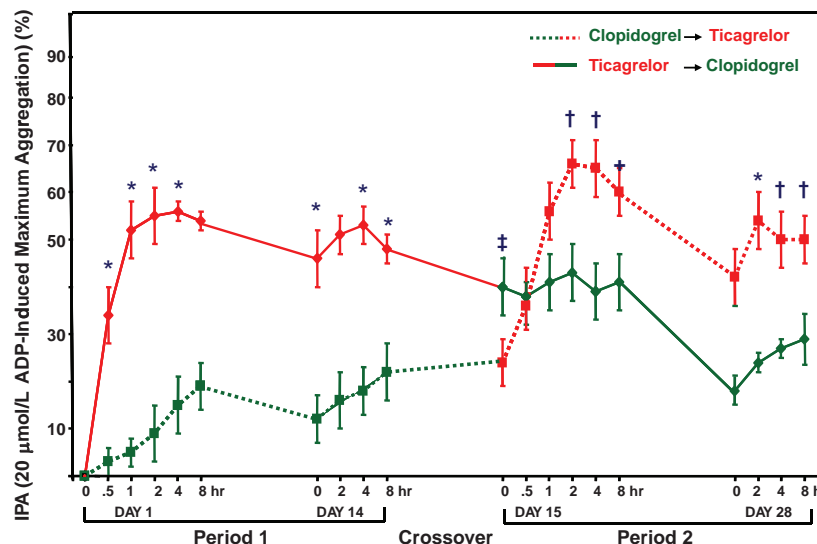


Figure 2. Inhibition of platelet aggregation in response to ADP (20 μ mol/L, maximum extent) in clopidogrel-nonresponsive patients. * $P<0.0001$, † $P<0.001$, ‡ $P<0.05$.

randomization after screening when a sufficient number of responders and nonresponders were identified on the basis of sample size calculation. Two patients voluntarily discontinued, and 1 patient had an adverse event before randomization. After 57 serial responders and 41 nonresponders were identified and randomized to treatment, no further patients were enrolled. Thirty-four nonresponders (83%) and 54 responders (95%) completed the study. In the nonresponder cohort, 5 patients discontinued because of an adverse event (3 during ticagrelor and 2 during clopidogrel treatment), 1 for noncompliance, and 1 for non-treatment-related reasons. In the responder cohort, 3 patients discontinued: 1 because of an adverse event and 2 for non-treatment-related reasons. Patients were aged 45 to 85 years and were predominantly white men. Demographics and concomitant medications were similar between groups except for a higher percentage of smokers in the responder cohort (Table 1). For nonresponders, the overall mean percent compliance at visits 3 and 5 was 79% and 89%, and for responders it was 79% and 91%, respectively.

Nonresponder Cohort

Primary Analysis

In the nonresponder cohort, the proportion of patients who responded to ticagrelor was higher than those who responded to clopidogrel ($P=0.005$; Table 2). In addition, the proportion of patients with an absolute change in platelet aggregation (20 $\mu\text{mol/L}$ ADP, maximum extent) $>30\%$ and $>50\%$ was also greater after ticagrelor therapy ($P<0.05$ for both) (Table 2). Platelet aggregation fell from $59\pm 9\%$ to $35\pm 11\%$ after patients switched from clopidogrel to ticagrelor treatment and increased from $36\pm 14\%$ to $56\pm 9\%$ in patients after they switched from ticagrelor to clopidogrel treatment ($P<0.0001$ for both). As analyzed by the repeated-measures mixed effect model, there was no center heterogeneity ($P=0.0998$) or treatment by time interaction ($P=0.2429$).

Inhibition of Platelet Aggregation

IPA (20 $\mu\text{mol/L}$ ADP, maximum extent) was higher at all times after the ticagrelor loading and maintenance doses and was maximal within 1 to 2 hours ($P\leq 0.05$; Figure 2). The highest IPA occurred after patients switched from clopidogrel therapy and loading with ticagrelor (Figure 2). At day 28 after patients switched from clopidogrel to ticagrelor, IPA was similar to the IPA in patients treated with ticagrelor in period 1. After patients switched from ticagrelor to clopidogrel therapy, an early carryover effect of increased IPA was present. However, at 14 days after switching of treatment, IPA was similar to the IPA at the end of period 1 during treatment with clopidogrel. IPA based on 5 $\mu\text{mol/L}$ ADP-induced and 2 $\mu\text{g/mL}$ collagen-induced aggregation was higher at steady state in nonresponders treated with ticagrelor versus clopidogrel (Table 3).

VerifyNow P2Y₁₂ Assay

The VerifyNow P2Y₁₂ assay findings were consistent with platelet aggregation (Figure 3). For nonresponders, PRU was significantly lower during ticagrelor therapy compared with clopidogrel therapy at all time points, except the initial crossover period up to 1 hour ($P\leq 0.05$). An early carryover

Table 3. Comparison of Difference in Response at Steady State (Day 14; 0, 2, 4, and 8 Hours) With Ticagrelor and Clopidogrel in Nonresponders

Time, h	Ticagrelor Least Squares Mean (95% CI)	Clopidogrel Least Squares Mean (95% CI)	Difference of Least Squares Means (Point Estimate, 95% CI)
% IPA (5 $\mu\text{mol/L}$ ADP-induced, maximum extent)			
0	57 (49–64)	22 (15–30)	34 (28–40)
2	65 (57–72)	30 (23–38)	34 (28–40)
4	64 (56–71)	30 (22–38)	34 (28–40)
8	62 (54–69)	34 (27–42)	27 (22–33)
% IPA (2 $\mu\text{g/mL}$ collagen-induced, maximum extent)			
0	48 (35–61)	26 (12–39)	22 (19–35)
2	66 (53–79)	38 (24–51)	29 (16–42)
4	60 (47–73)	42 (29–56)	18 (5–31)
8	63 (50–77)	41 (27–54)	23 (10–36)
P-selectin expression, % positive cells (stimulated minus nonstimulated)			
0	12 (7–17)	27 (22–32)	–16 (–22 to –10)
2	9 (3–14)	26 (21–31)	–18 (–24 to –12)
4	7 (2–12)	22 (17–27)	–15 (–21 to –9)
8	9 (4–14)	24 (19–30)	–15 (–21 to –9)
Activated glycoprotein IIb/IIIa receptor expression, MFI (stimulated minus nonstimulated)			
0	18 (9–26)	40 (31–49)	–22 (–33 to –12)
2	12 (3–21)	34 (25–43)	–22 (–33 to –11)
4	14 (5–23)	31 (22–40)	–17 (–27 to –6)
8	15 (7–25)	24 (15–33)	–8 (–19 to 3)

MFI indicates mean fluorescence intensity.

effect of lower PRUs was present after patients switched from ticagrelor to clopidogrel therapy.

VASP Phosphorylation

During treatment periods 1 and 2, PRI was lower in ticagrelor-treated patients, and a carryover effect was observed when patients were crossed over to clopidogrel therapy (Figure 4).

Platelet Receptors

P-selectin and activated glycoprotein IIb/IIIa expression levels were lower at steady state in nonresponders treated with ticagrelor compared with clopidogrel (Table 3).

Responder Cohort

Platelet Aggregation

Platelet aggregation (20 $\mu\text{mol/L}$ ADP, maximum extent) was lower after ticagrelor compared with clopidogrel therapy in

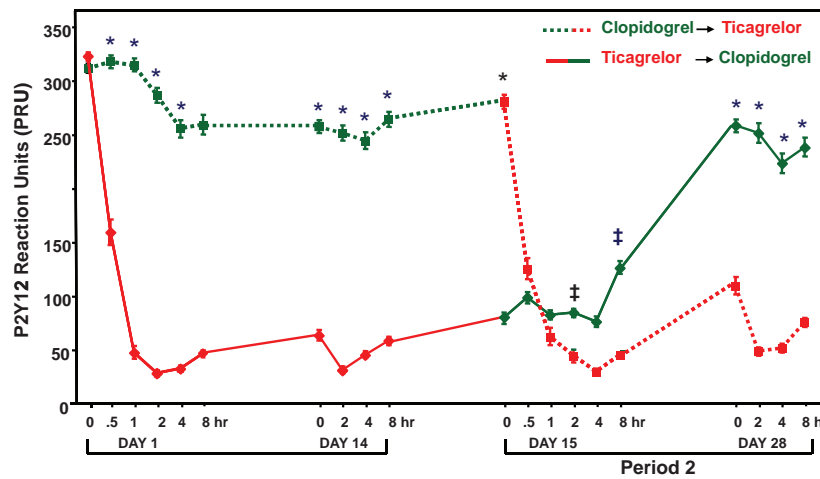


Figure 3. P2Y₁₂ reaction units in clopidogrel-nonresponsive patients. * $P<0.0001$, † $P<0.05$.

period 1 ($26\pm 9\%$ versus $49\pm 16\%$, $P<0.0001$ at day 1, 4 hours; $25\pm 11\%$ versus $47\pm 15\%$, $P<0.0001$ at day 14, 4 hours) and after crossing over in period 2 ($24\pm 9\%$ versus $37\pm 10\%$, $P<0.001$ at day 1, 4 hours; $32\pm 8\%$ versus $45\pm 8\%$, $P<0.001$ at day 14, 4 hours). In patients who continued on the same therapy, platelet aggregation was significantly lower at all the time points after steady state was reached in patients treated with ticagrelor ($P<0.05$).

Inhibition of Platelet Aggregation

IPA was higher at all time points after loading and maintenance ticagrelor therapy ($P<0.05$) except at period 2, day 15, 0 hours (Figure 5A). After patients switched from clopidogrel to ticagrelor, IPA was maximal within 1 hour after loading. Similar to the nonresponder group, loading with ticagrelor after patients switched from clopidogrel provided the greatest IPA. IPA at day 28 in patients switched from clopidogrel to ticagrelor was similar to IPA in patients treated with ticagrelor in period 1. In patients continued on the same therapy, IPA was higher with ticagrelor after steady state was reached ($P<0.05$; Figure 5B). IPA ($5\ \mu\text{mol/L}$ ADP-induced and $2\ \mu\text{g/mL}$ collagen-induced platelet aggregation, maximal extent) was also higher at steady state in patients treated with ticagrelor ($P<0.001$; data not shown).

VerifyNow P2Y₁₂ Assay

Results of the VerifyNow assay provided findings consistent with platelet aggregation data. PRU levels were significantly lower during ticagrelor therapy compared with clopidogrel therapy at all time points except the initial crossover period up to 1 hour (Figure 6A; $P\leq 0.05$); in patients who were continued on the same therapy, PRU levels were also significantly lower with ticagrelor after the initial steady state was reached ($P<0.05$; Figure 6B).

VASP Phosphorylation

For all comparisons at steady state, PRI was lower during ticagrelor treatment compared with clopidogrel treatment (Figure 7A and 7B). After treatments were switched, PRI was significantly lower during ticagrelor treatment compared with clopidogrel at all time points except on day 15 in patients who crossed over because of residual ticagrelor effect (Figure 7A). PRI in the noncrossover group was lower during steady state ticagrelor therapy at nearly all time points compared with clopidogrel therapy (Figure 7B).

Flow Cytometry Analysis

P-selectin and activated glycoprotein IIb/IIIa expression levels were consistently lower at steady state in responders

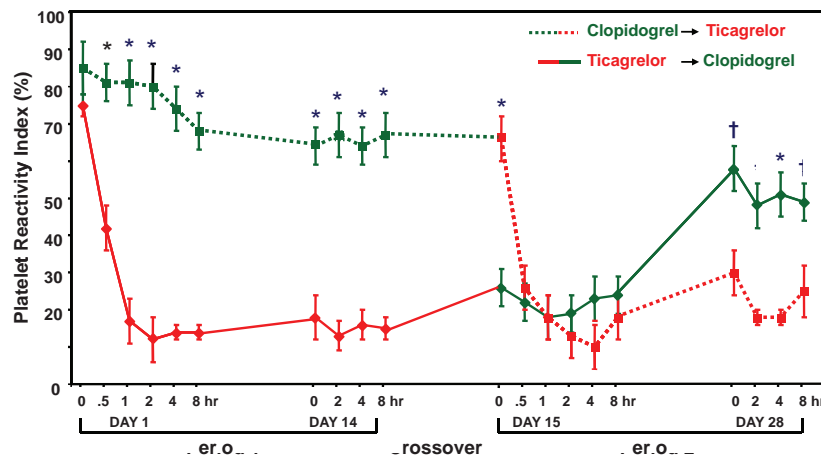


Figure 4. Platelet reactivity index measured by VASP phosphorylation in clopidogrel-nonresponsive patients. * $P<0.0001$, † $P<0.001$, ‡ $P<0.05$.

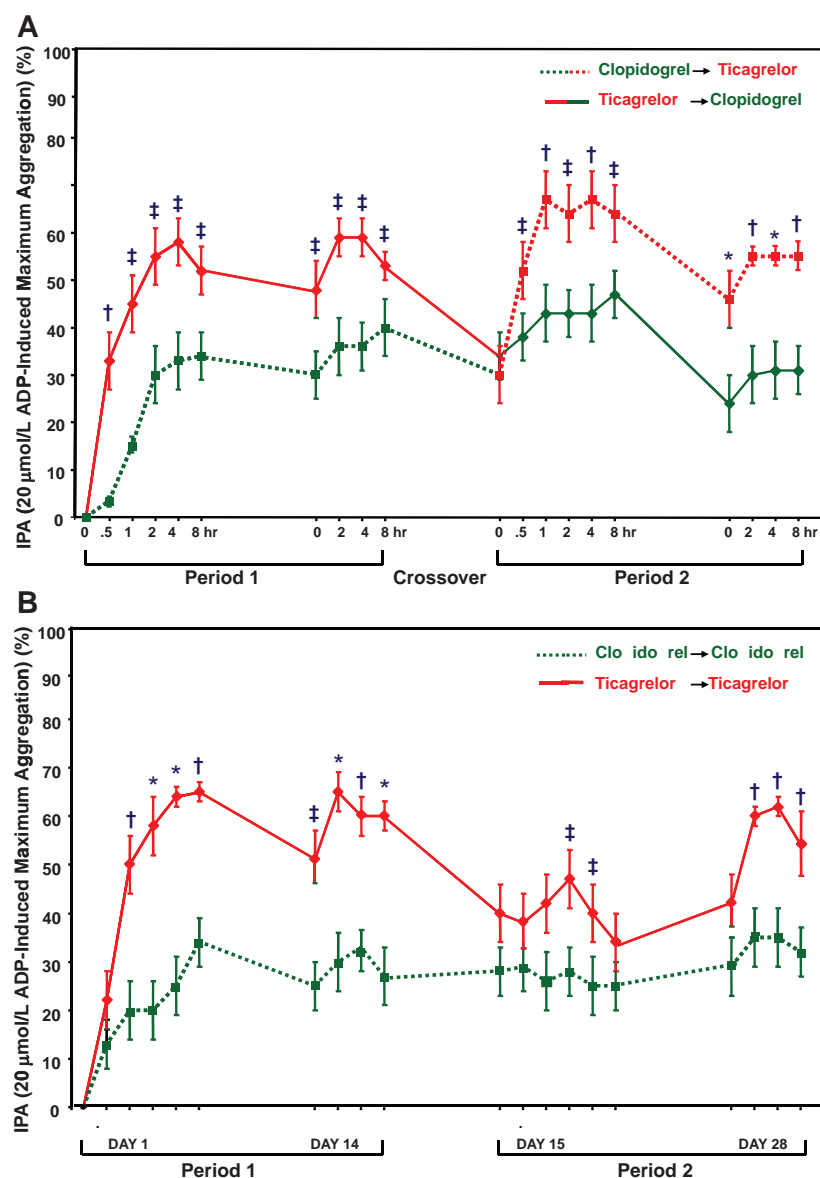


Figure 5. A, Inhibition of platelet aggregation in response to ADP (20 $\mu\text{mol/L}$, maximum extent) in clopidogrel-responsive patients before and after crossover. * $P<0.0001$, † $P<0.001$, ‡ $P<0.05$. B, IPA in response to ADP (20 $\mu\text{mol/L}$, maximum extent) in clopidogrel-responsive patients maintained on constant therapy. * $P<0.0001$, † $P<0.001$, ‡ $P<0.05$.

treated with ticagrelor compared with clopidogrel ($P<0.001$; data not shown).

Platelet Function in Relation to HPR Cutoff Values

The prevalence of patients with on-treatment HPR measured at 4 hours after the last maintenance dose in both responder and nonresponder groups treated with ticagrelor and clopidogrel is shown in Table 4. Overall, 98% to 100% of patients had platelet reactivity below the cut point as measured by platelet aggregation, the VerifyNow P2Y₁₂ assay, and VASP phosphorylation after ticagrelor therapy compared with 44% to 70% of patients after clopidogrel treatment. Ticagrelor was equally effective at overcoming HPR in both responders and nonresponders to clopidogrel therapy. Overall, the highest rate of HPR was identified by the VASP-PRI >50% cutoff.

Effect of Ticagrelor Versus Clopidogrel on IPA, VerifyNow, and VASP Phosphorylation: Responders Versus Nonresponders

Clopidogrel nonresponders exhibited less platelet inhibition and higher platelet reactivity while on clopidogrel maintenance therapy (Table 5). In contrast, the effect of ticagrelor did not differ between clopidogrel responders and nonresponders except as measured by VerifyNow. However, platelet reactivity measured by VerifyNow during ticagrelor therapy was low in both groups.

Safety

Four patients (2 patients were nonresponders, and 2 patients were responders) experienced the 5 serious adverse events, and all events occurred during or after ticagrelor therapy. The events were myocardial infarction, hypotension, atrial fibril-

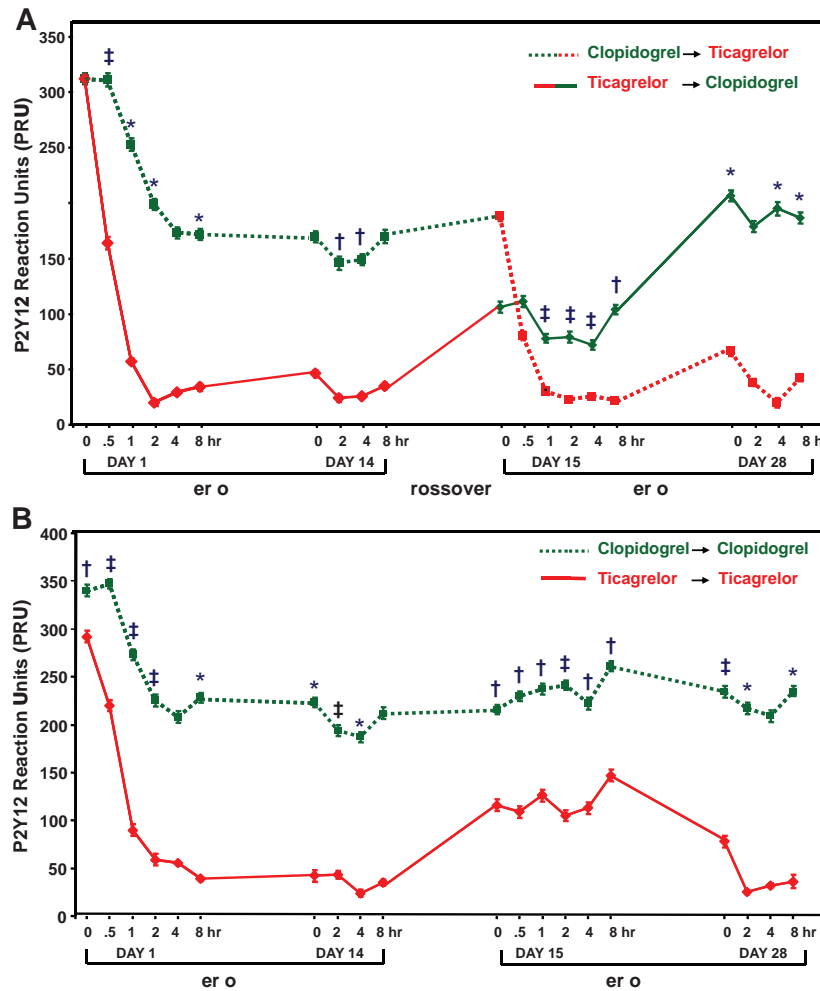


Figure 6. A, P2Y₁₂ reaction units in clopidogrel-responsive patients before and after crossover. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$. B, P2Y₁₂ reaction units in clopidogrel-responsive patients maintained on constant therapy. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$.

lation, and bradycardia during therapy. One death occurred on day 30 of follow-up after ticagrelor treatment and was not related to study treatment. One major and 3 minor bleeding events occurred during ticagrelor treatment, and no bleeding events occurred during clopidogrel treatment. Dyspnea was reported in 13 and 4 patients receiving ticagrelor and clopidogrel, respectively. Two nonresponder patients had dyspnea during switching of treatment. Most dyspnea episodes occurred early in the study, resolved without intervention, and did not result in discontinuation.

Discussion

The present study demonstrated that (1) ticagrelor therapy was associated with greater platelet inhibition compared with clopidogrel treatment in both clopidogrel responders and nonresponders; (2) the antiplatelet effect of ticagrelor was largely not influenced by clopidogrel response status; ticagrelor therapy overcame clopidogrel nonresponsiveness; (3) during switching of therapies, ticagrelor produced a rapid enhancement in platelet inhibition in both clopidogrel responders and nonresponders, whereas changing to clopidogrel therapy was associated with a reduction in platelet inhibition; and (4) ticagrelor was extremely effective in

reducing the prevalence of HPR using previously defined cutoffs; nearly all patients during ticagrelor therapy, irrespective of clopidogrel response status, had platelet reactivity below the cutoffs associated with ischemic risk determined by all assays.

Various limitations of clopidogrel therapy include variable and irreversible platelet inhibition, a comparatively slow onset of action, and an overall modest level of platelet inhibition, with a considerable proportion of patients exhibiting a limited response.⁴ Several strategies have been examined to improve responses to clopidogrel, including increasing dosages or adding other agents.^{4,12,15–17} Before the present study, there were no investigations designed to examine the effect of ticagrelor in clopidogrel nonresponders and the effect of changing therapy from clopidogrel to ticagrelor and vice versa. One prior study has shown that treatment with a direct-acting, reversible P2Y₁₂ inhibitor, elinogrel, can overcome clopidogrel nonresponsiveness.¹⁸ The data from the Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) study are consistent with this finding and also with phase II studies of ticagrelor treatment that demonstrated greater and faster platelet inhibition compared with clopidogrel.^{13,19,20}

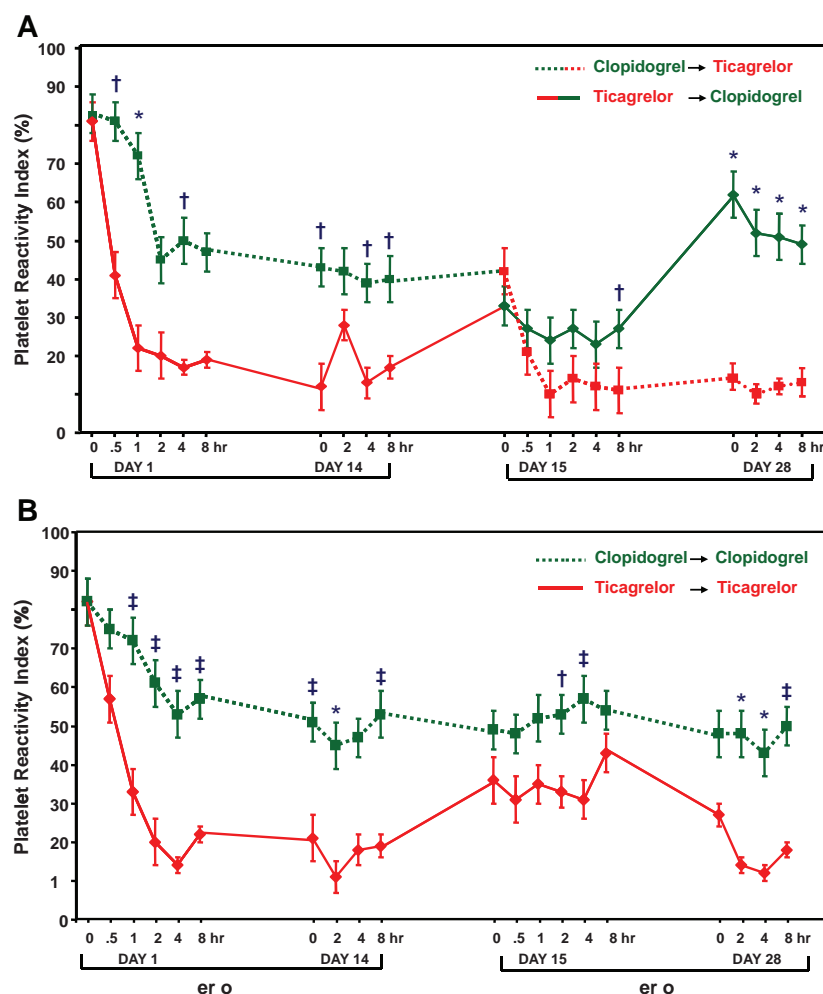


Figure 7. A, Platelet reactivity index measured by VASP phosphorylation in clopidogrel-responsive patients before and after crossover. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$. B, Platelet reactivity index measured by VASP phosphorylation in clopidogrel-responsive patients maintained on constant therapy. * $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.05$.

These pharmacodynamic properties may be related to the direct antiplatelet effect of ticagrelor compared with the requirement for active metabolite generation in the case of clopidogrel.¹³ In addition, we found that switching from clopidogrel to ticagrelor not only overcame clopidogrel nonresponsiveness (mean increase in IPA of $\approx 40\%$ in nonresponders) but also provided additional platelet inhibition in clopidogrel responders ($\approx 20\%$ increase in IPA).

The definition of nonresponders was based on a previous report in patients undergoing percutaneous coronary intervention. In that study, a 300-mg clopidogrel load was administered, and nonresponsiveness was estimated at $\approx 30\%$ at 24 hours after dosing.⁹ The present findings demonstrating an $\approx 28\%$ prevalence of nonresponsiveness are consistent with a previous investigation in which the prevalence of nonresponsiveness was 32% to a 300 mg-load as measured by the absolute change in platelet aggregation $\leq 10\%$ from baseline with the use of 20 $\mu\text{mol/L}$ ADP stimulation.¹⁰ Moreover, patients determined to be nonresponders at screening consistently had less clopidogrel-induced platelet inhibition by all assays after randomization. These data demonstrate that screening with a 300-mg clopidogrel load indeed discriminates patients who will have a reduced antiplatelet effect

measured by all assays after high-dose loading and during clopidogrel maintenance therapy.

The higher and more consistent IPA and lower platelet reactivity upon switching to ticagrelor demonstrate that the latter may be a reasonable strategy for clopidogrel nonresponders. The speed of the effect may improve treatment compared with previous strategies of repeated clopidogrel loading.¹¹ Our results also demonstrate that patients can switch directly from clopidogrel to ticagrelor without any reduction in antiplatelet effects. In contrast, responders who switched from ticagrelor to clopidogrel had a decrease in IPA $\approx 25\%$.

Results from the VASP analyses showed minor differences compared with the light transmittance aggregometry measurements. Flow cytometric assessment of VASP phosphorylation and the VerifyNow P2Y₁₂ assay have the advantage of measuring P2Y₁₂ function directly, whereas ADP-induced IPA is influenced by P2Y₁ receptor in addition to P2Y₁₂ being activated and contributing to platelet aggregation.²¹ Our findings demonstrating the near elimination of HPR during ticagrelor therapy using previously published cut points support the findings of the PLATO trial.^{4,8}

In the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in

Table 4. On-Treatment HPR Cut Points Associated With Ischemic Risk: Relation to Ticagrelor and Clopidogrel Therapy

	Ticagrelor		Clopidogrel		McNemar Test, Ticagrelor vs Clopidogrel		
	Patients, % (n/N)	95% CI	Patients, % (n/N)	95% CI	Difference, %	95% CI	P
Platelet aggregation (20 μ mol/L ADP, maximum extent) \leq 59%							
Nonresponder group	94 (31/33)	86–100	61 (20/33)	44–77	31	12–51	0.002
Responder group	100 (52/52)	94–100	76 (41/54)	65–87	21	4–39	0.01
Total group	98 (83/85)	94–100	70 (61/87)	60–80	27	14–40	<0.0001
VerifyNow P2Y ₁₂ -PRU \leq 235							
Nonresponder group	100 (32/32)	91–100	53 (17/32)	36–70	45	22–69	0.0002
Responder group	100 (51/51)	94–100	66 (35/53)	53–79	17	0–33	0.05
Total group	100 (83/83)	96–100	61 (52/85)	51–72	33	18–48	<0.0001
VASP-PRI \leq 50%							
Nonresponder group	100 (34/34)	92–100	29 (10/34)	14–45	71	42–99	<0.0001
Responder group	98 (52/53)	94–100	53 (28/53)	39–66	38	15–62	0.002
Total group	99 (86/87)	97–100	44 (35/87)	33–54	57	38–76	<0.0001

CI indicates confidence interval; PRU, P2Y₁₂ reaction units.

Myocardial Infarction 44 (PRINCIPLE-TIMI 44) study, the antiplatelet effect of clopidogrel was compared with prasugrel, a third-generation thienopyridine.²² IPA after a 60-mg prasugrel load and a 10-mg prasugrel maintenance dose was greater than the IPA after a 600-mg clopidogrel load and a 150-mg maintenance dose. After patients were switched from clopidogrel to prasugrel during the maintenance phase, there was increased platelet inhibition. However, in this study, there was no categorization of patients with respect to clopidogrel response status. Therefore, it is not possible to compare the antiplatelet effects of prasugrel versus ticagrelor in clopidogrel nonresponders. There have been no studies to determine the antiplatelet effect of prasugrel in clopidogrel nonresponders or that compare the antiplatelet effects of prasugrel with ticagrelor.

In the pharmacodynamic substudy of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Plate-

let Inhibition With Prasugrel (TRITON)–TIMI 38 trial, antiplatelet effects of prasugrel were compared with standard-dose clopidogrel.²³ In the TRITON substudy, \approx 15% of patients exhibited HPR as determined by 20 μ mol/L ADP-induced aggregation during maintenance prasugrel therapy compared with 2% during ticagrelor therapy in our study. Similarly, a greater antiplatelet effect was demonstrated during ticagrelor therapy by the presence of 1% of patients above the VASP phosphorylation cutoff for risk compared with 24% of patients treated with prasugrel in the TRITON substudy. The frequency of patients above the cut point during clopidogrel treatment in the TRITON substudy is consistent with our findings (43% versus 39%).²³ These results suggest that ticagrelor may be more effective than prasugrel in achieving optimal platelet reactivity. However, platelet reactivity may be influenced by the clinical disease state, with higher platelet reactivity observed in patients with

Table 5. Antiplatelet Effect of Clopidogrel and Ticagrelor: Responders vs Nonresponders

	Responder Least Squares Mean (95% CI)	Nonresponder Least Squares Mean (95% CI)	Responder vs Nonresponder	
			Difference (95% CI)	<i>P</i>
IPA (20 mmol/L ADP, maximum extent)				
Ticagrelor	57 (51–63)	50 (43–57)	7 (–2 to 16)	0.114
Clopidogrel	34 (28–40)	21 (14–28)	13 (4 to 21)	0.004
VerifyNow-PRU				
Ticagrelor	39 (15–64)	59 (31–86)	–20 (–55 to –16)	0.270
Clopidogrel	182 (157–206)	245 (218–273)	–64 (–99 to –29)	0.0004
VASP-PRI				
Ticagrelor	15 (9–21)	20 (14–27)	–5 (–13 to –3)	0.240
Clopidogrel	47 (42–53)	61 (54–67)	–13 (–21 to –5)	0.003

CI indicates confidence interval. For the responder cohort, both period 1 and 2 day-14, 4-hour data were used. For the crossover treatment groups, both period 1 and 2 day-14, 4-hour data were used. For stay-on-treatment groups, only period 1 day-14, 4-hour data were used.

acute coronary syndromes. The observation may, at least in part, explain the differences in HPR after prasugrel treatment in the TRITON substudy compared with ticagrelor treatment in the present study. A randomized comparison of prasugrel with ticagrelor will be necessary before any definitive conclusion can be made.

Limitations

The definition of clopidogrel nonresponsiveness remains controversial and is dependent on the time, dose, and method of assessment. However, in the present study, patients meeting the definition of clopidogrel nonresponsiveness at screening clearly had significantly lower IPA and higher PRI and PRU during clopidogrel therapy. The study is underpowered to look at safety end points. The RESPOND study population differs from the PLATO study that enrolled patients with unstable coronary artery disease.

Conclusion

In conclusion, this is the first study to demonstrate that ticagrelor therapy overcomes nonresponsiveness to and HPR during clopidogrel therapy. The antiplatelet effect of ticagrelor is essentially uniform and high in clopidogrel responders and nonresponders. In addition, platelet inhibition in patients responsive to clopidogrel was significantly enhanced by switching to ticagrelor therapy. The extremely low prevalence of HPR in patients treated with ticagrelor provides a mechanism for the clinical benefit of ticagrelor therapy, as demonstrated in the PLATO trial.

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Disclosures

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CLINICAL PERSPECTIVE

The Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) study is the first to demonstrate that ticagrelor therapy overcomes nonresponsiveness to and high platelet reactivity during clopidogrel therapy. The antiplatelet effect of ticagrelor is essentially uniform and high in both clopidogrel responders and nonresponders. Moreover, platelet inhibition in patients responsive and nonresponsive to clopidogrel is enhanced by switching to ticagrelor therapy. These data suggest that ticagrelor may be an important therapeutic alternative in patients who have experienced thrombotic events during clopidogrel therapy. The extremely low prevalence of high platelet reactivity associated with ticagrelor therapy as defined by cut points associated with ischemic event occurrence with the use of 3 different methods in the RESPOND study provides a mechanism for the clinical benefit demonstrated in the Platelet Inhibition and Patient Outcomes (PLATO) trial. All of these findings support the particular utility of ticagrelor in clinical settings associated with high platelet reactivity, such as acute coronary syndromes, percutaneous coronary intervention, and stent thrombosis.

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Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, et al. DISPERSE-2 Investigators. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol*. 2007;50:1844-51.

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Safety, Tolerability, and Initial Efficacy of AZD6140, the First Reversible Oral Adenosine Diphosphate Receptor Antagonist, Compared With Clopidogrel, in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome

Primary Results of the DISPERSE-2 Trial

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Objectives

Our goal was to compare the safety and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, with clopidogrel in patients with non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS).

Background

AZD6140 achieves higher mean levels of platelet inhibition than clopidogrel in patients with stable coronary artery disease.

Methods

A total of 990 patients with NSTEMI-ACS, treated with aspirin and standard therapy for ACS, were randomized in a 1:1:1 double-blind fashion to receive either twice-daily AZD6140 90 mg, AZD6140 180 mg, or clopidogrel 300-mg loading dose plus 75 mg once daily for up to 12 weeks.

Results

The primary end point, the Kaplan-Meier rate of major or minor bleeding through 4 weeks, was 8.1% in the clopidogrel group, 9.8% in the AZD6140 90-mg group, and 8.0% in the AZD6140 180-mg group ($p = 0.43$ and $p = 0.96$, respectively, vs. clopidogrel); the major bleeding rates were 6.9%, 7.1%, and 5.1%, respectively ($p = 0.91$ and $p = 0.35$, respectively, vs. clopidogrel). Although not statistically significant, favorable trends were seen in the Kaplan-Meier rates of myocardial infarction (MI) over the entire study period (MI: 5.6%, 3.8%, and 2.5%, respectively; $p = 0.41$ and $p = 0.06$, respectively, vs. clopidogrel). In a post-hoc analysis of continuous electrocardiograms, mostly asymptomatic ventricular pauses >2.5 s were more common, especially in the AZD6140 180-mg group (4.3%, 5.5%, and 9.9%, respectively; $p = 0.58$ and $p = 0.01$, respectively, vs. clopidogrel).

Conclusions

This initial experience with AZD6140 in patients with ACS showed no difference in major bleeding but an increase in minor bleeding at the higher dose with encouraging results on the secondary end point of MI. This agent is currently being studied in a large outcomes trial in 18,000 patients with ACS. (J Am Coll Cardiol 2007;50:1844-51) © 2007 by the American College of Cardiology Foundation

From the *TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; †Århus University Hospital, Århus, Denmark; ‡Duke Clinical Research Institute, Durham, North Carolina; §AstraZeneca, Mölndal, Sweden; ||AstraZeneca, Wilmington, Delaware; and ¶University of Sheffield, Sheffield, United Kingdom. This study was funded by AstraZeneca. In addition, Dr. Cannon receives research funding from Schering Plough, and the TIMI Study Group has received research funding from Daiichi-Sankyo, Eli Lilly and Company, Bristol-Myers Squibb, and Sanofi-Aventis, manufacturers of oral antiplatelet agents. Dr. Husted has received research grants from AstraZeneca. Dr.

Harrington has received research grants, consultancy fees, or honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Sanofi-Aventis, and The Medicines Company. Dr. Emanuelsson is an employee of AstraZeneca. Dr. Peters is a former employee of AstraZeneca. Dr. Storey has received research grants, consultancy fees, or honoraria from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly and Company, Sanofi-Aventis, and The Medicines Company. See the Online Appendix for a full list of investigators. See accompanying online Cardiosource Slide Set.

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Antiplatelet therapy with aspirin, thienopyridines (e.g., clopidogrel), or their combination has resulted in major reductions in cardiovascular events (1–6). This latter class inhibits platelet activation and aggregation by blocking the P2Y₁₂ receptor, 1 of 2 adenosine diphosphate (ADP) receptors on platelets (7). However, clopidogrel has several limitations: it is a pro-drug that requires hepatic conversion, leading to delay in onset of action, and there is wide interindividual variability in levels of platelet inhibition, with up to one-third of patients exhibiting minimal platelet inhibition (often referred to as “clopidogrel nonresponders”) (8–10). At steady state, clopidogrel achieves only 30% to 40% mean inhibition of platelet aggregation response to ADP, and its active metabolite binds irreversibly to P2Y₁₂ receptors, such that recovery of platelet function is precluded.

AZD6140 is the first reversible oral P2Y₁₂ receptor antagonist in a new chemical class of antiplatelet agents termed cyclopentyl-triazolo-pyrimidines with a half-life of approximately 12 h (11,12). Distinct from the thienopyridines, this agent does not require metabolic conversion to an active form; it binds directly to the P2Y₁₂ receptor, and it can more completely inhibit the sustained aggregation response to ADP. A study in patients with stable atherosclerosis found a dose-dependent increase in the level of inhibition with AZD6140, with levels being significantly higher than those achieved with clopidogrel (12). The DISPERSE (Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogrel in non-ST-segment Elevation myocardial infarction)-2 trial was a randomized, double-blind, double-dummy trial conducted to assess the safety, tolerability, and initial efficacy of AZD6140 plus aspirin in comparison with clopidogrel plus aspirin in patients with non-ST-segment elevation (NSTEMI) acute coronary syndromes (ACS).

Methods

Patients. Between October 3, 2004 and April 23, 2005, patients with NSTEMI-ACS were entered into the trial from 152 participating sites in 14 countries (Online Appendix 1). The study protocol was approved by the relevant institutional review boards, and written informed consent was obtained from all patients before the initiation of trial procedures.

Detailed entry criteria are in Online Appendix 2. Briefly, patients were eligible if they were hospitalized for NSTEMI-ACS within the preceding 48 h, experienced ischemic symptoms of ≥10 min duration at rest, with either biochemical marker evidence of myocardial infarction (MI) or electrocardiographic evidence of ischemia.

Study protocol. Patients received standard medical (anti-ischemic and antithrombotic) and interventional treatment for ACS, including aspirin at an initial dose of up to 325 mg followed by 75 to 100 mg daily with or without a glycoprotein IIb/IIIa inhibitor. Patients who had received clopidogrel before randomization were permitted in the study,

but open-label clopidogrel was discontinued after randomization and replaced with study drug.

Eligible patients were randomized in a 1:1:1 double-blind fashion to receive AZD6140 90 mg twice daily, AZD6140 180 mg twice daily, or clopidogrel 300 mg followed by 75 mg once daily for up to 3 months. Patients in the AZD6140 group were subrandomized to receive or not receive an initial loading dose of 270 mg. Patients were scheduled to receive 1, 2, or 3 months of study drug, depending on when during the trial period they were enrolled. For patients undergoing percutaneous coronary intervention (PCI) within 48 h post-randomization, an additional 300 mg of clopidogrel study drug or placebo (clopidogrel for patients in the clopidogrel group or placebo for patients in the AZD6140 group) could be administered at the discretion of the treating physician. Patients returned monthly for follow-up visits, and were contacted by telephone 7 days after stopping study drug for evaluation of any adverse events.

The primary objective was to assess the safety and tolerability of the different doses of AZD6140 plus aspirin, versus clopidogrel plus aspirin, in patients with NSTEMI-ACS by evaluating total bleeding events (major plus minor bleeding, but excluding minimal bleeds as adjudicated by the Independent Clinical Adjudication Committee) observed within the first 4 weeks of treatment (see Online Appendix 2 for definitions). Additional objectives of the trial were to assess: 1) individual and composite incidence of MI (including silent MI), death, stroke, and severe recurrent ischemia; and 2) incidence of recurrent ischemia with AZD6140 plus aspirin and clopidogrel plus aspirin, using total duration of ischemia as detected by continuous Holter electrocardiogram monitoring (LifeCard CF, DelMar Reynolds, Irvine, California) during the first 4 to 7 days after randomization.

Statistical analyses. Statistical analyses were performed using SAS version 8.1 (SAS Institute, Inc., Cary, North Carolina), with details provided in Online Appendix 2. An independent data safety monitoring board comprising clinical experts and a statistician monitored safety data on an ongoing basis to ensure that patient safety was maintained. Comparisons between AZD6140 and clopidogrel were made using the Cox proportional hazards model (time-to data), Fisher exact test (count data), and the t test (continuous data). The Thrombolysis In Myocardial Infarction (TIMI) study group has a copy of the database and has independently confirmed the data presented here.

Abbreviations and Acronyms

ACS	= acute coronary syndromes
ADP	= adenosine diphosphate
CABG	= coronary artery bypass grafting
CI	= confidence interval
IQR	= interquartile range
NSTEMI-ACS	= non-ST-segment acute coronary syndromes
PCI	= percutaneous coronary intervention

Table 1 Baseline Characteristics in the Primary Safety Cohort

	Clopidogrel 75 mg Daily (n = 327)	AZD6140 90 mg Twice Daily (n = 334)	AZD6140 180 mg Twice Daily (n = 323)	p Value (Global)
Age, yrs (mean ± SD)	62 ± 11.0	64 ± 12.1	63 ± 11.4	0.20
Men, n (%)	217 (66)	204 (61)	211 (65)	0.33
White race, n (%)	308 (94)	316 (95)	305 (94)	0.98
Diabetes, n (%)	81 (25)	83 (25)	77 (24)	0.95
Prior MI, n (%)	91 (28)	81 (24)	78 (24)	0.48
Prior PCI, n (%)	56 (17)	43 (13)	51 (16)	0.29
Prior CABG, n (%)	36 (11)	28 (8)	26 (8)	0.36
Weight, kg (mean ± SD)	83 ± 16.5	81 ± 17.0	81 ± 16.4	0.27
Body mass index, kg/m ² (mean ± SD)	29 ± 5.0	28 ± 5.4	29 ± 5.1	0.72
Prior clopidogrel, n (%)	92 (28)	87 (26)	86 (27)	0.83

Statistical testing done with analysis of variance for age, weight, body mass index, and Fisher exact test for all other variables.

CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Results

Patient population. A total of 1,018 patients were screened and provided informed consent, and 990 patients from 132 sites were randomized. After randomization, 984 patients received at least 1 dose of study drug and were included in the safety analysis dataset. A total of 491 (50%) were scheduled to receive study drug for 12 weeks, 243 (25%) for 8 weeks, and 250 (25%) for 4 weeks. The median duration of study drug treatment was 56 days.

The mean age of patients enrolled was 63 years (range 30 to 93 years), more than a third of were women, 24% had diabetes mellitus, and 48% had ST-segment depression ≥ 0.5 mm and 62% were coded as non-ST-segment elevation MI (Table 1). Ninety-eight percent of patients received aspirin, 85% received heparin (51% unfractionated heparin, 40% low-molecular-weight heparin, not mutually exclusive), 31% received glycoprotein IIb/IIIa inhibitors, 85% received beta-blockers, and 86% received statins, without differences between the treatment groups. A total of 67% of patients underwent coronary angiography, 42% had PCI (2% balloon angioplasty, 40% stenting, of which 48% had

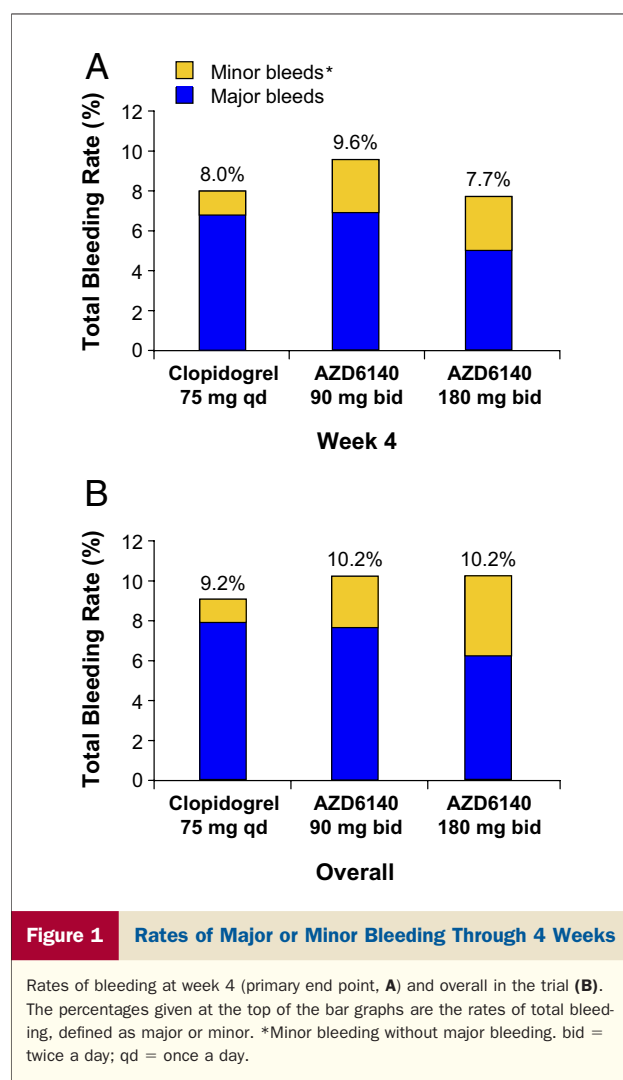
drug-eluting stents), and 9% underwent post-randomization coronary artery bypass grafting (CABG). The median time to PCI was 20 h after randomization (interquartile range [IQR] <2 to 72 h), and the median time to CABG was 10 days after randomization (IQR <7 to 19 days).

Primary end point. The Kaplan-Meier rate of the primary end point, protocol-defined major or minor bleeding at 4 weeks, was not different among the 3 groups, with 26 patients (8.1%) experiencing a bleeding episode in the clopidogrel group, compared with 32 (9.8%) in the AZD6140 90-mg group and 25 (8.0%) in the 180-mg group ($p = 0.43$ and $p = 0.96$ vs. clopidogrel, respectively) (Table 2). The rates of “major—fatal/life-threatening” bleeding and “major—other” bleeding were not different among the AZD6140 and clopidogrel groups (Fig. 1). There were 2 fatal bleeds, both in the AZD6140 90-mg group. Protocol-defined minor bleeding occurred in 4 patients (1.3%) in the clopidogrel group, 9 (2.7%) in the AZD6140 90-mg group, and 12 (3.8%) in the AZD6140 180-mg group over 4 weeks ($p = 0.18$ and $p = 0.05$ vs. clopidogrel, respectively). A similar pattern of bleeding was seen up through 12 weeks.

Table 2 Bleeding Events: Number of Events and Kaplan-Meier Event Rates

	Clopidogrel 75 mg Daily (n = 327)	AZD6140 90 mg Twice Daily (n = 334)	p Value vs. Clopidogrel	AZD6140 180 mg Twice Daily (n = 323)	p Value vs. Clopidogrel
Through week 4					
Total	26 (8.1)	32 (9.8)	0.43	25 (8.0)	0.96
Major	22 (6.9)	23 (7.1)	0.91	16 (5.1)	0.35
Major—fatal/life-threatening	14 (4.4)	11 (3.4)	0.53	10 (3.2)	0.44
Major—other	8 (2.5)	12 (3.7)	0.38	6 (1.9)	0.61
Minor	4 (1.3)	9 (2.7)	0.18	12 (3.8)	0.0504
Through week 12					
Total	30 (9.9)	34 (10.9)	0.62	33 (11.4)	0.72
Major	26 (8.7)	26 (8.6)	0.96	20 (6.3)	0.32
Major—fatal/life-threatening	16 (5.4)	13 (4.5)	0.55	14 (4.3)	0.61
Major—other	10 (3.3)	13 (4.2)	0.54	6 (1.9)	0.34
Minor	4 (1.3)	9 (2.7)	0.18	16 (6.1)	0.01

Values are n (%). Total bleeding is defined as major or minor bleeding. The number of events to the 2 time points is given with a Kaplan-Meier percent estimate of the event rate. Because follow-up ranged from 4 to 12 weeks, incidence rates and Kaplan-Meier event rates will differ. Statistical testing done using a Cox proportional hazards model.



The most common type of bleeding was epistaxis, followed by periprocedural hemorrhage or hematoma. Seventy-three percent of all bleeds in the clopidogrel group were procedure related versus 53% and 52% in the AZD6140 90- and 180-mg groups, respectively. Gastrointestinal bleeding occurred in 3 clopidogrel patients (0.9%), 7 AZD6140 90-mg patients (2.1%), and 4 AZD6140 180-mg patients (1.2%). Bleeding episodes that led to discontinuation of study treatment occurred in 3 clopidogrel patients (0.9%), 8 patients (2.4%) in the AZD6140 90-mg group, and 5 (1.5%) in the AZD6140 180-mg group. For the entire study period, blood transfusions were required by 22 patients (6.7%) in the clopidogrel group, 24 (7.2%) in the AZD6140 90-mg group, and 15 (4.6%) in the AZD6140 180-mg group; the median number of units transfused was 3 (IQR 2 to 4 U). Protocol-defined minimal bleeding (nonadjudicated) occurred in 70 (21%) patients in the clopidogrel group and in 89 (27%) and 100 (31%) patients in the AZD6140 90- and 180-mg groups, respectively, over

the entire study period ($p = 0.12$ and $p = 0.006$, vs. clopidogrel, respectively).

Assessment of bleeding by AZD6140 loading dose showed that major bleeding within the first 48 h occurred in 8 clopidogrel patients (2.4%), compared with 3 (1.8%), 2 (1.3%), and 6 (1.8%) patients in the AZD6140 90-, 180-, and 270-mg groups, respectively (Fig. 2). Protocol-defined minor bleeding within the first 48 h occurred in 1 (0.3%) clopidogrel patient and in 1 (0.6%), 0, and 6 (1.8%) patients in the AZD6140 90-, 180-, and 270-mg groups, respectively.

Among the 84 patients who underwent CABG, median times (IQRs) to the procedure from the last dose of study drug were 96 (40 to 168), 55 (30 to 124), and 60 (29 to 144) h in the clopidogrel, AZD6140 90-mg, and AZD6140 180-mg groups, respectively. One of 2 clopidogrel patients and 5 of 10 AZD6140 patients who underwent CABG within 1 day of receiving study drug had a major bleed. Among those undergoing CABG between 1 and 5 days after the last dose, the rate of major bleeding was numerically lower in the AZD6140 group (10 of 28 patients; 36%), compared with the clopidogrel group (9 of 14; 64%). Beyond 5 days, the rate of major bleeding was 60% (6 of 10) for clopidogrel patients and 50% (10 of 20) for AZD6140 recipients.

The rates of death or cardiovascular death were not different among groups (Table 3). There was a numerical trend toward lower rates of MI in the AZD6140 groups, with 15 (5.6%) patients in the clopidogrel group, 12 (3.8%) in the AZD6140 90-mg group, and 8 (2.5%) in the AZD6140 180-mg group experiencing an MI. The respective hazard ratios were 0.80 and 0.53, with confidence intervals (CIs) of 0.37 to 1.70 and 0.23 to 1.25. The Kaplan-Meier event rate of cardiovascular death, MI, or stroke, the combined end point used in the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial, showed similar rates between clopidogrel (6.2%) and

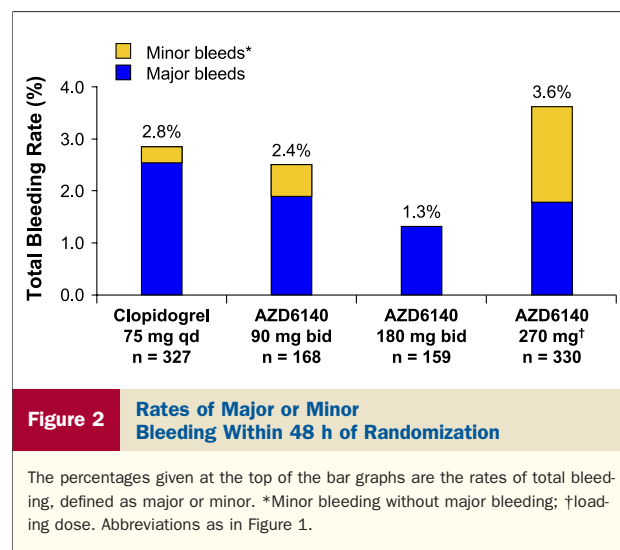


Table 3 Clinical End Points: Number of Events and Kaplan-Meier Event Rates

End Point, %	Clopidogrel 75 mg Daily (n = 327)	AZD6140 90 mg Twice Daily (n = 334)	p Value vs. Clopidogrel	AZD6140 180 mg Twice Daily (n = 329)	p Value vs. Clopidogrel
Through 4 weeks, n (%)					
All-cause death	2 (0.6)	6 (1.9)	0.18	3 (1.0)	0.64
CV death	2 (0.6)	6 (1.9)	0.18	3 (1.0)	0.64
MI	11 (3.5)	7 (2.2)	0.34	3 (1.0)	0.047
Stroke	1 (0.3)	2 (0.6)	0.57	0 (0.0)	0.99
SRI	2 (0.6)	2 (0.6)	0.99	4 (1.3)	0.41
RI	5 (1.6)	10 (3.2)	0.21	4 (1.6)	0.98
CV death/MI/stroke	12 (3.8)	14 (4.3)	0.71	6 (1.9)	0.17
Through 12 weeks, n (%)					
All-cause death	4 (1.3)	7 (2.4)	0.38	6 (1.7)	0.72
CV death	4 (1.3)	6 (1.9)	0.54	6 (1.7)	0.72
MI	15 (5.6)	12 (3.8)	0.41	8 (2.5)	0.06
Stroke	1 (0.3)	2 (0.6)	0.57	0 (0.0)	0.99
SRI	3 (1.4)	5 (2.3)	0.50	9 (3.7)	0.09
RI	9 (3.0)	13 (4.9)	0.29	9 (3.4)	0.78
CV death/MI/stroke	17 (6.2)	19 (6.0)	0.90	11 (3.5)	0.12

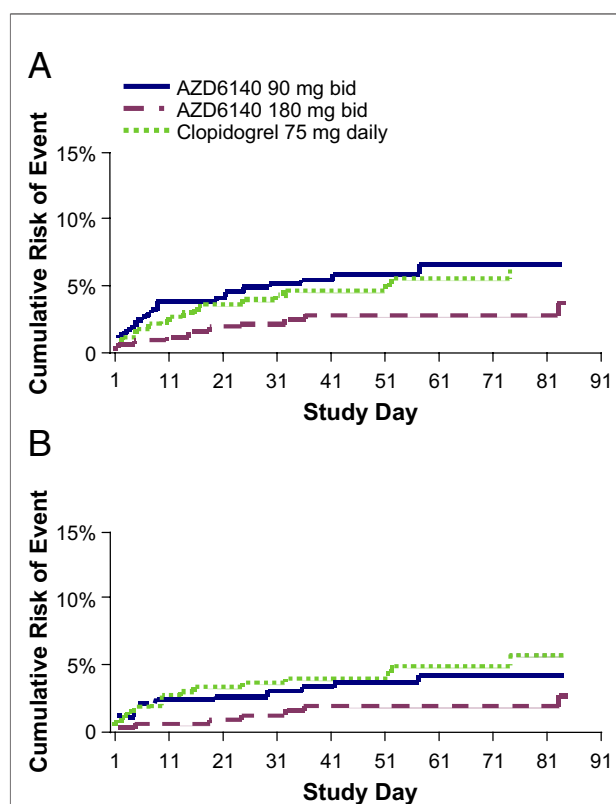
None of these rates were statistically significantly different between the treatment groups. The number of events to the 2 time points is given, with a Kaplan-Meier % estimate of the event rate. Because follow-up ranged from 4 to 12 weeks, incidence rates and Kaplan-Meier event rates will differ. Statistical testing done using a Cox proportional hazards model.

CV = cardiovascular; MI = myocardial infarction; RI = recurrent ischemia; SRI = severe recurrent ischemia.

AZD6140 90-mg (6.0%) but a numerically lower rate of 3.5% in the AZD6140 180-mg group, with a hazard ratio of 0.65 and a 95% CI of 0.30 to 1.38 (Fig. 3). Rates of periprocedural MI were 1.5% for the clopidogrel group and 2.1% and 0.9% for the AZD6140 90- and 180-mg groups, respectively. This accounted for 43% of the overall number of MI and was similar in each of the groups. No silent MIs or CABG-associated MIs were reported. After discontinuation of study medication, the number of major cardiovascular events in the clopidogrel, AZD6140 90- and 180-mg groups were 5, 12, and 6, respectively. The numbers of cardiovascular deaths were 1, 6, and 3, and MIs were 3, 3, and 2, respectively.

Table 4 lists crude incidence rates of other investigator-reported adverse events. Nonspecific factors, such as headache, were common. There appeared to be a higher rate of nausea, dyspepsia, and hypotension reported among AZD6140 recipients. Dyspnea was more common in the AZD6140 groups (Table 4). Of those who reported dyspnea, 27% of the patients had resolution of this symptom within 24 h, 25% had resolution of the dyspnea after 24 h, and 48% experienced persistent symptoms during treatment (>15 days). The overall incidence of persistent dyspnea was approximately 2% for clopidogrel, and 6% for each of the AZD6140 groups. Discontinuation rates were low and similar between groups: 6% of patients receiving AZD6140 90 mg twice a day, 7% of patients receiving AZD6140 180 mg twice a day, and 6% of patients receiving clopidogrel 75 mg once a day.

Table 5 presents the results of the arrhythmia analysis from 885 patients (89.4% of all patients enrolled). There was no difference in the rates of ventricular tachycardias among the 3 treatment groups. However, there were a greater number of mostly asymptomatic ventricular pauses


Figure 3 Kaplan-Meier Estimates of Clinical End Points

Cumulative risk of (A) composite clinical end point (cardiovascular death, myocardial infarction, or stroke), and (B) myocardial infarction events. bid = twice a day.

Table 4 Crude Incidence Rates of Investigator-Reported Adverse Events

	Clopidogrel 75 mg Daily (n = 327)	AZD6140 90 mg Twice Daily (n = 334)	p Value vs. Clopidogrel	AZD6140 180 mg Twice Daily (n = 323)	p Value vs. Clopidogrel
Dyspnea	21 (6.4)	35 (10.5)	0.07	51 (15.8)	<0.0002
Chest pain	29 (8.9)	25 (7.5)	0.57	24 (7.4)	0.57
Headache	28 (8.6)	32 (9.6)	0.69	21 (6.5)	0.37
Nausea	11 (3.4)	22 (6.6)	0.07	21 (6.5)	0.07
Dyspepsia	9 (2.8)	16 (4.8)	0.22	10 (3.1)	0.82
Insomnia	9 (2.8)	18 (5.4)	0.12	15 (4.6)	0.22
Diarrhea	11 (3.4)	10 (3.0)	0.83	24 (7.4)	0.02
Hypotension	2 (0.6)	4 (1.2)	0.004	12 (3.7)	0.01
Dizziness	10 (3.1)	14 (4.2)	0.53	11 (3.4)	0.83
Syncope	2 (0.6)	4 (1.2)	0.69	5 (1.5)	0.28
Rash	2 (0.6)	3 (0.9)	1.00	6 (1.9)	0.17

The rates are crude incidences of number of patients with reported events divided by the total number of patients in the safety cohort. Median exposure of patients was approximately 2 months. Statistical testing done with Fisher exact test.

lasting >2.5 s detected post hoc among patients receiving AZD6140 compared with those receiving clopidogrel. Of the patients who experienced pauses >5 s, 7 were due to sinus block or sinus node exit block and 4 were due to complete heart block.

Discussion

This trial evaluated the first reversible oral ADP antagonist, AZD6140, in a patient population with ACS. As reported in the DISPERSE-2 substudy companion paper (13), the doses tested yielded a level of platelet inhibition that was nearly double that of clopidogrel, indicating that more effective P2Y₁₂ inhibition is feasible. With respect to the primary objective of assessing the overall safety and tolerability of AZD6140, the current study demonstrated no significant difference, despite the higher level of platelet inhibition, between this agent and clopidogrel in the rate of protocol-defined major bleeding (which is similar to the definition of TIMI major or minor bleeding). Slightly more protocol-defined minor bleeding was observed in the AZD6140 groups, but with numerically lower rates of major bleeding. Thus, the rate of overall protocol-defined major or minor bleeding was not different among the AZD6140 and

clopidogrel groups. The bleeding rates also were not different among patients who had or had not previously received clopidogrel or among those who did or did not receive a loading dose of AZD6140 or did or did not receive glycoprotein IIb/IIIa inhibitors. Thus, in this initial experience, it appears that the higher level of inhibition of P2Y₁₂ is reasonably well tolerated, even in the face of multiple additional antithrombotic agents and with invasive procedures being performed in more than two-thirds of patients.

There was an intriguing, numerically lower rate of bleeding in AZD6140-treated patients undergoing CABG between 1 and 5 days after stopping study drug, which would be consistent with a recovery of platelet function due to the reversible binding of AZD6140 to the P2Y₁₂ receptor. However, further study in a larger number of patients is needed to confirm such a benefit with this agent, compared with the nonreversible effects of clopidogrel (or other thienopyridines). If these results were confirmed, however, the use of the reversible agent AZD6140, with a half-life of 12 h, would allow greater flexibility for use of P2Y₁₂ inhibitors. One could treat all patients at the time of presentation with ACS, but stop the treatment for patients who are found on coronary angiography to need CABG.

Table 5 Arrhythmia Events Detected on Continuous ECG Monitoring Begun at Randomization

	Clopidogrel 75 mg Once Daily n = 297, n (%)	AZD6140 90 mg Twice Daily n = 305, n (%)	AZD6140 180 mg Twice Daily n = 283, n (%)	p Values*
VTs				
Patients with sustained VT >30 s	1 (0.3)	0 (0.0)	1 (0.3)	0.49, 1.00
Patients with at least 1 NSVT	65 (22%)	67 (22%)	74 (26%)	1.00, 0.24
Patients with at least 1 triplet	93 (31%)	89 (29%)	77 (27%)	0.59, 0.32
Ventricular pauses				
Patients with at least 1 pause >2.5 s	13 (4.3%)	17 (5.5%)	28 (9.9%)	0.58, 0.014
Patients with >3 episodes of pauses >2.5 s	1 (0.3%)	6 (2.0%)	14 (4.9%)	0.12, <0.001
Patients with at least 1 pause >5 s	1 (0.3%)	5 (1.6%)	6 (2.1%)	0.22, 0.06

*p values calculated with Fisher exact test. The first compares AZD6140 90 mg versus clopidogrel, and the second AZD6140 180 mg versus clopidogrel. Ventricular tachycardia (VT) was categorized into sustained VT (lasting >30 s), nonsustained ventricular tachycardia (NSVT) (≥4 beats and <30 s in length), and triplets (3 ventricular beats). A ventricular pause was defined as either sinus or ventricular pause that results in the absence of a QRS complex that lasts for >2.5 s.

ECG = electrocardiogram.

This would avoid the need to make patients wait 5 days for CABG, as recommended in current American College of Cardiology/American Heart Association guidelines and supported by recent studies (14–16). Similarly, for patients treated chronically post-ACS, it would potentially allow greater flexibility for other types of elective surgery.

There were not sufficient numbers of clinical events to reliably determine the efficacy of AZD6140 versus clopidogrel. The overall rates of clinical events, however, were consistent with prior ACS trials, and there was an apparent dose-response in the MI rate among AZD6140 recipients, with the highest rate being observed among patients treated with clopidogrel, and lower rates among those who had received the 90- and 180-mg doses of AZD6140. The overall composite rate of cardiovascular death, MI, or stroke appeared to be numerically lower only at the higher dose, but the CIs for these clinical events are wide, and thus a large phase III trial (which is ongoing) will be required to evaluate the true efficacy of this agent. It is notable, however, that the benefit of AZD6140 in preventing MI appeared to be present both surrounding the time of PCI and also during the 1- to 3-month follow-up period, with 57% of the MIs being spontaneous in this study.

Judging by the rate of discontinuation of (blinded) study medication, the overall tolerability of AZD6140 was good, with a similar percentage of patients discontinuing study medication in each of the 3 groups. There were differences in the adverse events reported between drugs, however, with higher incidences of dyspnea, hypotension, and nausea among AZD6140 recipients. There also was a mild increase in uric acid levels with AZD6140. The number of patients who discontinued study treatment due to these reported side effects, however, was small (1% to 4% overall). Nonetheless, this observation highlights the fact that each new class of drugs has the potential for specific side effects. Thrombocytopenia or neutropenia was not observed with either AZD6140 or clopidogrel in this study.

The present study confirmed the dose-dependent increase in reported dyspnea in the AZD6140 groups as first reported in the DISPERSE study, but also reports a rate of dyspnea in the clopidogrel group. As in the DISPERSE study (12), the episodes were reported as mild or moderate in severity, were often self-limited, and rarely led to study drug discontinuation. There were not reported signs of fluid retention, congestive heart failure, or bronchospasm in the cases of AZD6140-related dyspnea, suggesting it does not relate to heart failure. Investigations are ongoing to determine if any physiologic basis might exist for this finding.

The greater number of mostly asymptomatic ventricular pauses detected post hoc in patients receiving AZD6140 was both unexpected and not previously reported in studies of AZD610. Although there is no known mechanism to explain this observation, it is possible that AZD6140, although itself not an ATP or adenosine analog, may affect adenosine metabolism. Several agents, such as dipyridamole, drafazine, and iodotubercidin, modulate intra- and paracellular adeno-

sine concentration via interference with adenosine degradation and reuptake inhibition. If AZD6140 has similar actions, it is possible that the increased incidence of asymptomatic ventricular pauses and other observed side effects of AZD6140 such as dyspnea and hyperuricemia may also be mediated via modulation of adenosine metabolism (17,18). Further assessments of the effects of AZD6140 on adenosine metabolism and on cardiac conduction are required.

Conclusions

This study has demonstrated that AZD6140 shows similar safety and tolerability to clopidogrel. Because AZD6140 is a reversible inhibitor of the P2Y₁₂ receptor, it offers the potential for flexibility with respect to more rapid initiation of coronary bypass and other surgical procedures after discontinuation of the drug. With the lack of increased major bleeding and the encouraging trends in efficacy observed in the current study, this agent is currently being studied in PLATO (PLATElet inhibition and patient Outcomes), a large outcomes trial in 18,000 patients with ACS.

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APPENDIX

For a full list of investigators, and detailed entry criteria, definitions, and statistical analysis, please see the online version of this article.

REFERENCE

Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y₁₂ antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J. 2006;27:1038-47.

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Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y₁₂ antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin

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KEYWORDS

Platelets;
Drugs;
Atherosclerosis

Aims This double-blind, parallel-group study was conducted to assess the pharmacodynamics, pharmacokinetics, and safety of AZD6140, the first oral, reversible adenosine diphosphate (ADP) receptor antagonist.

Methods and results Patients ($n = 200$) with atherosclerosis were randomized to receive AZD6140 50, 100, or 200 mg twice daily (bid) or 400 mg daily (qd) or clopidogrel 75 mg qd for 28 days. All groups received aspirin 75–100 mg qd. AZD6140 (100 and 200 mg bid, 400 mg qd) rapidly and nearly completely inhibited ADP-induced platelet aggregation after initial dosing (day 1) and at day 28. On day 1, peak final-extent inhibition of platelet aggregation (IPA) was observed 2–4 h post-dose with AZD6140, whereas clopidogrel minimally inhibited platelet aggregation (mean percentage IPA < 20%, all time points). Four hour post-dose at steady state, the three higher doses of AZD6140 produced comparable final-extent mean percentage IPA (~90–95%), which exceeded that with AZD6140 50 mg bid or clopidogrel (~60%). AZD6140 was generally well tolerated. All bleeding events, except one in a patient receiving 400 mg qd, were minor and of mild-to-moderate severity.

Conclusion AZD6140 100 and 200 mg bid were well tolerated and were superior to AZD6140 50 mg bid and clopidogrel 75 mg qd with regard to antiplatelet efficacy.

Introduction

Oral antiplatelet agents—particularly aspirin and the thienopyridines clopidogrel and ticlopidine—constitute a cornerstone of therapy for vascular disease given the integral role of platelets in the progression of atherosclerosis and in acute clinical events including myocardial infarction, ischaemic stroke, and sudden death.^{1–3} Aspirin and the thienopyridines each significantly reduce the risk of these events when given as daily therapy.^{4–6} Risk reduction is greater with adjunctive use of clopidogrel and aspirin than with aspirin alone,^{5,7,8} a finding consistent with the drugs' complementary mechanisms of action. Aspirin inhibits cyclo-oxygenase to reduce the production of the platelet activator thromboxane A₂. The thienopyridines inhibit multiple pro-aggregatory actions of the platelet agonist adenosine-5'-diphosphate (ADP) by blocking the P2Y₁₂ platelet ADP receptor.⁹

Although these antiplatelet agents have improved the management of atherosclerotic disease, additional therapeutic options are needed. Many patients experience thromboembolic events despite daily antiplatelet therapy, and aspirin and clopidogrel resistance have been observed.^{1,9–13} Additional limitations of the thienopyridines, which are prodrugs, include high interpatient variability in plasma concentrations and antiplatelet effects, relatively modest inhibition of the *ex vivo* platelet aggregation response to ADP, irreversible binding to P2Y₁₂ receptors such that recovery of platelet function is precluded, and toxicities including thrombotic thrombocytopenic purpura and neutropenia.^{14–16}

The oral, reversible P2Y₁₂ receptor antagonist AZD6140 is being developed for the prevention of thromboembolic events in patients with atherosclerosis. AZD6140 is the first of a new chemical class of antiplatelet agents, the cyclopentyltriazolopyrimidines. Like the thienopyridines, AZD6140 blocks the platelet P2Y₁₂ receptor to inhibit ADP's prothrombotic effects. Unlike the thienopyridines, which are irreversible antagonists, AZD6140 binds reversibly

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to the P2Y₁₂ receptor and nearly completely inhibits ADP-induced platelet aggregation *ex vivo*. Also unlike the thienopyridines, AZD6140 is orally active without the requirement for metabolic activation. AZD6140 has one known active metabolite that is present in blood at about one third the concentration of the parent in studies in healthy volunteers (AstraZeneca data on file, Phase I studies SC-532-5169, SC-532-5171). This metabolite is approximately as potent as AZD6140 at blocking the P2Y₁₂ receptor *in vitro* and is thought to contribute to antiplatelet effects after oral dosing with AZD6140.

In studies in healthy volunteers, AZD6140 given as single oral doses of 100–400 mg had linear pharmacokinetics, nearly completely inhibited platelet aggregation 2 h post-dose with a lessening of inhibition over the 24 h post-dose period, and was well tolerated.¹⁷ This randomized, double-blind, parallel-group study was conducted to assess the pharmacodynamics, pharmacokinetics, safety, and tolerability of AZD6140 with aspirin relative to those of clopidogrel with aspirin in patients with atherosclerotic disease. A range of AZD6140 doses was assessed with the aim of identifying doses for further investigation in larger clinical studies.

Methods

Patients

Males and postmenopausal or surgically sterile females ages 25–85 years were eligible for the study, if they had received aspirin 75–100 mg daily during at least 2 weeks before randomization for confirmed atherosclerotic disease as demonstrated by (i) a history of coronary artery disease with coronary artery stenosis $\geq 50\%$ on coronary angiogram or previously documented myocardial infarction occurring ≥ 3 months before randomization and/or (ii) peripheral artery occlusive disease (i.e. effort-induced claudication of presumed atherosclerotic origin and ankle/brachial systolic blood pressure ratio ≤ 0.85 in either leg at rest) or history of peripheral artery occlusive disease with peripheral vascular surgery or other intervention and/or (iii) carotid, vertebral, or intracerebral artery stenosis $\geq 50\%$, or previously documented ischaemic non-disabling stroke with a modified Rankin score ≤ 1 , or a transient ischaemic attack with cerebral artery stenosis $\geq 50\%$ occurring ≥ 3 months before randomization. Exclusion criteria included acute coronary syndrome within 3 months or any percutaneous intervention with balloon or stent within 4 months before randomization, conditions associated with increased risk of bleeding, screening creatinine level ≥ 1.2 times the upper limit of normal, haemoglobin $\geq 5\%$ below the lower limit of normal, platelet count $< 125 \times 10^9/L$, known active liver disease or screening laboratory tests indicative of liver disease, and use of an anticoagulant within 10 days or antiplatelet therapy other than aspirin within 7 days before randomization.

Procedures

This randomized, double-blind, double-dummy study performed at 13 sites across Denmark, Hungary, and Norway was conducted in a manner consistent with Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by the Ethics Committees in participating countries, and all patients provided written informed consent. Eligible patients were randomized to receive AZD6140 (50 mg bid, 100 mg bid, 200 mg bid, or 400 mg qd) or clopidogrel 75 mg qd for 28 days. Randomization was done by assigning patients sequentially to a code from a computer-generated randomization list generated by AstraZeneca Research and Development, Charnwood. Blinding of all study treatments was ensured by the provision of one capsule (clopidogrel or

placebo) and three tablets (AZD6140 or placebo) daily for all treatment arms using a double-dummy design. All patients received, in addition to AZD6140 or clopidogrel, aspirin 75–100 mg qd maintained at a stable dose for a given patient. Clinic visits occurred at screening, randomization (day 1), and on days 7, 14, 21, and 28.

Medications prohibited during the study included heparin, low-molecular-weight heparin, oral anticoagulants, fibrinolytic agents, glycoprotein IIb/IIIa inhibitors, prostacyclin (PGI₂), antiplatelet therapies other than the aspirin taken with study medication, digoxin, cytochrome P450 inhibitors or substrates with a narrow therapeutic index, and non-selective non-steroidal anti-inflammatory drugs.

Measures

Inhibition of platelet aggregation

The main pharmacodynamic measure was the inhibition of ADP-induced platelet aggregation as measured in duplicate by optical aggregometry of platelet-rich plasma (PRP) obtained from blood samples taken pre-dose, post-dose at 2, 4, 8, and 12 h on days 1, 14, and 28, and post-dose at 24 h on days 14 and 28. On day 28, no drug was administered at the 12 h time point for the bid regimens. Both final extent of aggregation and maximal extent of aggregation were measured in response to 20 μM ADP. Final extent of inhibition of platelet aggregation (IPA) was determined 6 min after the addition of 20 μM ADP. Final-extent IPA is mediated primarily by the P2Y₁₂ receptor, whereas maximal-extent IPA depends on both P2Y₁ and P2Y₁₂ receptors and, therefore, is only partly modifiable by P2Y₁₂ receptor antagonists.¹⁸ Effects of study medication on the inhibition of 4 $\mu g/mL$ collagen-induced platelet aggregation were also assessed with the same methods used to assess the inhibition of ADP-induced platelet aggregation.

Blood samples for the measurement of platelet aggregation were drawn from an indwelling venous cannula for repeat sampling or by direct venipuncture. On each sampling occasion, the first millilitre of blood was discarded, and saline was used to keep the cannulae patent. One 15 mL venous blood sample was collected in a plain syringe. From this sample, 7.2 mL was transferred into two tubes, each containing 0.8 mL trisodiumcitrate dihydrate.

PRP was obtained by centrifugation at room temperature for 10 min at 180g. After centrifugation, the upper turbid layer of PRP was removed, and the residual blood was centrifuged for 10 min at 1500g to obtain platelet poor plasma (PPP). The platelet count of the PRP was measured, and PPP was used to adjust the platelet count to 250 000 platelets/ μL . Preparation of PRP began within 15 min of obtaining blood samples so that aggregation studies could start 1 h (± 10 min) after the blood sampling.

Bleeding time

Bleeding times were assessed pre-dose on day 1 and 8 h post-dose on day 28 with the Simplate method at a distending venous pressure of 40 mmHg applied with a standard sphygmomanometer cuff. Blood was blotted in a systematic manner with a filter paper disc every 30 s through 30 min and, if blood flow had not ceased, every 60 s thereafter through 60 min.

Pharmacokinetics

The pharmacokinetics of AZD6140 and its active metabolite AR-C124910XX were assessed from blood samples taken pre-dose and post-dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h on days 1, 14, and 28 and post-dose at 24 h on days 14 and 28. Blood samples for measurement of drug concentrations were drawn through the same cannula used for pharmacodynamic sampling. The blood was taken into lithium heparin tubes and placed on ice until centrifugation (1500g, 4°C, 10 min) within 30 min of sampling to collect the plasma, which was transferred to plain polypropylene tubes and frozen upright at or below $-20^\circ C$ until analysis at York Bioanalytical Solutions, York, UK. Human heparinized plasma samples were assessed for total concentrations of AZD6140 and

AR-C124910XX by protein precipitation with acetonitrile followed by analysis with reversed-phase liquid chromatography and negative-ion atmospheric pressure chemical ionization tandem mass spectrometry (-APCI/LC/MS/MS). The quantification range and limit of quantification of the method for AZD6140 were 1.0–500 and 1.0 ng/mL, respectively. The corresponding values for the method for the active metabolite were 2.5–500 and 2.5 ng/mL.

Safety and tolerability

The primary tolerability measure was the incidence of adverse events, defined as any untoward medical occurrences developing or worsening after administration of study medication regardless of suspected cause. Reports of adverse events could originate from investigator observations at clinic visits, volunteer self-reports, and volunteer reports as the result of direct questioning by study personnel. Adverse events involving bleeding were classified as major or minor. A major bleeding event was defined as one that occurred in a critical site (e.g. intracranial, intraocular, spinal, pericardial, joint, or retroperitoneal), was clinically overt and led to the transfusion of ≥ 2 units of packed red cells of whole blood, was clinically overt and associated with a fall in haemoglobin ≥ 20 g/L, or was fatal. All other bleeding events were classified as minor. All adverse events including bleeding events were classified by the investigator as being mild (easily tolerated), moderate (causing discomfort that interferes with normal activities), or severe (incapacitating, preventing normal activities).

Other safety and tolerability assessments included 12-lead electrocardiograms (ECGs) obtained at screening as well as pre-dose and 3 h post-dose on days 1, 14, and 28, clinical laboratory tests (haematology, clinical chemistry, urinalysis) on days 1, 7, 14, 21, and 28, and vital signs on days 1, 7, 14, 21, and 28.

Statistics

A total of 200 patients were randomized to study treatment. With 40 patients per group, the study had precision for estimating the mean percentage IPA for each dose group in the study within $\pm 10\%$ and the ability to distinguish differences of ~ 8 –12% between the mean of any AZD6140 group and the mean of the clopidogrel group. The primary outcome variable of interest was the final extent percentage inhibition of ADP-induced platelet aggregation, as this measure best reflects P2Y₁₂ receptor blockade. No formal hypothesis testing was undertaken, but confidence intervals were provided for the primary outcome variable to assist in the interpretation of results. All other data were summarized with descriptive statistics. All patients, who were randomized to treatment and received at least one dose of study medication, were included in the analysis of platelet aggregation, bleeding time, pharmacokinetics, and safety outcome variables.

Inhibition of platelet aggregation

Mean percentage inhibition of ADP- and collagen-induced platelet aggregation (final extent and maximal extent) for each measured time point on days 14 and 28 was summarized as percentage change from the pre-dose baseline aggregation value on day 1. Percentage-inhibition values in the range of 0–100% were recorded; any value falling outside that range was truncated to the appropriate limit. Differences in least squares mean values between treatment groups were calculated from an analysis of covariance (ANCOVA) with factors for treatment group and country and a covariate for baseline platelet aggregation. The ANCOVA model accounted for the expected heterogeneity of variance within each treatment group. The treatment group comparisons of primary interest were the four pairwise comparisons with clopidogrel. No adjustment to the significance levels and corresponding confidence intervals were made.

Bleeding times

Mean and median bleeding times on days 1 and 28 were calculated. Bleeding times of 60 min or longer were recorded as ≥ 60 min rather than the exact value.

Pharmacokinetics

For AZD6140 and its active metabolite, area under the plasma concentration vs. time curve (AUC), maximum plasma concentration (C_{\max}), time to C_{\max} (t_{\max}), apparent terminal half-life ($t_{1/2}$), and total plasma oral clearance (CL/F) were estimated using actual sampling times in non-compartmental analyses. The AUC was calculated using the linear trapezoidal rule. The $t_{1/2}$ was calculated as $\ln(2)/k$. The CL/F was calculated as dose/AUC. Pharmacokinetic parameters were summarized for each treatment group as a function of gender or age (≤ 65 years, > 65 years).

Safety and tolerability

Adverse events, clinical laboratory tests, vital signs, and results of 12-lead ECGs were summarized for each treatment group with descriptive statistics for all patients who received at least one dose of study medication.

Results

Patients

From September 2003 to December 2003, 201 patients were randomized, of whom one withdrew before receiving study medication and 200 received study medication (AZD6140 50 mg bid $n = 41$, 100 mg bid $n = 39$, 200 mg bid $n = 37$, 400 mg qd $n = 46$, clopidogrel 75 mg qd $n = 37$) (Figure 1). Of the 200 patients who received study medication, 185 completed the study and 15 prematurely withdrew. Reasons for withdrawal were adverse events ($n = 10$), failure to meet eligibility criteria ($n = 1$), and other miscellaneous reasons ($n = 4$) (Table 1). Pharmacodynamic, pharmacokinetic, and safety/tolerability data were summarized for all 200 patients who received at least one dose of study medication.

Demographics and baseline clinical characteristics were comparable among treatment groups (Table 1). All patients had atherosclerotic disease, although the distributions of patients having particular disorders varied slightly among treatment groups (Table 1). Concomitant medications, the most common of which were statins and beta-blockers (Table 1), were balanced across treatment groups.

Inhibition of platelet aggregation

AZD6140 inhibited ADP-induced platelet aggregation (final extent) at 2 h post-dose after initial dosing (day 1) and at steady state (day 28) (Figure 2). With AZD6140 100 mg bid, 200 mg bid, and 400 mg qd, the magnitude of inhibition at steady state was greater than that with either AZD6140 50 mg bid or clopidogrel (Figure 2 and Table 2). Least squares mean differences between the three higher doses of AZD6140 and clopidogrel in percentage IPA ranged from 25 to 30% on day 14 and from 24 to 31% on day 28 (Table 2). The three higher doses of AZD6140 did not substantially differ from one another with respect to mean percentage IPA. A similar pattern of results was observed for maximal-extent IPA although, as expected, inhibition was lower for maximal extent than final extent (Figure 2). Figure 3 shows mean and median percentage IPA (final extent and maximal extent) and 10th, 25th, 75th, and 90th percentile values pre-dose and 4 h post-dose on day 14.

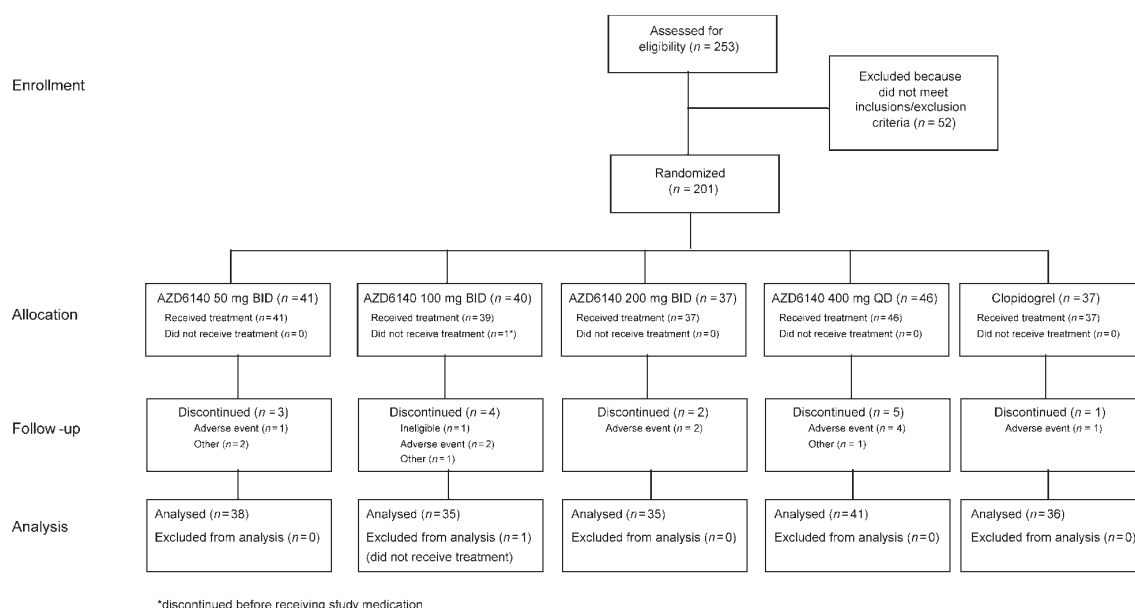


Figure 1 Patient disposition showing enrolment to the completion of study.

Table 1 Patient disposition, demographics, and baseline clinical characteristics

	AZD6140				
	50 mg bid (<i>n</i> = 41)	100 mg bid (<i>n</i> = 39)	200 mg bid (<i>n</i> = 37)	400 mg qd (<i>n</i> = 46)	Clopidogrel (<i>n</i> = 37)
Patient disposition, <i>n</i>					
Randomized	41	40	37	46	37
Entered treatment	41	39	37	46	37
Discontinued early	3	4	2	5	1
Completed study	38	35	35	41	36
Male, <i>n</i> (%)	27 (66)	29 (74)	28 (76)	36 (78)	26 (70)
White race, <i>n</i> (%)	41 (100)	39 (100)	37 (100)	46 (100)	37 (100)
Mean (SD) age (years)	64 (10.3)	63 (9.3)	64 (7.9)	64 (10.1)	61 (9.4)
Mean (SD) weight (kg)	79 (14.3)	79 (12.9)	83 (18.7)	81 (12.5)	81 (16.9)
Hypertension, <i>n</i> (%)	20 (49)	20 (51)	21 (57)	27 (59)	15 (41)
Diabetes, <i>n</i> (%)	11 (27)	4 (10)	9 (24)	3 (7)	8 (22)
Atherosclerotic disease, <i>n</i> (%)					
Coronary artery disease	26 (63)	20 (51)	28 (76)	31 (67)	29 (78)
Peripheral artery disease	9 (22)	10 (26)	5 (14)	7 (15)	4 (11)
Cerebrovascular disease	4 (10)	3 (8)	3 (8)	3 (7)	4 (11)
Cardiovascular history, <i>n</i> (%)					
Myocardial infarction	26 (63)	20 (51)	24 (65)	29 (63)	23 (62)
Stroke	6 (15)	7 (18)	4 (11)	12 (26)	3 (8)
Transient ischaemic attack	3 (7)	1 (3)	3 (8)	1 (2)	2 (5)
Current smoking status, <i>n</i> (%)					
Non-smoker	21 (54)	25 (64)	28 (76)	31 (67)	25 (68)
Smoker	19 (46)	14 (36)	9 (24)	15 (33)	12 (32)
Most common concomitant medications, <i>n</i> (%) ^a					
Statins	31 (76)	28 (72)	31 (84)	30 (65)	31 (84)
Beta-blockers	21 (51)	19 (49)	24 (65)	27 (59)	24 (65)
Angiotensin-converting enzyme inhibitors	11 (27)	15 (38)	17 (46)	14 (30)	11 (30)
Organic nitrates	8 (20)	5 (13)	14 (38)	10 (22)	9 (24)
Dihydropyridine derivatives	9 (22)	7 (18)	10 (27)	12 (26)	5 (14)
Sulfonamides (diuretics)	5 (12)	6 (15)	6 (16)	9 (20)	5 (14)
Angiotensin II antagonists	6 (15)	2 (5)	2 (5)	10 (22)	4 (11)

^aConcomitant medications used by >20% of patients in any treatment group are listed. Aspirin, which was used by all patients, is not included in this listing.

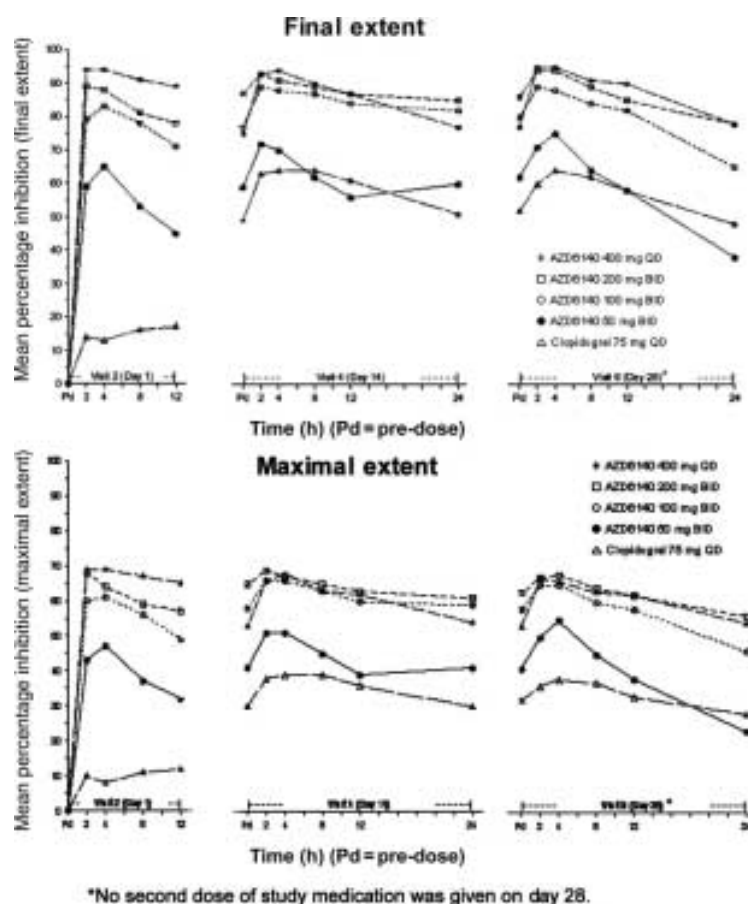


Figure 2 Mean percentage inhibition of ADP-induced platelet aggregation (final extent, top graph; maximal extent, bottom graph) in patients with atherosclerotic disease treated with AZD6140 50 mg bid, 100 mg bid, 200 mg bid, or 400 mg qd or clopidogrel 75 mg qd for 28 days.

Table 2 Least squares mean and median differences between AZD6140 and clopidogrel for percentage inhibition of ADP-induced platelet aggregation (final extent)

Comparison with clopidogrel	n ^a	Least squares mean difference (SEM) and 95% CI	Median difference and 95% CI
Day 14, 4 h post-dose			
AZD6140 50 mg bid	75	7 (5.1) -4, 17	7 -3, 18
AZD6140 100 mg bid	73	25 (4.2) 16, 33	23 14, 33
AZD6140 200 mg bid	72	27 (4.3) 18, 36	25 18, 34
AZD6140 400 mg qd	81	30 (4.1) 22, 38	29 19, 38
Day 28, 4 h post-dose			
AZD6140 50 mg bid	73	11 (4.5) 2, 20	13 3, 23
AZD6140 100 mg bid	70	24 (3.7) 16, 31	25 16, 33
AZD6140 200 mg bid	68	30 (3.5) 23, 37	30 20, 40
AZD6140 400 mg qd	76	31 (3.4) 24, 38	31 23, 40

^aThe combined numbers of patients for each treatment group comparison on therapy.

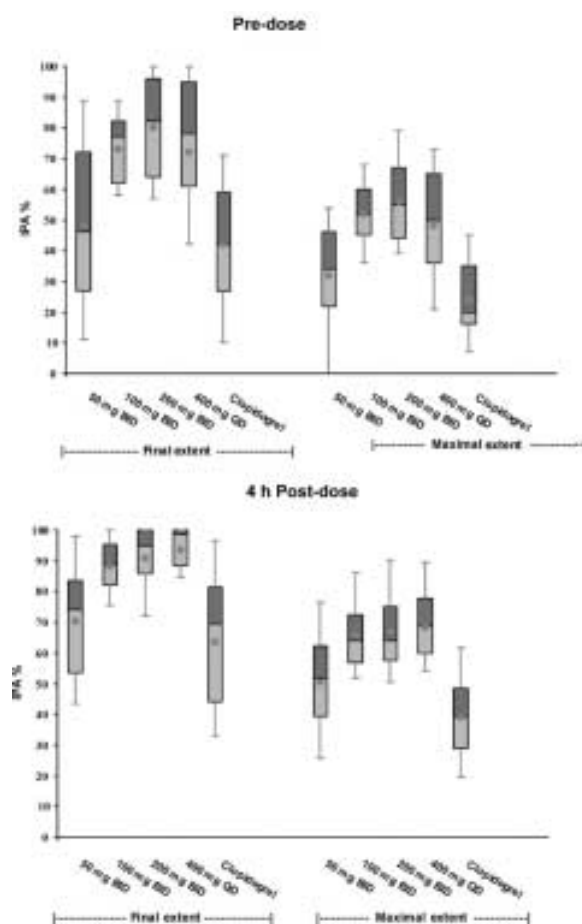


Figure 3 Mean and median percentage IPA (final extent and maximal extent) and 10th, 25th, 75th, and 90th percentile pre-dose (top graph) and 4 h post-dose (bottom graph) on day 14. The line within the box represents the median. The circle represents the mean. Upper and lower edges of the box represent the 75th and 25th percentiles. Upper and lower whiskers represent the 90th and 10th percentiles, respectively.

The pattern of results for the inhibition of collagen-induced platelet aggregation was comparable to that for the inhibition of ADP-induced platelet aggregation (Figure 4). The magnitude of inhibition of collagen-induced platelet aggregation was similar to that of maximal-extent ADP-induced aggregation. This finding is in keeping with the sensitivity of ADP-induced platelet aggregation, but not collagen-induced platelet aggregation, to ADP-receptor antagonists.

Bleeding times

Bleeding times on day 28 were increased relative to the day 1 baseline in all treatment groups (Table 3). AZD6140 (all doses) appeared to increase bleeding times to a greater extent than clopidogrel, but no obvious dose-response relationship was observed.

Pharmacokinetics

Plasma concentrations of AZD6140 and its active metabolite AR-C124910XX increased linearly and dose proportionally on day 1 and were stable and predictable at steady state, which was achieved by day 14 (Table 4 and Figure 5). At day 28, AZD6140 200 mg bid and 400 mg qd exhibited slightly greater than dose-proportional pharmacokinetics with dose-normalized AUCs that were ~50% more than dose-proportional and with correspondingly lower CL/F relative to the 50 mg and 100 mg bid regimens. Exposure to AR-C124910XX at steady state was ~35% of exposure to AZD6140. AZD6140 and AR-C124910XX C_{max} and AUC did not vary significantly as a function of sex (male, female) or age (≤ 65 years, > 65 years).

Pharmacokinetic/pharmacodynamic relationship

The onset of maximum IPA effect was rapid and corresponded with the time of maximum plasma concentrations. Increases in dose beyond 100 mg bid resulted in only small additional increases in IPA. The 100 mg bid regimen had peak blood levels of about 800 ng/mL. The 200 mg bid dose, which had concentrations more than two-fold

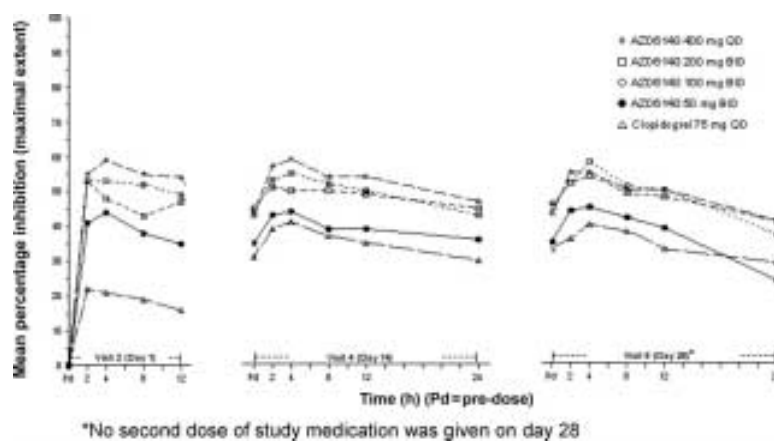


Figure 4 Mean percentage inhibition of collagen-induced platelet aggregation (maximal extent) in patients with atherosclerotic disease treated with AZD6140 50 mg bid, 100 mg bid, 200 mg bid, or 400 mg qd or clopidogrel 75 mg qd for 28 days. Final-extent data (data not shown) were comparable to the maximal-extent data.

Table 3 Actual bleeding time minutes (day 28 vs. day 1)

Treatment group	<i>n</i>	Median (range)
AZD6140 50 mg bid		
Day 1	41	5.0 (2.0–60.0)
Day 28	38	14.8 ^a (3.0–60.0)
AZD6140 100 mg bid		
Day 1	39	5.0 (1.0–10.0)
Day 28	36	17.8 ^a (4.8–60.0)
AZD6140 200 mg bid		
Day 1	37	5.5 (2.8–9.5)
Day 28	36	23.0 ^a (4.0–60.0)
AZD6140 400 mg qd		
Day 1	46	5.1 (2.5–16.5)
Day 28	43	15.5 ^a (2.3–60.0)
Clopidogrel 75 mg qd		
Day 1	37	5.0 (0.0–15.0)
Day 28	36	10.5 ^a (3.6–60.0)

^aAt least one bleeding time >60 min was recorded.

higher than the 100 mg bid dose, yielded only a small increase in IPA.

Safety and tolerability

The most common adverse event was bleeding, the incidence of which increased with the three higher doses of AZD6140 compared with AZD6140 50 mg bid and clopidogrel (Table 5). One major bleeding event (gastrointestinal haemorrhage with drop in haemoglobin) in a patient receiving AZD6140 400 mg qd was reported. The remaining bleeding events were classified as minor and of mild-to-moderate severity. Bleeding excepted, adverse events reported in at least 10% of patients in any treatment group were dyspnoea, dizziness, headache, and red blood cells in the urine (Table 5). The incidence of dyspnoea appeared to increase with increasing dose of AZD6140 (reported in 10% of patients with AZD6140 50 mg bid and 100 mg bid, 16% of patients with 200 mg bid, and 20% of patients with 400 mg qd). Among the 23 AZD6140-treated patients with dyspnoea, 29 instances of dyspnoea (21 considered mild and eight considered moderate) were reported. None of the incidents of dyspnoea was considered to be serious, and none was associated with congestive heart failure or bronchospasm.

No deaths occurred during the study. In the AZD6140 groups, the numbers of patients withdrawing prematurely from the study because of adverse events were one (for a minor bleeding event) for 50 mg bid, two (for dyspnoea/diarrhoea, a minor bleeding event) for 100 mg bid, two (for a minor bleeding event, an overdose) for 200 mg bid, and four (for three minor bleeding events, one major bleeding event) for 400 mg qd. One clopidogrel-treated patient withdrew prematurely because of an adverse event (polyarthrititis).

No notable time- or treatment-related changes in any haematology, clinical chemistry, or urinalysis parameters were observed with the exception of changes in mean uric acid levels (increases of 5–10% in all AZD6140 groups and a decrease of ~10% in the clopidogrel group). No treatment-related changes in vital signs or 12-lead ECGs were observed.

Table 4 Mean (coefficient of variation %) pharmacokinetic parameters of AZD6140 and its active metabolite AR-C124910XX

	AZD6140 50 mg bid				AZD6140 100 mg bid				AZD6140 200 mg bid				AZD6140 400 mg qd			
	Day 1	Day 14	Day 28		Day 1	Day 14	Day 28		Day 1	Day 14	Day 28		Day 1	Day 14	Day 28	
AZD6140																
<i>n</i>	41	39	38		39	34	33		37	32	35		46	42	39	
<i>t</i> _{max} (h)	3.66 (41)	2.54 (56)	3.33 (56)		3.05 (50)	2.82 (74)	2.52 (55)		3.09 (57)	2.61 (69)	2.74 (82)		2.03 (63)	2.41 (149)	2.12 (71)	
<i>C</i> _{max} (ng/mL)	287 (70)	375 (50)	387 (57)		594 (55)	810 (41)	798 (59)		1224 (35)	2278 (31)	2200 (41)		3374 (41)	3653 (41)	3827 (42)	
AUC (ng h/mL)	1640 (50)	2666 (47)	2688 (56)		3648 (56)	5530 (48)	5337 (45)		7581 (35)	16 364 (39)	15 104 (39)		NA	31 723 (43)	31 338 (53)	
CL/F (L/h)	NA	22.9 (45)	23.7 (48)		NA	21.6 (42)	22.6 (44)		NA	13.7 (34)	15.3 (39)		NA	15.0 (41)	15.6 (39)	
AR-C124910XX																
<i>n</i>	41	39	38		39	34	33		37	32	35		46	42	39	
<i>t</i> _{max} (h)	4.23 (33)	3.31 (65)	3.25 (61)		3.69 (32)	3.00 (42)	3.22 (45)		3.71 (43)	3.31 (63)	3.16 (69)		3.17 (41)	3.24 (49)	3.26 (53)	
<i>C</i> _{max} (ng/mL)	73 (109)	114 (48)	118 (61)		135 (50)	261 (41)	239 (38)		271 (39)	654 (41)	660 (51)		595 (32)	848 (41)	860 (47)	
AUC (ng h/mL)	418 (58)	915 (45)	906 (48)		899 (46)	2108 (40)	1881 (32)		1753 (32)	5448 (37)	5268 (41)		—	10 233 (38)	10 446 (45)	

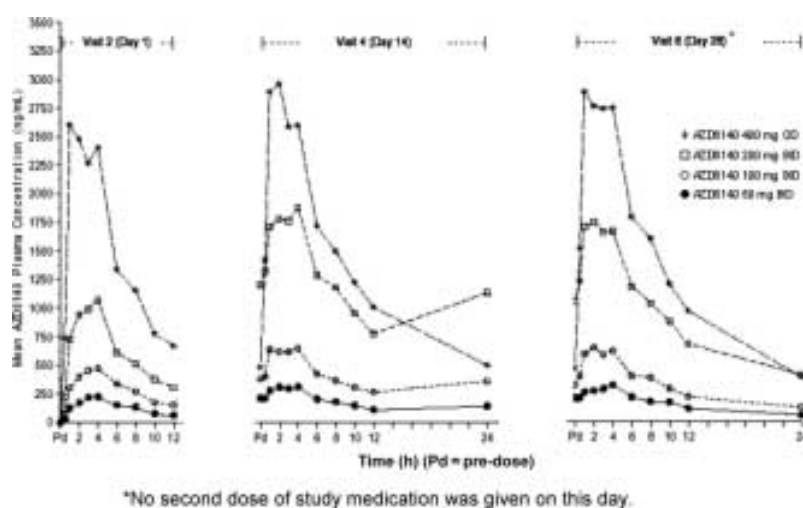


Figure 5 Mean plasma concentrations of AZD6140 vs. time in patients with atherosclerosis treated with AZD6140 50 mg bid, 100 mg bid, 200 mg bid, or 400 mg qd for 28 days. (Data are from all patients who received at least one dose of study medication and had valuable pharmacokinetic data.)

Table 5 Number (percentage) of patients with adverse events

	AZD6140				Clopidogrel 75 mg qd
	50 mg bid	100 mg bid	200 mg bid	400 mg qd	
Minor bleeding events ^a	12 (29)	17 (44)	19 (51)	22 (48)	12 (32)
Venipuncture site bruise	1 (2)	0 (0)	1 (3)	2 (4)	4 (11)
Epistaxis	1 (2)	4 (10)	4 (11)	8 (17)	2 (5)
Contusion	5 (12)	9 (23)	9 (24)	12 (26)	8 (22)
Red blood cells in urine	3 (7)	0 (0)	4 (11)	0 (0)	1 (3)
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)

Adverse events reported in at least 10% of patients in any treatment group are listed.

^aNumber (percentage) of patients with at least one minor bleeding event. A given patient could have experienced more than one minor bleeding event.

Discussion

In this randomized, double-blind study, the first to investigate AZD6140 in patients with atherosclerosis, AZD6140 100 mg bid, 200 mg bid, and 400 mg qd rapidly and nearly completely inhibited P2Y₁₂-mediated platelet aggregation as measured by optical aggregometry after initial dosing and at steady state. These three doses of AZD6140 were associated with greater steady-state IPA than AZD6140 50 mg bid or clopidogrel 75 mg qd. The pattern of results was similar regardless of whether platelet aggregation inhibition was assessed from the final extent of aggregation (i.e. that observed at the end of the platelet aggregation response) or from the maximal extent of aggregation. However, as expected, maximal-extent measures were associated with smaller absolute responses than final-extent measures. Maximal-extent platelet aggregation inhibition is only partly modifiable by a P2Y₁₂ receptor antagonist because it depends on both P2Y₁ and P2Y₁₂ receptors.¹⁸ The final-extent response is more sensitive to modification by a P2Y₁₂ receptor antagonist because it is mediated

primarily by the P2Y₁₂ receptor. The pattern of results for the inhibition of collagen-induced platelet aggregation was comparable to that for the inhibition of maximal ADP-induced platelet aggregation (Figure 4), a finding that confirms that at least part of the aggregation response is mediated by interaction with P2Y₁₂ receptors.¹⁹

The early onset of peak IPA, occurring by 2 h post-dose on the first day of dosing with AZD6140, distinguishes it from clopidogrel, which minimally inhibited platelet aggregation on day 1. The latter finding is consistent with the previous observation that, with the maintenance dose of 75 mg, clopidogrel does not achieve full antiplatelet activity for 4–8 days.³ Although loading doses have been used in an attempt to circumvent this problem, neither the best timing nor the best dose for a prompt antiplatelet effect of clopidogrel have been firmly established, particularly for acute applications.⁹ Loading doses of AZD6140 and clopidogrel were not administered in this study because study medication was not initiated during the acute disease state. Additional studies will compare loading doses of the drugs.

In addition to having an earlier onset of effect than clopidogrel, AZD6140 more robustly inhibited platelet aggregation in this study. All three of the higher doses of AZD6140 (100 mg bid, 200 mg bid, and 400 mg qd) showed higher levels of platelet inhibition than clopidogrel 75 mg qd both at the initiation of therapy (day 1) and at steady state (day 14 and 28). IPA with AZD6140 was reversible as indicated by the declining levels of platelet inhibition at 24 h after the last dose. Reversibility may be an important characteristic in some clinical settings, such as surgery, in which recovery of platelet function is needed sooner than the 5–7 days required for clopidogrel. IPA with the three highest doses of AZD6140 remained higher than that with clopidogrel at 24 h on day 28, when only a single dose was administered. This finding shows that platelet inhibition remains adequate if a dose is missed.

The level of IPA achieved with clopidogrel in this study is consistent with that in previous studies of the drug.^{20,21} Clopidogrel only moderately inhibits the *ex vivo* platelet aggregation response to ADP. The magnitude of IPA by clopidogrel is highly variable between patients, and resistance to the antiplatelet effects of clopidogrel has been observed.^{10–13} The degree of resistance to clopidogrel inhibition of ADP-induced platelet aggregation was directly related to degree of risk for a recurrent cardiovascular event in a study of 60 patients who had suffered acute myocardial infarction.¹¹

Both AZD6140 and clopidogrel were given with aspirin in this study, a practice consistent with present use of the currently available P2Y₁₂ antagonists in clinical practice. Clopidogrel 75 mg qd with aspirin 75–325 mg per day, a regimen comparable to that assessed in this study, reduced the risk of a cardiovascular event of death, myocardial infarction, or stroke by 20% relative to the reduction in risk by aspirin alone in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study, which had a mean treatment duration of 9 months.⁵ The aspirin dosage of 75–100 mg chosen for use in this study was supported by the *post hoc* analysis of the CURE study, which shows this dose range to be optimal when aspirin is combined with clopidogrel.²²

Pharmacokinetic data show that plasma concentrations of AZD6140 and its active metabolite AR-C124910XX were stable and predictable. Pharmacokinetics were linear after initial dosing on day 1 and slightly greater than dose-proportional at the 200 mg bid and 400 mg qd doses at steady state. Pharmacokinetic parameters were not affected by sex or age.

The onset and magnitude of effect of AZD6140 on IPA appear to be related to plasma concentrations of AZD6140 and its metabolite given that the mean time to peak IPA (IPA_{max}) (2–4 h across AZD6140 doses) mirrored the mean *t*_{max} of 2–3 h for both AZD6140 and its metabolite. Results for the active metabolite in this study in patients with atherosclerosis are similar to previous findings in healthy volunteers (AstraZeneca data on file, Phase I studies SC-532-5169, SC-532-5171). The parent compound accounts for the majority of the antiplatelet effect.

AZD6140 was generally well tolerated across the dose range evaluated in this study. All bleeding events except one in a patient receiving 400 mg qd were considered to be minor. The observed events were those expected with antiplatelet therapy (i.e. skin and mucous-membrane

bleeds). The only two adverse events that appeared to increase in incidence with dose of AZD6140 were minor bleeding events and dyspnoea, all instances of which were mild or moderate. Dyspnoea, a non-specific symptom that has previously been reported with clopidogrel, was not reported with clopidogrel in this study and has not previously been reported with AZD6140. The frequency of dyspnoea after administration of AZD6140 and its aetiology will be investigated further in future studies.

In conclusion, AZD6140 100 mg and 200 mg bid appeared to have a more beneficial safety and tolerability profile than AZD6140 400 mg qd and were superior to AZD6140 50 mg bid and clopidogrel 75 mg qd with regard to antiplatelet efficacy. For these reasons, these two doses have been carried forward for further clinical evaluation.

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Conflict of interest: none declared.

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**Appendix to Advisory Committee Briefing
Document - Efficacy**

Drug	Ticagrelor
Study Code	D5130C00000
Edition	1
Date	23 June 2010

**BRILINTA Advisory Committee Briefing Document
Appendix B (Efficacy)**

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APPENDIX FOR EFFICACY

[Table 1](#) presents the efficacy endpoint definitions in PLATO.

[Figure 1](#) depicts the actual treatment pathways for patients in the PLATO study. Each junction represents a clinical decision or classification. Multiple tests of robustness of efficacy results in PLATO confirm the advantage of ticagrelor over clopidogrel. These include the secondary efficacy endpoints presented above, and also analyses corresponding to subgroups formed along the patient journey depicted in [Figure 1](#). Each junction represents a clinical decision or classification.

Table 1 Efficacy endpoint definitions in PLATO

Endpoint	Subtype	Definition
Myocardial infarction	Recurrent MI within 18 hours of onset of a previous MI	New ST elevation of ≥ 1 mm (0.1 mV) in at least 2 contiguous leads <u>and</u> recurrent cardiac ischemic symptoms ^a ≥ 20 minutes at rest ^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: - Recurrent cardiac ischemic symptoms ^a ≥ 20 minutes at rest ^b or - One of the following ECG changes - New ST elevation of ≥ 1 mm (0.1 mV) in at least 2 contiguous leads - Development of new pathological Q waves ^c on the ECG - New LBBB.
	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 ^d with at least 1 of the following: - Recurrent cardiac ischemic symptoms ^a ≥ 20 minutes at rest ^b - Development of new pathological Q waves ^c on the ECG - ECG changes indicative of ischemia ^e or - Pathological findings of an acute MI.
	MI within 24 hours after PCI	- CK-MB ≥ 3 x local or central laboratory upper normal limit ^f , and, if the pre-PCI CK-MB was $> \text{ULN}$, 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 - Development of new pathological Q waves ^c on the ECG (no symptoms are required).

Table 1 **Efficacy endpoint definitions in PLATO**

Endpoint	Subtype	Definition
	MI within 24 hours after CABG	<ul style="list-style-type: none"> - CK-MB ≥ 5x local or central laboratory upper normal limit^f, 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^c on the ECG (no symptoms are required) or - CK-MB ≥ 10x local or central laboratory upper normal limit^f 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).
	For patients who die of suspected MI and for whom no myocardial necrosis biomarkers were obtained	<ul style="list-style-type: none"> - The presence of new ST-segment elevation^e and new cardiac ischemic symptoms^a or - Pathological evidence of an acute MI.
	Silent MI	Development of new or presumed new pathological Q waves ^c , in the absence of cardiac ischemic symptoms ^a .
Recurrent cardiac ischemia	Recurrent cardiac ischemia	Cardiac ischemic symptoms ^g ≥ 10 minutes at rest ^h , resulting in hospitalization if an outpatient or prolongation of hospitalization if an inpatient but not fulfilling criteria for MI.

Table 1 **Efficacy endpoint definitions in PLATO**

Endpoint	Subtype	Definition
	Severe recurrent cardiac ischemia	<p>Recurrent cardiac ischemia and at least one of the following, but not fulfilling the criteria for MI:</p> <ul style="list-style-type: none"> -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) -Leading to urgent revascularization (PCI or CABG) unless not advised on reasoned grounds. <p>Urgent revascularization (PCI or CABG) must occur during the same hospitalization as an in-patient episode of recurrent ischemia or be performed during the rehospitalization 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 (ie, 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).</p>

Table 1 **Efficacy endpoint definitions in PLATO**

Endpoint	Subtype	Definition
Stroke/TIA	Stroke	<p>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.</p> <p>Stroke will be further sub-classified as:</p> <ul style="list-style-type: none"> - Hemorrhagic: A stroke with documentation of intracranial hemorrhage on imaging (eg, 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).
	TIA	<p>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.</p>
Other arterial thrombotic events		<p>Other arterial thrombotic events include events such as renal infarction, retinal infarction, bowel infarction or foot amputation or gangrene due to peripheral ischemia. For inclusion in the third secondary composite efficacy endpoint the event must either require hospitalization if an outpatient or prolong hospitalization if an inpatient.</p>

Table 1 **Efficacy endpoint definitions in PLATO**

Endpoint	Subtype	Definition
Death		<p>All deaths reported post-enrollment will be recorded and adjudicated.</p> <p>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:</p> <ul style="list-style-type: none"> - Vascular death: sudden death, MI, UA, 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 (eg, liver failure or renal failure). <p>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. Death within 30 days of an MI should not be reported as an SAE, but should be reported as two endpoints, MI and Death. [Note: for Drug Safety reporting purposes any death with unknown/uncertain cause should be reported as death, if the cause of death becomes known, then the cause is reported as the SAE.]</p>

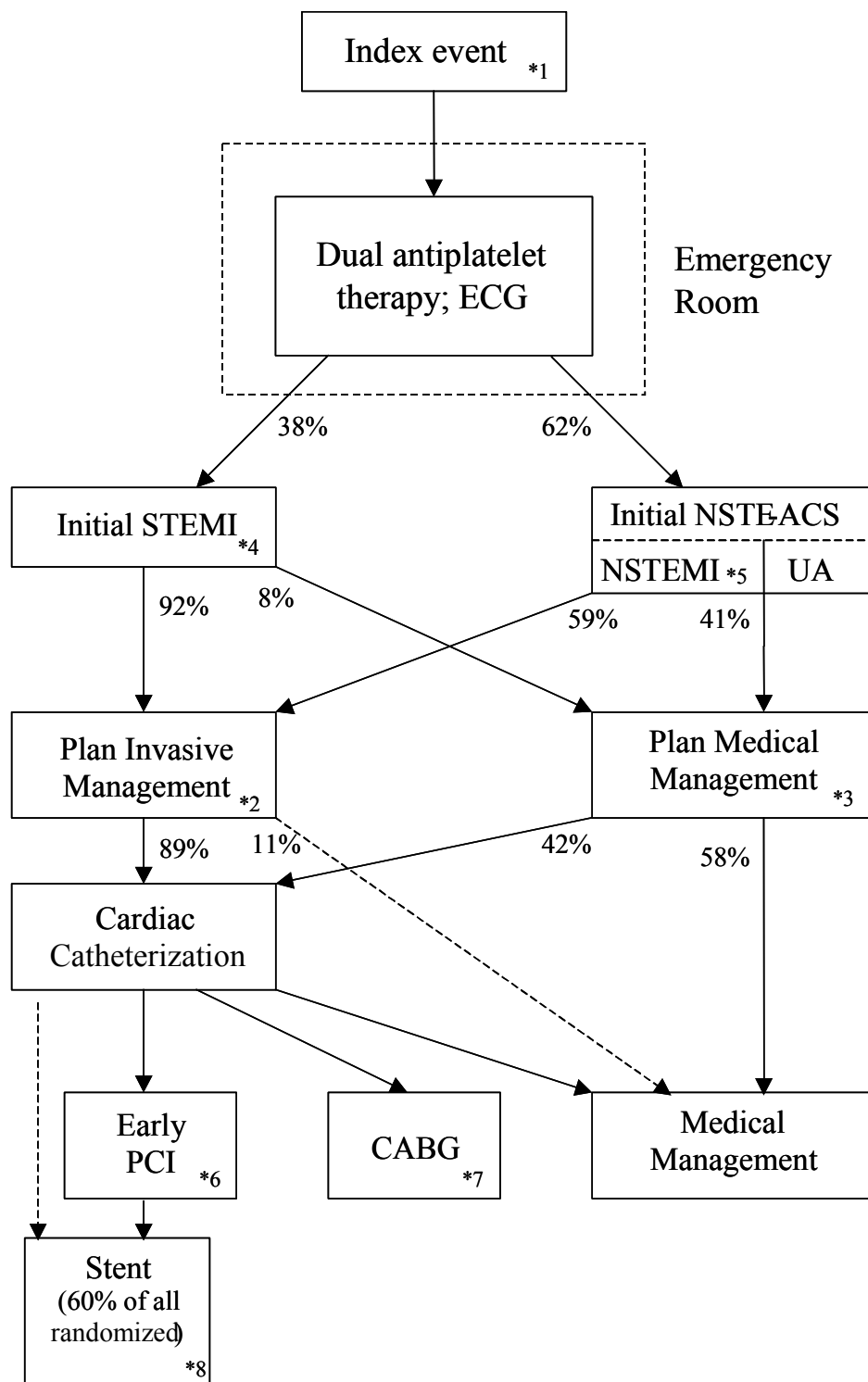
Table 1 Efficacy endpoint definitions in PLATO

Endpoint	Subtype	Definition
Stent thrombosis	Definite stent thrombosis ⁱ	<p>Angiographic confirmation of stent thrombosis^j</p> <p>The presence of a thrombus^c 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 time window:</p> <ul style="list-style-type: none"> - Acute onset of ischemic symptoms at rest - New ischemic ECG changes that suggest acute ischemia <ul style="list-style-type: none"> - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI) - Nonocclusive thrombus: <p>Intracoronary thrombus is 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 a visible embolization of intraluminal material downstream.</p> - Occlusive thrombus: <p>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).</p> <p>Pathological confirmation of stent thrombosis:</p> <p>Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.</p>
	Probable stent thrombosis	<p>Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:</p> <ul style="list-style-type: none"> - Any unexplained death within the first 30 days^l - 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.

Table 1 Efficacy endpoint definitions in PLATO

Endpoint	Subtype	Definition
	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.
Data derived from CSR D5130C05262.		
^a	Cardiac ischemic symptoms: chest pain or discomfort or equivalent (eg, neck or jaw symptoms, dyspnoea believed to represent an angina pectoris equivalent) believed due to impaired coronary flow secondary to atherosclerotic disease.	
^b	At rest: started with exercise or spontaneously and did not resolve with rest.	
^c	Development of pathological Q waves: Development of any new or presumed new Q waves that are ≥ 0.03 sec in width and ≥ 1 mm (0.1 mV) in depth in at least 2 contiguous leads.	
^d	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 $\mu\text{g/L}$. 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 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.	
^e	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.	
^f	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.	
^g	Cardiac ischemic symptoms: chest pain or discomfort or equivalent (eg, neck or jaw symptoms, dyspnoea 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	Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.	
^j	The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).	
^k	Intracoronary thrombus.	
^l	For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.	

Figure 1 Treatment pathways for ACS patients in PLATO



Numbered asterisks denote population subgroups with specific pre-specified analyses, either in the formal statistical hierarchy of testing, or exploratory.



**Appendix to Advisory Committee Briefing
Document – Treatment-by-region interaction**

Drug	Ticagrelor
Study Code	D5130C00000
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**BRILINTA Advisory Committee Briefing Document
Appendix C (Treatment-by-region interaction)**

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1. LIKELIHOOD OF SPURIOUS FINDINGS WITHOUT MULTIPLE ADJUSTMENT

Table 1 Likelihood of spurious findings without multiple adjustment

Correlation between tests	Probability of at least 1 significant test	Equivalent adjusted p-value to retain overall false-positive error rate at 5%
0	0.7910	0.002
0.5	0.5126	0.004
0.95	0.1294	0.019
0.99	0.0790	0.031

This analysis provides the probability of observing at least 1 significant result by chance alone out of 31 tests based on 5000 simulations of a multivariate Normal distribution. With 31 statistical tests, the probability of observing at least one test with $p < 0.05$ by chance alone is high unless tests are very highly correlated. For example, if the correlation between tests was 0.5, the probability of observing at least one chance finding is over 50%. An adjusted p-value of 0.004 would need to be applied to each of the 31 tests to retain overall false-positive error rate at 5%. By this measure, the observed treatment by region interaction with $p = 0.045$ would fail to reach significance. Even with a correlation between tests as implausibly high as 0.95, the probability of at least one chance finding is approximately 13% and an adjusted p-value of 0.019 would need to be applied to each test to control the overall false-positive error rate. And, again, the observed treatment by region interaction would fail to reach significance.

2. RESULTS OF MULTIVARIATE ANALYSIS – FULL PLATO POPULATION

An exploratory multivariate analysis of the overall trial population including all factors evaluated in the study was conducted. The analysis was complex, in that it included terms for each factor as well as 2-way terms for each factor by country (US vs non US) interaction, 2-way terms for each factor by randomised treatment (US vs non US) interaction and, finally, 3-way terms for terms for each factor by country (US vs non US) by randomized treatment interaction. Given the large number of terms included, a Cox model was used with a stepwise procedure with a $p=0.1$ threshold for entry and exit into the model. Results for the resultant final model are shown below. While many of the terms retained in the MV were prognostic for the primary endpoint, as shown in the **bolded** font, only ASA maintenance dose during therapy and troponin status demonstrated a significant treatment-by-region interaction, of which only maintenance dose during therapy showed a qualitative interaction with randomized treatment.

Table 2 **Multivariate analysis in the full PLATO population – PLATO full analysis set**

Factor	Degrees of freedom	Chi-square	Pr>Chi-square
Age (continuous)	1	117.5	0.0001
Diabetes history	1	62.1	0.0001
Having PCI	1	47.2	0.0001
Prior MI	1	36.8	0.0001
Compliance	1	35.5	0.0001
Troponin (pos or neg)	2	34.2	0.0001
Prior CABG	1	28.3	0.0001
Cath lab access	3	25.2	0.0001
Weight (continuous)	1	23.7	0.0001
Randomized treatment	1	23.0	0.0001
Stent use	1	19.4	0.0001
ASA maintainance dose by randomized treatment interaction	1	15.2	0.0001

Table 2 **Multivariate analysis in the full PLATO population – PLATO full analysis set**

Factor	Degrees of freedom	Chi-square	Pr>Chi-square
Index event	3	16.7	0.0008
PPI at randomization	1	9.9	0.0016
Pre index anti-platelet	4	17.2	0.0018
Race	3	11.7	0.0086
Troponin by randomized treatment interaction	2	8.75	0.0126
Invasive or medically managed	1	4.05	0.0442
Waist circumference	2	6.14	0.0464
GPIIb/IIIa at rand.	1	3.55	0.0597
ASA maintenance dose	1	0.98	0.3218

In this analysis, ASA dose was calculated based on ASA given from Day 2 of study drug and first of a primary event or cessation of randomized treatment for any reason (therefore excluding the ASA loading dose on Day 1 of randomization).

ASA Acetylsalicylic acid; CABG Coronary artery bypass grafting; GPIIb/IIIa Glycoprotein IIa/IIb;
MI Myocardial infarction; PCI Percutaneous coronary intervention; PPI Proton pump inhibitor

3. RESULTS OF UNIVARIATE ANALYSIS IN THE NON-US PLATO POPULATION

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

Characteristic	Group	Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585			Hazard Ratio (95% CI)	p-value	p- value (Int.)
		n	Patients with events	KM %	n	Patients with events	KM %			
Age Group	<65 years	4872	316 (6.5%)	6.8	4897	391 (8.0%)	8.5	0.81 (0.70, 0.94)	0.0056 **	0.9626
	≥65 years	3753	463 (12.3%)	13.1	3687	556 (15.1%)	16.3	0.81 (0.71, 0.91)	0.0007 ***	
	<75 years	7318	575 (7.9%)	8.3	7202	710 (9.9%)	10.5	0.79 (0.71, 0.88)	<0.0001 ***	
	≥75 years	1307	204 (15.6%)	16.7	1382	237 (17.1%)	18.5	0.91 (0.75, 1.09)	0.3035	
Sex	Male	6168	527 (8.5%)	9.0	6161	645 (10.5%)	11.3	0.81 (0.72, 0.91)	0.0004 ***	0.9556
	Female	2458	253 (10.3%)	10.9	2424	302 (12.5%)	13.2	0.82 (0.69, 0.97)	0.0179 *	
Race	Caucasian	7928	693 (8.7%)	9.3	7887	840 (10.7%)	11.4	0.82 (0.74, 0.90)	<0.0001 ***	0.7831
	Black	52	8 (15.4%)	15.5	40	8 (20.0%)	20.2	0.72 (0.27, 1.93)	0.5157	
	Asian	539	65 (12.1%)	12.4	548	76 (13.9%)	14.8	0.86 (0.62, 1.20)	0.3772	
	Other	106	14 (13.2%)	13.9	110	23 (20.9%)	21.9	0.59 (0.30, 1.15)	0.1221	
Weight	<60 kg	619	75 (12.1%)	12.8	622	102 (16.4%)	17.3	0.73 (0.54, 0.98)	0.0368 *	0.4286
	≥60 kg	7980	699 (8.8%)	9.3	7937	837 (10.5%)	11.3	0.83 (0.75, 0.91)	0.0002 ***	
	<60 kg	619	75 (12.1%)	12.8	622	102 (16.4%)	17.3	0.73 (0.54, 0.98)	0.0368 *	0.0525
	60-80 kg	4201	434 (10.3%)	10.9	4221	478 (11.3%)	12.1	0.91 (0.80, 1.04)	0.1661	
	>80 kg	3779	265 (7.0%)	7.5	3716	359 (9.7%)	10.4	0.72 (0.61, 0.84)	<0.0001 ***	

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

		Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585					p-value (Int.)
Characteristic	Group	n	Patients with events	KM %	n	Patients with events	KM %	Hazard Ratio (95% CI)	p-value	
	<80 kg	4276	457 (10.7%)	11.3	4301	522 (12.1%)	13.0	0.88 (0.77, 1.00)	0.0431 *	0.0859
	≥80 kg	4323	317 (7.3%)	7.8	4258	417 (9.8%)	10.5	0.74 (0.64, 0.86)	<0.0001 ***	
Weight(median)	<Sex Specific Median	4272	457 (10.7%)	11.3	4299	506 (11.8%)	12.6	0.91 (0.80, 1.03)	0.1435	0.0122 *
	≥Sex Specific Median	4327	317 (7.3%)	7.8	4260	433 (10.2%)	10.9	0.71 (0.62, 0.82)	<0.0001 ***	
BMI	<30 kg/m2	6253	587 (9.4%)	9.9	6308	704 (11.2%)	11.9	0.84 (0.75, 0.93)	0.0015 **	0.4152
	≥30 kg/m2	2332	185 (7.9%)	8.5	2229	230 (10.3%)	11.2	0.76 (0.63, 0.93)	0.0062 **	
Waist(cm)	<100 cm	4561	416 (9.1%)	9.6	4506	475 (10.5%)	11.2	0.86 (0.75, 0.98)	0.0241 *	0.2061
	≥100 cm	3643	321 (8.8%)	9.4	3646	421 (11.5%)	12.4	0.76 (0.66, 0.88)	0.0002 ***	
Troponin I	Positive	6953	668 (9.6%)	10.1	6960	815 (11.7%)	12.5	0.82 (0.74, 0.90)	<0.0001 ***	0.2037
	Negative	1425	91 (6.4%)	6.8	1372	88 (6.4%)	6.9	1.00 (0.74, 1.34)	0.9856	
Index Event	Unstable Angina	1473	116 (7.9%)	8.4	1497	123 (8.2%)	8.8	0.97 (0.75, 1.25)	0.8109	0.1774
	NSTEMI	3527	372 (10.5%)	11.1	3479	463 (13.3%)	14.3	0.78 (0.68, 0.90)	0.0004 ***	
	STEMI	3391	267 (7.9%)	8.3	3413	327 (9.6%)	10.2	0.82 (0.70, 0.96)	0.0151 *	
	Other	212	20 (9.4%)	10.1	179	31 (17.3%)	18.3	0.51 (0.29, 0.89)	0.0180 *	
Unstable Angina	No	7130	659 (9.2%)	9.8	7071	821 (11.6%)	12.4	0.79 (0.71, 0.87)	<0.0001 ***	0.1375

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

		Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585					p-value (Int.)
Characteristic	Group	n	Patients with events	KM %	n	Patients with events	KM %	Hazard Ratio (95% CI)	p-value	
NSTEMI	Yes	1473	116 (7.9%)	8.4	1497	123 (8.2%)	8.8	0.97 (0.75, 1.25)	0.8114	
	No	5076	403 (7.9%)	8.4	5089	481 (9.5%)	10.1	0.84 (0.73, 0.96)	0.0092 **	0.4639
STEMI	Yes	3527	372 (10.5%)	11.1	3479	463 (13.3%)	14.3	0.78 (0.68, 0.90)	0.0004 ***	
	No	5212	508 (9.7%)	10.3	5155	617 (12.0%)	12.9	0.81 (0.72, 0.91)	0.0004 ***	0.8975
Antiplatelet	Yes	3391	267 (7.9%)	8.3	3413	327 (9.6%)	10.2	0.82 (0.70, 0.96)	0.0151 *	
	None	5700	440 (7.7%)	8.1	5703	547 (9.6%)	10.2	0.80 (0.71, 0.91)	0.0005 ***	0.4542
	Clopidogrel	130	21 (16.2%)	17.4	124	17 (13.7%)	16.5	1.25 (0.66, 2.36)	0.5014	
	ASA	2295	247 (10.8%)	11.7	2247	298 (13.3%)	14.3	0.80 (0.68, 0.95)	0.0115 *	
	Clopidogrel+ASA	476	66 (13.9%)	14.1	480	81 (16.9%)	18.5	0.82 (0.59, 1.13)	0.2248	
Antiplatelet: None	Other	25	6 (24.0%)	24.4	31	4 (12.9%)	13.9	1.94 (0.55, 6.86)	0.3061	
	No	2926	340 (11.6%)	12.5	2882	400 (13.9%)	15.0	0.83 (0.72, 0.96)	0.0130 *	0.6739
Antiplatelet: Clopidogrel	Yes	5700	440 (7.7%)	8.1	5703	547 (9.6%)	10.2	0.80 (0.71, 0.91)	0.0005 ***	
	No	8496	759 (8.9%)	9.4	8461	930 (11.0%)	11.7	0.81 (0.73, 0.89)	<0.0001 ***	0.1873
Antiplatelet: ASA	Yes	130	21 (16.2%)	17.4	124	17 (13.7%)	16.5	1.25 (0.66, 2.36)	0.5013	
	No	6331	533 (8.4%)	8.8	6338	649 (10.2%)	10.9	0.82 (0.73, 0.92)	0.0006 ***	0.8738
	Yes	2295	247 (10.8%)	11.7	2247	298 (13.3%)	14.3	0.80 (0.68, 0.95)	0.0113 *	

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

Characteristic	Group	Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585			Hazard Ratio (95% CI)	p-value	p- value (Int.)
		n	Patients with events	KM %	n	Patients with events	KM %			
Antiplatelet: Clopidogrel- ASA	No	8150	714 (8.8%)	9.3	8105	866 (10.7%)	11.4	0.82 (0.74, 0.90)	<0.0001 ***	0.9851
	Yes	476	66 (13.9%)	14.1	480	81 (16.9%)	18.5	0.82 (0.59, 1.13)	0.2246	
ASA	No	414	48 (11.6%)	12.3	425	57 (13.4%)	14.8	0.86 (0.59, 1.26)	0.4445	0.7695
	Yes	8212	732 (8.9%)	9.4	8160	890 (10.9%)	11.6	0.81 (0.74, 0.90)	<0.0001 ***	
Diabetes History	No	6541	502 (7.7%)	8.1	6480	622 (9.6%)	10.2	0.79 (0.71, 0.89)	0.0001 ***	0.4341
	Yes	2085	278 (13.3%)	14.1	2105	325 (15.4%)	16.7	0.86 (0.73, 1.01)	0.0649	
MI History	No	6933	559 (8.1%)	8.5	6841	662 (9.7%)	10.3	0.83 (0.74, 0.93)	0.0012 **	0.6178
	Yes	1693	221 (13.1%)	13.9	1744	285 (16.3%)	17.7	0.79 (0.66, 0.94)	0.0076 **	
PCI History	No	7569	653 (8.6%)	9.1	7565	811 (10.7%)	11.4	0.80 (0.72, 0.89)	<0.0001 ***	0.4057
	Yes	1057	127 (12.0%)	13.0	1020	136 (13.3%)	14.7	0.89 (0.70, 1.14)	0.3635	
CABG History	No	8223	714 (8.7%)	9.2	8118	851 (10.5%)	11.2	0.83 (0.75, 0.91)	0.0002 ***	0.6221
	Yes	403	66 (16.4%)	17.6	467	96 (20.6%)	22.2	0.76 (0.55, 1.04)	0.0845	
Time (event to drug)	<12 hours	4581	353 (7.7%)	8.2	4513	445 (9.9%)	10.6	0.78 (0.68, 0.90)	0.0004 ***	0.5310
	≥12 hours	3966	418 (10.5%)	11.0	3995	488 (12.2%)	13.0	0.86 (0.75, 0.97)	0.0191 *	
	unknown	79	9 (11.4%)	14.5	77	14 (18.2%)	18.7	0.64 (0.28, 1.47)	0.2931	

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

Characteristic	Group	Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585			Hazard Ratio (95% CI)	p-value	p- value (Int.)
		n	Patients with events	KM %	n	Patients with events	KM %			
Treatment Approach	Invasive	6073	495 (8.2%)	8.6	6012	610 (10.1%)	10.8	0.80 (0.71, 0.90)	0.0002 ***	0.5471
	Medically	2553	285 (11.2%)	11.9	2573	337 (13.1%)	14.1	0.85 (0.72, 0.99)	0.0403 *	
TIMI score NSTEMI	0-2	357	14 (3.9%)	3.9	328	12 (3.7%)	4.0	1.07 (0.49, 2.31)	0.8670	0.3003
	3-4	2496	192 (7.7%)	8.2	2491	256 (10.3%)	11.2	0.74 (0.62, 0.90)	0.0018 **	
	5-7	2147	282 (13.1%)	13.9	2157	318 (14.7%)	15.6	0.89 (0.75, 1.04)	0.1387	
TIMI score STEMI	0-2	1849	82 (4.4%)	4.7	1906	111 (5.8%)	6.2	0.76 (0.57, 1.01)	0.0608	0.2706
	3-6	1426	165 (11.6%)	12.3	1373	178 (13.0%)	13.7	0.89 (0.72, 1.10)	0.2784	
	>6	116	20 (17.2%)	17.9	134	38 (28.4%)	30.3	0.57 (0.33, 0.98)	0.0414 *	
CYP	No	7723	692 (9.0%)	9.5	7717	847 (11.0%)	11.8	0.81 (0.73, 0.90)	<0.0001 ***	0.8420
	Yes	903	88 (9.7%)	10.3	868	100 (11.5%)	12.2	0.84 (0.63, 1.12)	0.2245	
GPIIb/IIIa	No	6454	589 (9.1%)	9.7	6404	711 (11.1%)	12.0	0.82 (0.73, 0.91)	0.0003 ***	0.9426
	Yes	2172	191 (8.8%)	9.3	2181	236 (10.8%)	11.4	0.81 (0.67, 0.98)	0.0303 *	
Heparin	No	3121	310 (9.9%)	10.5	3101	368 (11.9%)	12.8	0.83 (0.72, 0.97)	0.0189 *	0.6937
	Yes	5505	470 (8.5%)	9.0	5484	579 (10.6%)	11.2	0.80 (0.71, 0.91)	0.0004 ***	
Lipid	No	1715	184 (10.7%)	11.3	1744	189 (10.8%)	11.5	1.00 (0.82, 1.23)	0.9876	0.0252 *

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

		Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585					p-value (Int.)
Characteristic	Group	n	Patients with events	KM %	n	Patients with events	KM %	Hazard Ratio (95% CI)	p-value	
	Yes	6911	596 (8.6%)	9.1	6841	758 (11.1%)	11.9	0.77 (0.69, 0.86)	<0.0001 ***	
Beta Blockers	No	2229	192 (8.6%)	9.1	2148	236 (11.0%)	11.9	0.78 (0.64, 0.94)	0.0095 **	0.5711
	Yes	6397	588 (9.2%)	9.7	6437	711 (11.0%)	11.8	0.83 (0.74, 0.92)	0.0007 ***	
ACE Inhibitors	No	3680	323 (8.8%)	9.1	3684	378 (10.3%)	10.9	0.85 (0.73, 0.99)	0.0333 *	0.4543
	Yes	4946	457 (9.2%)	9.9	4901	569 (11.6%)	12.5	0.79 (0.70, 0.89)	0.0002 ***	
ARB	No	7895	707 (9.0%)	9.5	7856	860 (10.9%)	11.7	0.81 (0.74, 0.90)	<0.0001 ***	0.8843
	Yes	731	73 (10.0%)	10.5	729	87 (11.9%)	13.4	0.83 (0.61, 1.14)	0.2496	
CCB	No	7381	661 (9.0%)	9.5	7303	782 (10.7%)	11.5	0.83 (0.75, 0.92)	0.0005 ***	0.3250
	Yes	1245	119 (9.6%)	10.1	1282	165 (12.9%)	13.6	0.73 (0.58, 0.93)	0.0093 **	
Smoking	Non-Smoker	3383	359 (10.6%)	11.2	3457	414 (12.0%)	12.9	0.88 (0.77, 1.02)	0.0806	0.2127
	Ex-Smoker	2132	207 (9.7%)	10.4	2063	242 (11.7%)	12.8	0.82 (0.68, 0.99)	0.0399 *	
	Habitual Smoker	3104	214 (6.9%)	7.3	3059	291 (9.5%)	10.0	0.72 (0.60, 0.86)	0.0003 ***	
Sites	Sites with <4 events	8580	773 (9.0%)	9.5	8539	943 (11.0%)	11.8	0.81 (0.74, 0.89)	<0.0001 ***	0.1828
	Sites with 4 and above events	46	7 (15.2%)	15.2	46	4 (8.7%)	9.2	1.84 (0.54, 6.28)	0.3319	
Site 5499	No	8626	780 (9.0%)	9.6	8585	947 (11.0%)	11.8	0.82 (0.74, 0.90)	<0.0001 ***	

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

Characteristic	Group	Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585			Hazard Ratio (95% CI)	p-value	p- value (Int.)
		n	Patients with events	KM %	n	Patients with events	KM %			
Site 1602	No	8594	777 (9.0%)	9.6	8553	944 (11.0%)	11.8	0.81 (0.74, 0.90)	<0.0001 ***	0.7747
	Yes	32	3 (9.4%)	9.4	32	3 (9.4%)	9.9	1.03 (0.21, 5.10)	0.9718	
Site 5275	No	8626	780 (9.0%)	9.6	8585	947 (11.0%)	11.8	0.82 (0.74, 0.90)	<0.0001 ***	
Site 5490	No	8626	780 (9.0%)	9.6	8585	947 (11.0%)	11.8	0.82 (0.74, 0.90)	<0.0001 ***	
Site 1634	No	8612	776 (9.0%)	9.5	8571	946 (11.0%)	11.8	0.81 (0.74, 0.89)	<0.0001 ***	0.0861
	Yes	14	4 (28.6%)	28.6	14	1 (7.1%)	7.1	4.40 (0.49, 39.39)	0.1848	
Site 5203	No	8626	780 (9.0%)	9.6	8585	947 (11.0%)	11.8	0.82 (0.74, 0.90)	<0.0001 ***	
Site 5316	No	8626	780 (9.0%)	9.6	8585	947 (11.0%)	11.8	0.82 (0.74, 0.90)	<0.0001 ***	
Site 5249	No	8626	780 (9.0%)	9.6	8585	947 (11.0%)	11.8	0.82 (0.74, 0.90)	<0.0001 ***	
Site 5387	No	8626	780 (9.0%)	9.6	8585	947 (11.0%)	11.8	0.82 (0.74, 0.90)	<0.0001 ***	
Compliance	No	458	64 (14.0%)	16.5	443	86 (19.4%)	21.6	0.71 (0.51, 0.98)	0.0371 *	0.3811
	Yes	8168	716 (8.8%)	9.2	8142	861 (10.6%)	11.3	0.82 (0.75, 0.91)	0.0001 ***	
NSAIDs	No	8612	778 (9.0%)	9.6	8577	945 (11.0%)	11.8	0.82 (0.74, 0.90)	<0.0001 ***	0.7290

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

Characteristic	Group	Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585			Hazard Ratio (95% CI)	p-value	p- value (Int.)
		n	Patients with events	KM %	n	Patients with events	KM %			
ASA Dose	Yes	14	2 (14.3%)	14.3	8	2 (25.0%)	34.4	0.58 (0.08, 4.09)	0.5807	
	≤100mg	7449	546 (7.3%)	7.8	7443	699 (9.4%)	10.1	0.77 (0.69, 0.87)	<0.0001 ***	0.1175
	>100 - <300mg	503	62 (12.3%)	13.1	511	63 (12.3%)	13.9	1.00 (0.71, 1.42)	0.9932	
ASA Dose H-L	≥300mg	140	28 (20.0%)	21.5	140	23 (16.4%)	17.0	1.24 (0.71, 2.14)	0.4523	
	Low: <300mg	7952	608 (7.6%)	8.1	7954	762 (9.6%)	10.3	0.79 (0.71, 0.88)	<0.0001 ***	0.1199
	High: ≥300mg	140	28 (20.0%)	21.5	140	23 (16.4%)	17.0	1.24 (0.71, 2.14)	0.4523	
ASA at Randomization	Low: <300mg	5345	491 (9.2%)	9.7	5208	592 (11.4%)	12.2	0.80 (0.71, 0.90)	0.0003 ***	0.7870
	High: ≥300mg	2718	222 (8.2%)	8.6	2649	249 (9.4%)	9.9	0.87 (0.72, 1.04)	0.1185	
	Unknown	563	67 (11.9%)	12.8	728	106 (14.6%)	15.9	0.83 (0.61, 1.12)	0.2214	
PCI	No	4326	468 (10.8%)	11.5	4293	560 (13.0%)	14.0	0.82 (0.73, 0.93)	0.0020 **	0.7633
	Yes	4300	312 (7.3%)	7.6	4292	387 (9.0%)	9.6	0.80 (0.69, 0.93)	0.0034 **	
DES or BMS	No	3420	344 (10.1%)	10.7	3390	416 (12.3%)	13.3	0.82 (0.71, 0.94)	0.0055 **	0.9634
	Yes	5206	436 (8.4%)	8.8	5195	531 (10.2%)	10.8	0.81 (0.72, 0.92)	0.0014 **	
ASA Region	75 mg countries	2581	222 (8.6%)	9.0	2552	273 (10.7%)	11.3	0.80 (0.67, 0.96)	0.0143 *	0.2884
	100 mg countries	5133	474 (9.2%)	9.9	5120	552 (10.8%)	11.6	0.85 (0.76, 0.97)	0.0115 *	
	Mixed dose countries	912	84 (9.2%)	9.6	913	122 (13.4%)	14.4	0.67 (0.51, 0.88)	0.0048 **	

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

Characteristic	Group	Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585			Hazard Ratio (95% CI)	p-value	p- value (Int.)
		n	Patients with events	KM %	n	Patients with events	KM %			
Angiography quartile 1	High access catheterization laboratory	1786	143 (8.0%)	8.8	1770	166 (9.4%)	10.2	0.85 (0.68, 1.07)	0.1626	0.1748
	Medium high access catheterization laboratory	1655	179 (10.8%)	11.3	1635	187 (11.4%)	12.2	0.95 (0.77, 1.16)	0.5946	
	Medium low access catheterization laboratory	2952	218 (7.4%)	7.7	2941	305 (10.4%)	10.9	0.70 (0.59, 0.84)	<0.0001 ***	
	Low access catheterization laboratory	2233	240 (10.7%)	11.4	2239	289 (12.9%)	14.0	0.83 (0.70, 0.98)	0.0297 *	
High catheterization	No	6840	637 (9.3%)	9.8	6815	781 (11.5%)	12.2	0.81 (0.73, 0.90)	<0.0001 ***	0.6598
	Yes	1786	143 (8.0%)	8.8	1770	166 (9.4%)	10.2	0.85 (0.68, 1.07)	0.1632	
Medium high catheterization	No	6971	601 (8.6%)	9.2	6950	760 (10.9%)	11.7	0.78 (0.70, 0.87)	<0.0001 ***	0.1086
	Yes	1655	179 (10.8%)	11.3	1635	187 (11.4%)	12.2	0.95 (0.77, 1.16)	0.5939	
Medium low catheterization	No	5674	562 (9.9%)	10.5	5644	642 (11.4%)	12.3	0.87 (0.78, 0.97)	0.0145 *	0.0469 *
	Yes	2952	218 (7.4%)	7.7	2941	305 (10.4%)	10.9	0.70 (0.59, 0.84)	<0.0001 ***	

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

Characteristic	Group	Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585			Hazard Ratio (95% CI)	p-value	p- value (Int.)
		n	Patients with events	KM %	n	Patients with events	KM %			
Angiography quartile 2	High access catheterization laboratory	1945	161 (8.3%)	9.0	1930	186 (9.6%)	10.5	0.86 (0.70, 1.06)	0.1567	0.1769
	Medium high access catheterization laboratory	1496	161 (10.8%)	11.2	1475	167 (11.3%)	11.9	0.95 (0.76, 1.18)	0.6413	
	Medium low access catheterization laboratory	2952	218 (7.4%)	7.7	2941	305 (10.4%)	10.9	0.70 (0.59, 0.84)	<0.0001 ***	
	Low access catheterization laboratory	2233	240 (10.7%)	11.4	2239	289 (12.9%)	14.0	0.83 (0.70, 0.98)	0.0296 *	
High catheterization	No	6681	619 (9.3%)	9.7	6655	761 (11.4%)	12.2	0.80 (0.72, 0.89)	<0.0001 ***	0.5859
	Yes	1945	161 (8.3%)	9.0	1930	186 (9.6%)	10.5	0.86 (0.70, 1.06)	0.1571	
Medium high catheterization	No	7130	619 (8.7%)	9.2	7110	780 (11.0%)	11.8	0.79 (0.71, 0.87)	<0.0001 ***	0.1233
	Yes	1496	161 (10.8%)	11.2	1475	167 (11.3%)	11.9	0.95 (0.76, 1.18)	0.6408	
Medium low catheterization	No	5674	562 (9.9%)	10.5	5644	642 (11.4%)	12.3	0.87 (0.78, 0.97)	0.0145 *	0.0469 *
	Yes	2952	218 (7.4%)	7.7	2941	305 (10.4%)	10.9	0.70 (0.59, 0.84)	<0.0001 ***	

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

Characteristic	Group	Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585			Hazard Ratio (95% CI)	p-value	p- value (Int.)
		n	Patients with events	KM %	n	Patients with events	KM %			
PPI	No	5736	488 (8.5%)	9.0	5687	590 (10.4%)	11.1	0.81 (0.72, 0.92)	0.0008 ***	0.9924
	Yes	2890	292 (10.1%)	10.6	2898	357 (12.3%)	13.1	0.82 (0.70, 0.95)	0.0098 **	
Clopidogrel loading(24h)	300 to 375 mg	1843	161 (8.7%)	9.2	5143	589 (11.5%)	12.2	0.76 (0.63, 0.90)	0.0016 **	0.5841
	600 to 675 mg	1240	83 (6.7%)	7.1	1699	143 (8.4%)	9.0	0.79 (0.61, 1.04)	0.0957	
	Other	640	56 (8.8%)	9.4	1261	142 (11.3%)	11.9	0.77 (0.56, 1.05)	0.0962	
	Continuing on Clopidogrel	407	65 (16.0%)	16.5	428	67 (15.7%)	17.6	1.04 (0.74, 1.47)	0.8061	
	No Clopidogrel >75 mg	4496	415 (9.2%)	9.8	54	6 (11.1%)	11.3	0.74 (0.33, 1.66)	0.4625	
Clopidogrel 300-375mg loading (24h)	No	6783	619 (9.1%)	9.7	3442	358 (10.4%)	11.2	0.88 (0.77, 1.00)	0.0445 *	0.1811
	Yes	1843	161 (8.7%)	9.2	5143	589 (11.5%)	12.2	0.76 (0.63, 0.90)	0.0016 **	
Clopidogrel 600-675mg loading (24h)	No	7386	697 (9.4%)	10.0	6886	804 (11.7%)	12.5	0.80 (0.72, 0.89)	<0.0001 ***	0.9532
	Yes	1240	83 (6.7%)	7.1	1699	143 (8.4%)	9.0	0.79 (0.61, 1.04)	0.0957	
Clopidogrel other loading (24h)	No	7986	724 (9.1%)	9.6	7324	805 (11.0%)	11.8	0.82 (0.74, 0.91)	0.0001 ***	0.6935
	Yes	640	56 (8.8%)	9.4	1261	142 (11.3%)	11.9	0.77 (0.56, 1.05)	0.0962	

Table 3 ICAC-adjudicated primary endpoint: Univariate treatment interactions by patient characteristics: Non-US

Characteristic	Group	Ticagrelor 90 mg bid N=8626			Clopidogrel 75 mg qd N=8585			Hazard Ratio (95% CI)	p-value	p- value (Int.)
		n	Patients with events	KM %	n	Patients with events	KM %			
Clopidogrel continuing loading (24h)	No	8219	715 (8.7%)	9.2	8157	880 (10.8%)	11.5	0.80 (0.73, 0.88)	<0.0001 ***	0.1441
	Yes	407	65 (16.0%)	16.5	428	67 (15.7%)	17.6	1.04 (0.74, 1.47)	0.8060	

ACE Angiotensin converting enzyme; ARB Angiotensin receptor blocker; ASA Acetylsalicylic acid; bid Twice daily; BMI Body mass index; BMS Bare metal stent; CABG Coronary artery bypass grafting; CCB Calcium channel blocker CI Confidence interval; CYP Cytochrome P450; DES Drug-eluting stent; h Hour; KM Kaplan-Meier; qd Once daily.; MI Myocardial infarction; NSAID Nonsteroidal anti-inflammatory drugs; NSTEMI Non-ST segment elevation myocardial infarction; PCI Percutaneous coronary intervention; PPI Proton pump inhibitor; qd Once daily; STEMI ST segment elevation myocardial infarction; TIA Transient ischemic attack; TIMI Thrombolysis in Myocardial Infarction.



**Appendix to Advisory Committee Briefing
Document - Bleeding**

Drug	Ticagrelor
Study Code	D5130C00000
Edition	1
Date	23 June 2010

**BRILINTA Advisory Committee Briefing Document
Appendix D (Bleeding)**

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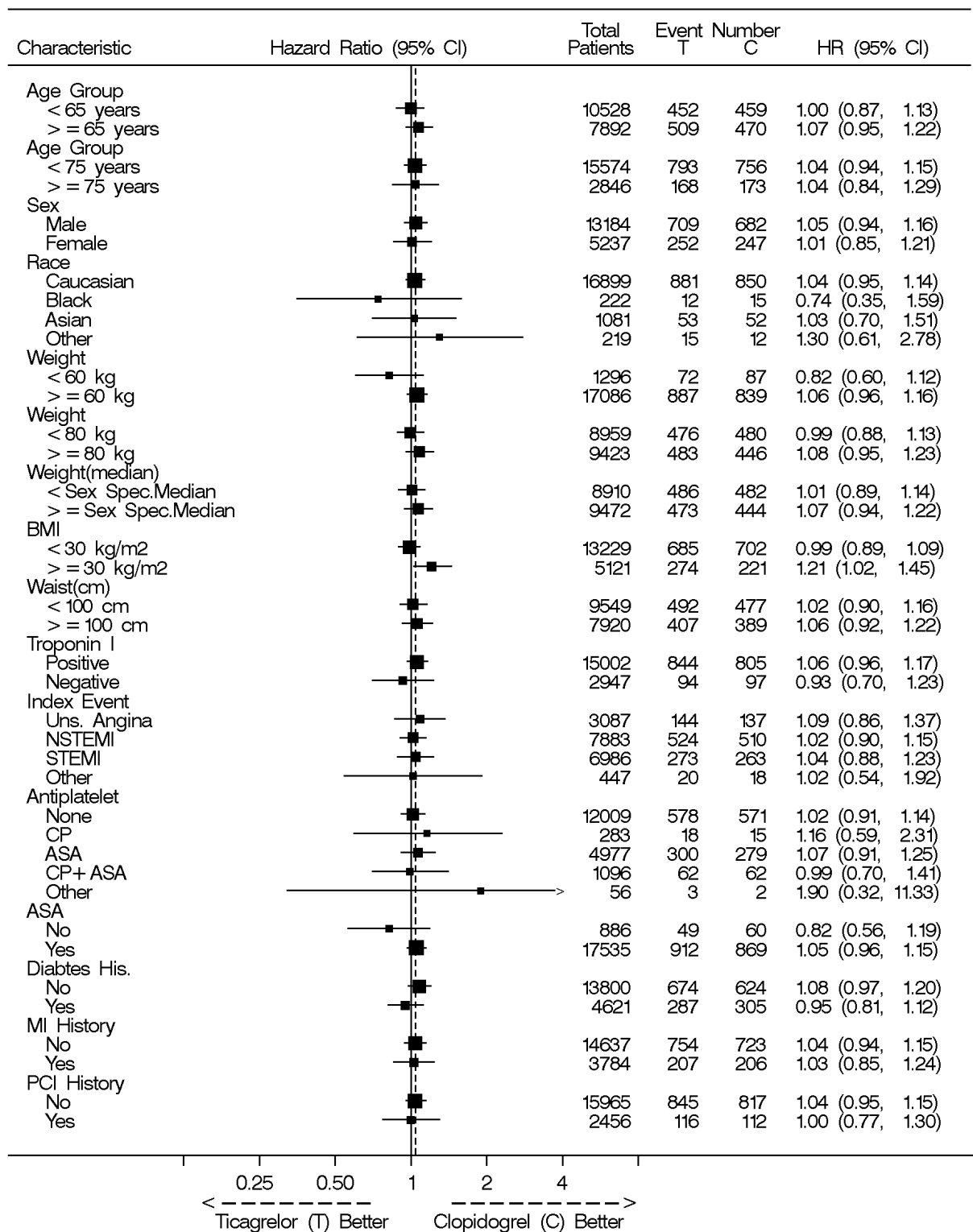
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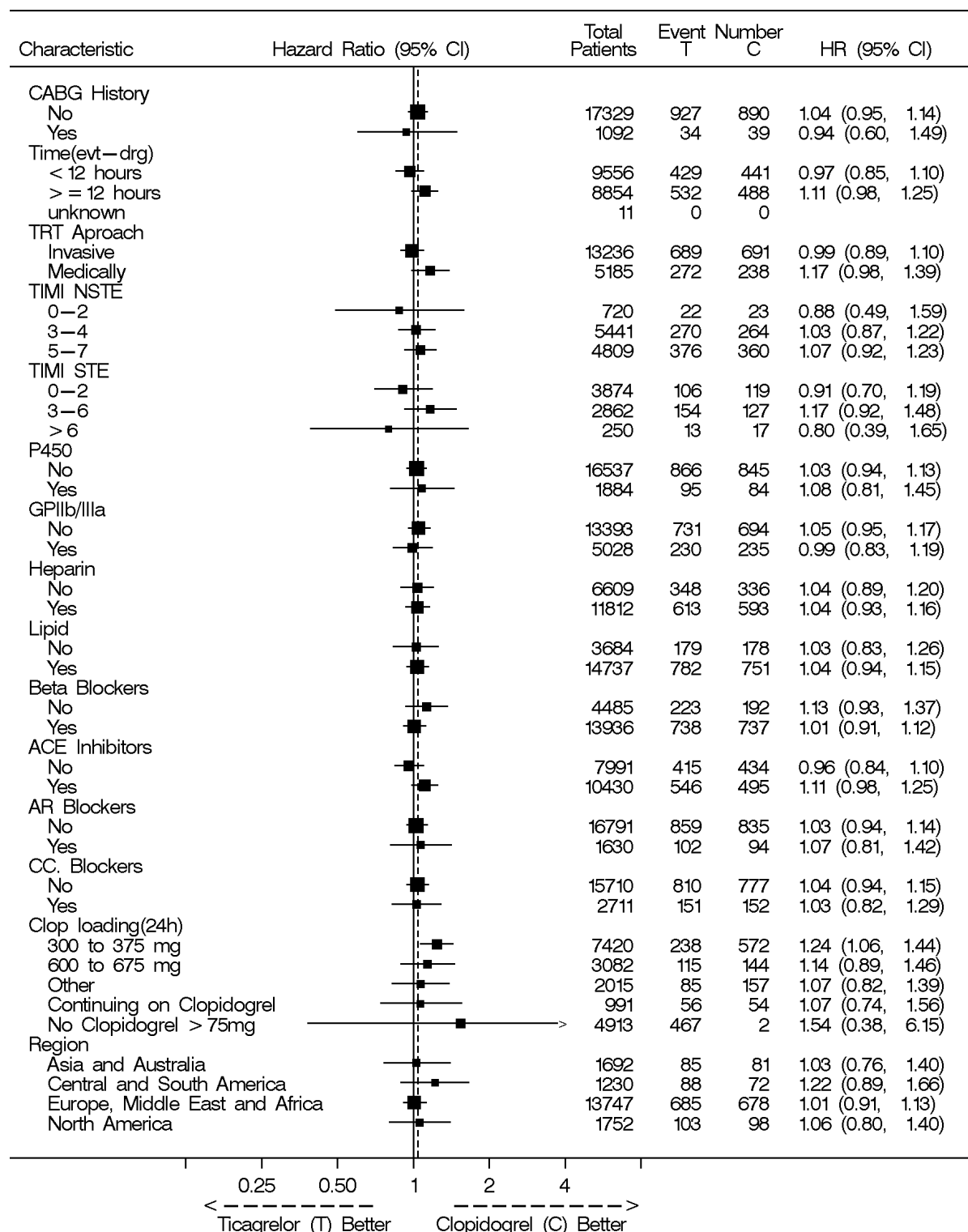
APPENDIX FOR BLEEDING

Subgroup analysis for ‘Total Major,’ ‘Total Major’ non-CABG and ‘Total Major’ non-procedural bleeding

Figure 1 presents hazard ratios and rates for ‘Total Major’ bleeding. Figure 2 presents hazard ratios and rates for ‘Total Major’ non-CABG bleeding. Figure 3 presents hazard ratios and rates for ‘Total Major’ non-procedural bleeding.

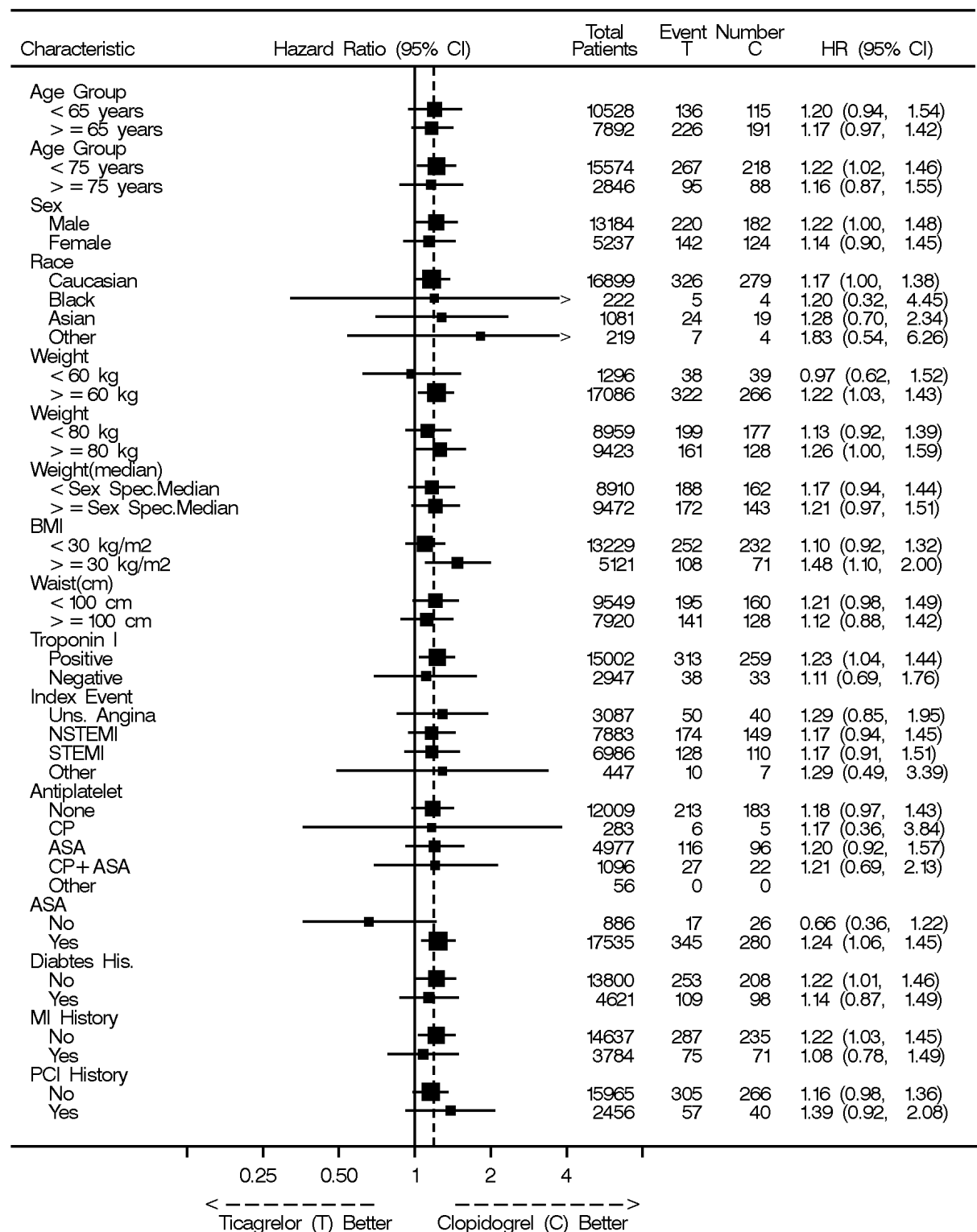
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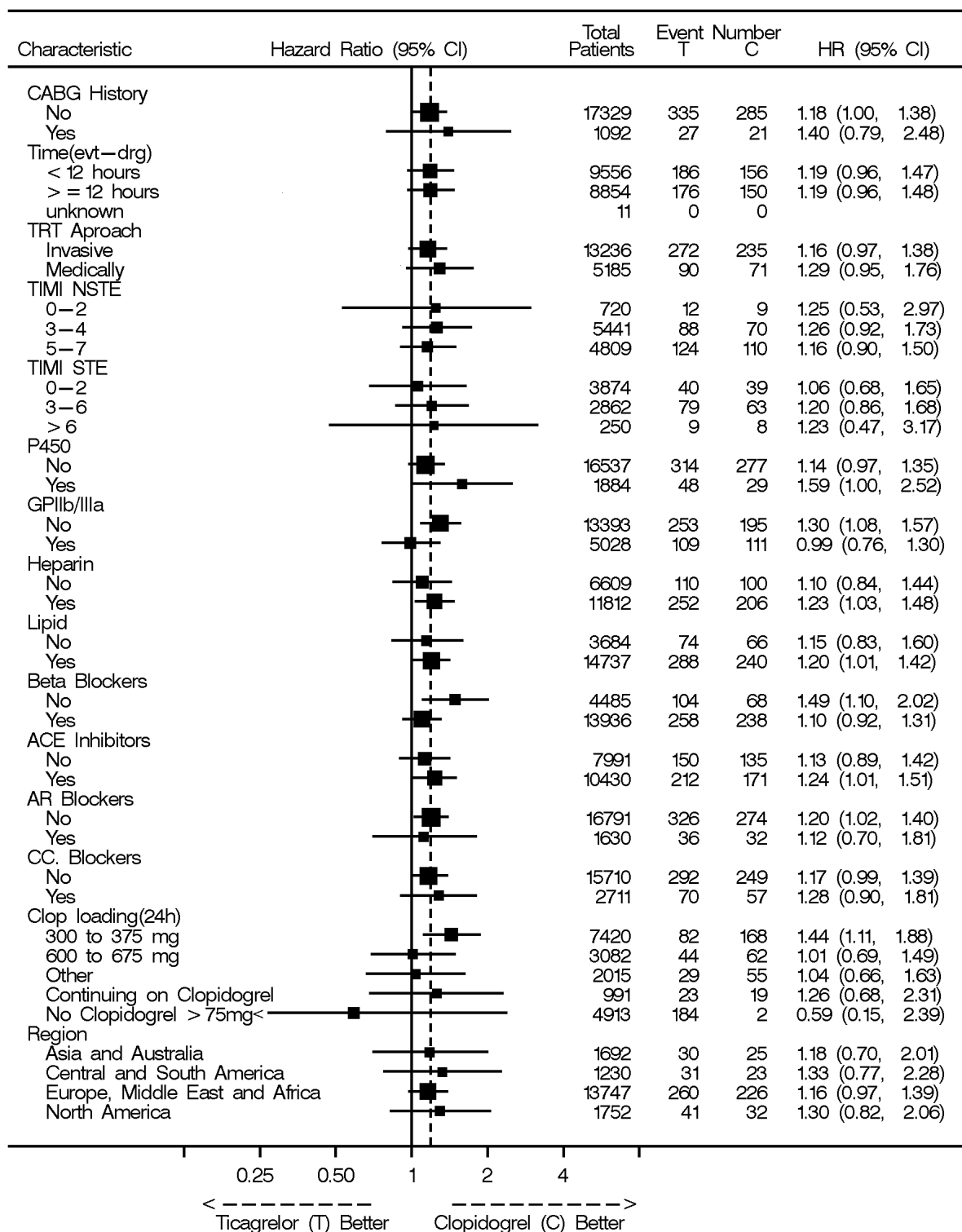




ASA Acetylsalicylic acid; BMI Body mass index; CABG Coronary artery bypass graft; CI Confidence interval; eCRF Electronic case report form; CYP3A Cytochrome P450 isoenzyme 3A; HR Hazard ratio; KM Kaplan-Meier; MI Myocardial infarction; NSTEMI Non-ST elevated myocardial infarction; PCI percutaneous coronary intervention; STEMI ST-segment elevation myocardial infarction; Trt Treatment.

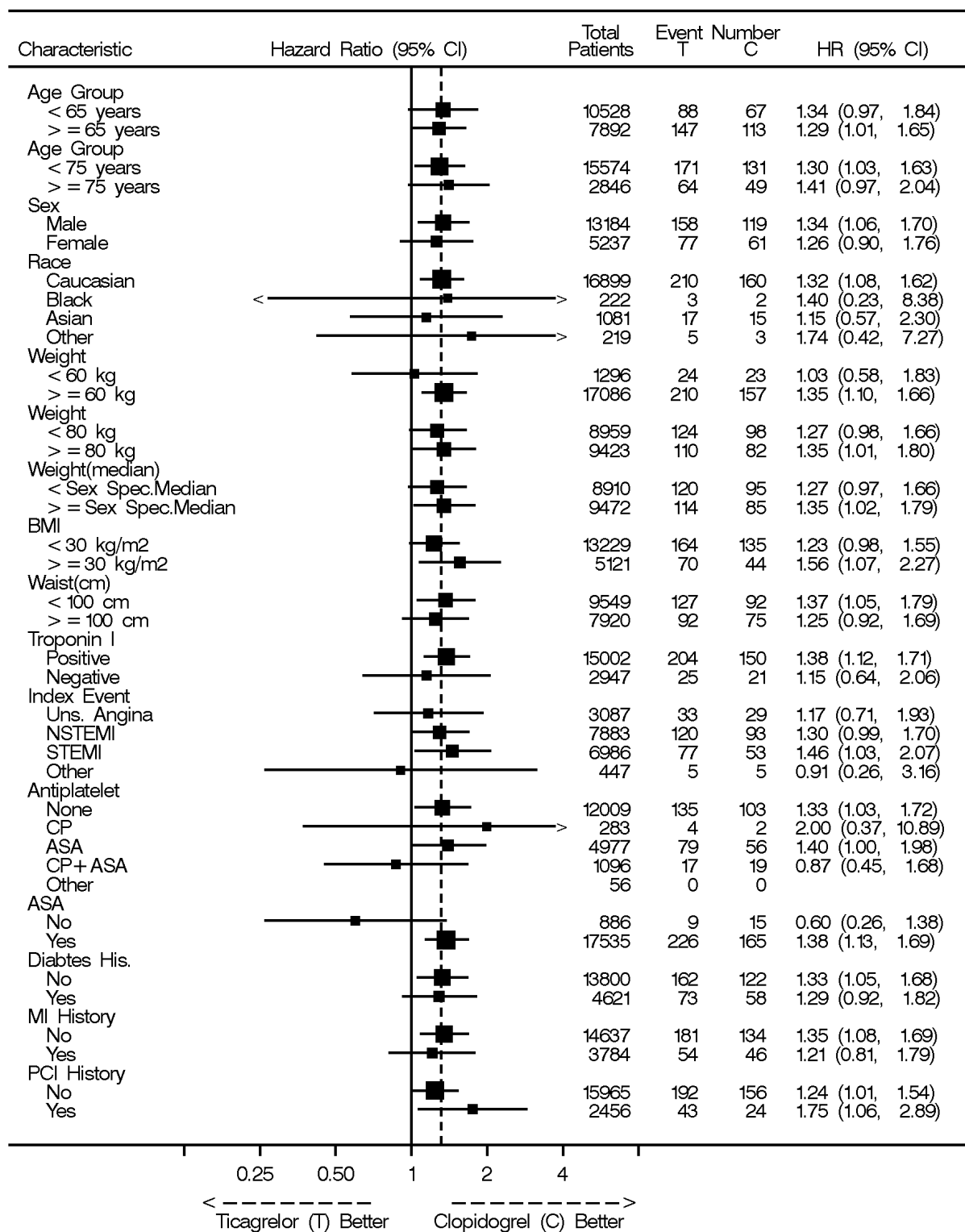
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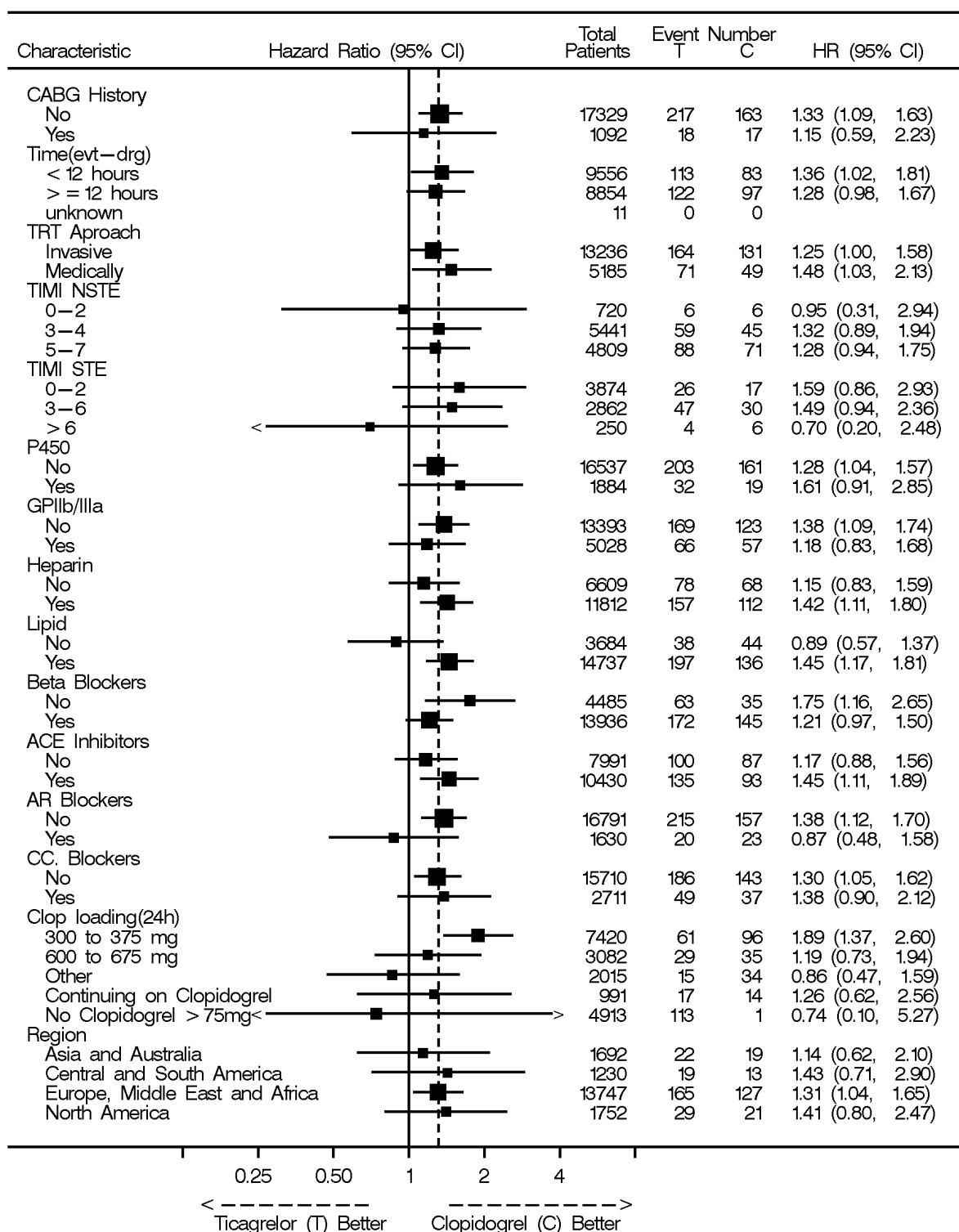




ASA Acetylsalicylic acid; BMI Body mass index; CI Confidence interval; eCRF Electronic case report form;
CSR Clinical study report; CYP3A Cytochrome P450 isoenzyme 3A; HR Hazard ratio;
KM Kaplan-Meier; NSTEMI Non-ST elevated myocardial infarction; STEMI ST-segment elevation
myocardial infarction; TIA Transient ischemic attack.

Figure 3 Hazard ratios and rates of ‘Total Major’ non-procedural bleeding events by selected subgroups of study patients - safety analysis set





ASA Acetylsalicylic acid; BMI Body mass index; CI Confidence interval; eCRF Electronic case report form;
CSR Clinical study report; CYP3A Cytochrome P450 isoenzyme 3A; HR Hazard ratio;
KM Kaplan-Meier; NSTEMI Non-ST elevated myocardial infarction; STEMI ST-segment elevation
myocardial infarction; TIA Transient ischemic attack.

Listing of patients with ICH

[Table 1](#) presents a listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH.

Table 1 Listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH

Patient number E-code	Age/ gender/ country/ race	Randomized treatment/ Time from first dose to ICH	Prior history of TIA/ stroke	Definite^a history of ICH or probable cerebral hemorrhage component	Fatal ICH	Index event	PPI at random- ization	Median ASA	Hypertension history/ SBP/DBP (days prior to ICH when measurement taken)	AstraZeneca comment from patient narrative review / Cause of death classification
Ticagrelor Fatal ICH										
E1004009	66/ Male/ Argentina/ Caucasian	Ticagrelor 90 mg bid/ 143	No	No	Yes	NSTEMI	No	100 mg	Yes/ 135/80 (-51)	No comment/ Vascular – Death from bleeding (non- trauma)
E1016043	71/ Male/ Argentina/ Caucasian	Ticagrelor 90 mg bid/ 8	No	No	Yes	STEMI	No	100 mg	Yes/ 140/80 (-6)	ICH – next day septic shock / Non-vascular - Sepsis
E1435005	52/ Female/ Brazil/ Mixed Race	Ticagrelor 90 mg bid/ 6	No	No	Yes	NSTEMI	Yes	100 mg	Yes/ 120/78 (-5)	ICH detected after cardiac arrest and resuscitation/ Vascular - Stroke
E1511018	43/ Male/ Bulgaria/ Caucasian	Ticagrelor 90 mg bid/ 88	No	No	Yes	NSTEMI	No	100 mg	Yes/ 120/80 (-49)	Head injury at work – SDH and SAH/ Non-vascular - Trauma
E1803008	79/ Male/ Czech Republic/ Caucasian	Ticagrelor 90 mg bid/ 348	No	Probable	Yes	STEMI	No	100 mg	Yes/ 150/74 (-66)	No comment/ Vascular - Stroke

Table 1 Listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH

Patient number E-code	Age/ gender/ country/ race	Randomized treatment/ Time from first dose to ICH	Prior history of TIA/ stroke	Definite^a history of ICH or probable cerebral hemorrhage component	Fatal ICH	Index event	PPI at random- ization	Median ASA	Hypertension history/ SBP/DBP (days prior to ICH when measurement taken)	AstraZeneca comment from patient narrative review / Cause of death classification
E2610085	62/ Female/ Hungary/ Caucasian	Ticagrelor 90 mg bid/ 12	No	No	Yes	STEMI	Yes	100 mg	Yes/ 135/80 (-10)	Ischemic stroke – received thrombolysis = Hemorrhagic transformation / Vascular – Death from bleeding (non- trauma)
E2610113	57/ Male/ Hungary/ Caucasian	Ticagrelor 90 mg bid/ 82	No	No	Yes	STEMI	Yes	100 mg	Yes/ 140/80 (-48)	No comment/ Vascular – Death from bleeding (non- trauma)
E2805007	56/ Male/ Indonesia/ Asian	Ticagrelor 90 mg bid/ 269	No	No	Yes	NSTEMI	No	100 mg	Yes/ 128/64 (-82)	No comment/ Vascular - Stroke
E3410012	85/ Male/ Norway/ Caucasian	Ticagrelor 90 mg bid/ 173	No	No	Yes	Unstable angina pectoris	No	75 mg	Yes/ 101/68 (-71)	Head injury Day 173 (fall) – SDH + ICH / Vascular – Death from bleeding (non- trauma)

Table 1 Listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH

Patient number E-code	Age/ gender/ country/ race	Randomized treatment/ Time from first dose to ICH	Prior history of TIA/ stroke	Definite^a history of ICH or probable cerebral hemorrhage component	Fatal ICH	Index event	PPI at random- ization	Median ASA	Hypertension history/ SBP/DBP (days prior to ICH when measurement taken)	AstraZeneca comment from patient narrative review / Cause of death classification
E3624138	66/ Female/ Poland/ Caucasian	Ticagrelor 90 mg bid/ 155	No	No	Yes	STEMI	Yes	75 mg	Yes/ 135/80 (-61)	No comment / Vascular - Stroke
E4414032	67/ Male/ Spain/ Caucasian	Ticagrelor 90 mg bid/ 24	No	No	Yes	NSTEMI	Yes	100 mg	Yes/ 119/69 (-23)	MRSA/ Vascular – Death from bleeding (non- trauma)
Ticagrelor non-Fatal ICH										
E1602002	54/ Male/ Canada/ Caucasian	Ticagrelor 90 mg bid/ 8	No	No	No	STEMI	No	203 mg	No/ 115/80 (-6)	No comment/ Not applicable
E1708062	51/ Male/ China/ Asian	Ticagrelor 90 mg bid/ 75	No	No	No	Unstable angina pectrois	No	100 mg	No / 150/100 (-41)	No comment/ Not applicable
E1809127	76/ Female/ Czech Republic/ Caucasian	Ticagrelor 90 mg bid/ 185	No	No	No	STEMI	Yes	100 mg	No/ 118/67 (-94)	Brain neoplasm with hemorrhage/ Not applicable

Table 1 **Listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH**

Patient number E-code	Age/ gender/ country/ race	Randomized treatment/ Time from first dose to ICH	Prior history of TIA/ stroke	Definite^a history of ICH or probable cerebral hemorrhage component	Fatal ICH	Index event	PPI at random- ization	Median ASA	Hypertension history/ SBP/DBP (days prior to ICH when measurement taken)	AstraZeneca comment from patient narrative review / Cause of death classification
E2326002	58/ Male/ Germany/ Caucasian	Ticagrelor 90 mg bid/ 50	No	No	No	STEMI	No	100 mg	No/ 110/70 (0)	No comment/ Not applicable
E2344001	58/ Female/ Germany/ Caucasian	Ticagrelor 90 mg bid/ 202	No	No	No	STEMI	No	100 mg	No/ 125/75 (-24)	No comment/ Not applicable
E3203046	74/ Male/ Mexico/ Caucasian	Ticagrelor 90 mg bid/ 3	No	No	No	STEMI	No	10 mg	Yes/ 140/80 (-1)	Ischemic and hemorrhagic strokes; enoxaparin, tirofiban / Not applicable
E3330010	66/ Female/ Netherlands/ Caucasian	Ticagrelor 90 mg bid/ 138	Yes	No	No	NSTEMI	No	Not known	No/ 155/87 (-56)	No comment/ Not applicable
E3505001	52/ Male/ Philippines/ Asian	Ticagrelor 90 mg bid/ 66	No	No	No	Unstable angina pectoris	No	80 mg	Yes/ 150/90 (-64)	Recent CABG/ Not applicable

Table 1 Listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH

Patient number E-code	Age/ gender/ country/ race	Randomized treatment/ Time from first dose to ICH	Prior history of TIA/ stroke	Definite^a history of ICH or probable cerebral hemorrhage component	Fatal ICH	Index event	PPI at random- ization	Median ASA	Hypertension history/ SBP/DBP (days prior to ICH when measurement taken)	AstraZeneca comment from patient narrative review / Cause of death classification
E3641002	54/ Male/ Poland/ Caucasian	Ticagrelor 90 mg bid/ 369	No	No	No	NSTEMI	No	100 mg	Yes/ 140/80 (-3)	3 days after end of study – off study drug/ Not applicable
E3801028	77/ Female/ Romania/ Caucasian	Ticagrelor 90 mg bid/ 60	No	No	No	NSTEMI	Yes	75 mg	No/ 140/80 (-25)	Fall out of bed: Epidural hematoma/ Not applicable
E3806049	72/ Male/ Romania/ Caucasian	Ticagrelor 90 mg bid/ 148	No	No	No	Unstable angina pectoris	No	100 mg	Yes/ 120/60 (-60)	Ischemic stroke on CT – died 3 days later – “hemorrhagic transformation” – cause of death “Cardiopulmonary arrest”/ Vascular - Other
E3806050	66/ Male/ Romania/ Caucasian	Ticagrelor 90 mg bid/ 22	Yes	No	No	NSTEMI	No	100 mg	Yes/ 150/80 (-21)	Clinical diagnosis of hemorrhagic stroke – not confirmed by imaging/ Not applicable
E3907032	48/ Male/ Russia/ Caucasian	Ticagrelor 90 mg bid/ 3	Yes	No	No	STEMI	No	125 mg	Yes/ 140/90 (-1)	History of CVA, head trauma with concussion; SAH/ Not applicable

Table 1 **Listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH**

Patient number E-code	Age/ gender/ country/ race	Randomized treatment/ Time from first dose to ICH	Prior history of TIA/ stroke	Definite^a history of ICH or probable cerebral hemorrhage component	Fatal ICH	Index event	PPI at random- ization	Median ASA	Hypertension history/ SBP/DBP (days prior to ICH when measurement taken)	AstraZeneca comment from patient narrative review / Cause of death classification
E4502012	80/ Male/ Sweden/ Caucasian	Ticagrelor 90 mg bid/ 108	No	No	No	NSTEMI	No	75 mg	Yes/ 150/70 (-1)	Day 25 CVA, Day 107 ischemic stroke with secondary bleeding/ Not applicable
E5268001	68/ Female/ USA/ Caucasian	Ticagrelor 90 mg bid/ 117	Yes	No	No	Unstable angina pectoris	Yes	325 mg	Yes/ 122/76 (0)	History. Of CVA. chest pain, syncope, fall with head injury; SAH Not applicable

Table 1 **Listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH**

Patient number E-code	Age/ gender/ country/ race	Randomized treatment/ Time from first dose to ICH	Prior history of TIA/ stroke	Definite^a history of ICH or probable cerebral hemorrhage component	Fatal ICH	Index event	PPI at random- ization	Median ASA	Hypertension history/ SBP/DBP (days prior to ICH when measurement taken)	AstraZeneca comment from patient narrative review / Cause of death classification
Clopidogrel Fatal ICH										
E3801001	78/ Male/ Romania/ Caucasian	Clopidogrel 75 mg qd/ 271	No	No	Yes	NSTEMI	No	75 mg	Yes/ SBP 190 after surgery	Diagnosis of brain tumor on Day 263; Post-surgical ICH on Day 271; Left parietal brain tumor status post brain surgery with concomitant LMWH/ Intracranial hemorrhage (left fronto-parietal cerebral parenchymal hematoma, subarachnoid hemorrhage and cerebral edema)
E4102025	39/ Male/ Singapore/ Asian	Clopidogrel 75 mg qd/ 3	No	No	Yes	STEMI	No	100 mg	Yes/ 109/65 (-1)	No comment/ Vascular - Death from bleeding (non- trauma)

Table 1 Listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH

Patient number E-code	Age/ gender/ country/ race	Randomized treatment/ Time from first dose to ICH	Prior history of TIA/ stroke	Definite ^a history of ICH or probable cerebral hemorrhage component	Fatal ICH	Index event	PPI at random- ization	Median ASA	Hypertension history/ SBP/DBP (days prior to ICH when measurement taken)	AstraZeneca comment from patient narrative review / Cause of death classification
Clopidogrel non-Fatal ICH										
E1701001	65/ Male/ China/ Asian	Clopidogrel 75 mg qd/ 157	Yes	Definite	No	STEMI	No	300 mg	Yes/ 160/80 (-62)	History of CVA and ICH/ Vascular – Sudden death
E1809162	66/ Male/ Czech Republic/ Caucasian	Clopidogrel 75 mg qd/ 10	Yes	No	No	STEMI	Yes	250 mg	Yes/ 117/87 (-8)	Day 8 cardiogenic shock; Post- ischemic subacute hemorrhage/ Vascular – Myocardial infarction
E2127016	61/ Male/ France/ Caucasian	Clopidogrel 75 mg qd/ 42	No	No	No	Unstable angina pectoris	No	160 mg	No/ 120/60 (-4)	No comment/ Not applicable
E2312015	79/ Female/ Germany/ Caucasian	Clopidogrel 75 mg qd/ 6	No	No	No	NSTEMI	Yes	100 mg	Yes/ 145/70 (-4)	No comment/ Not applicable
E2326011	55/ Male/ Germany/ Caucasian	Clopidogrel 75 mg qd/ 372	Yes	Definite	No	STEMI	No	100 mg	Yes/ 180/110 (-43)	History of CVA; history of traumatic cerebral bleed, uncontrolled HTN/ Vascular - myocardial infarction

Table 1 Listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH

Patient number E-code	Age/ gender/ country/ race	Randomized treatment/ Time from first dose to ICH	Prior history of TIA/ stroke	Definite^a history of ICH or probable cerebral hemorrhage component	Fatal ICH	Index event	PPI at random- ization	Median ASA	Hypertension history/ SBP/DBP (days prior to ICH when measurement taken)	AstraZeneca comment from patient narrative review / Cause of death classification
E2915056	86/ Male/ Israel/ Caucasian	Clopidogrel 75 mg qd/ 232	No	No	No	STEMI	No	100 mg	Yes/ 140/90 (-35)	Uncontrolled HTN, Fall with head injury, SDH/ Not applicable
E3038003	60/ Male/ Italy/ Asian	Clopidogrel 75 mg qd/ 3	No	No	No	NSTEMI	No	160 mg	No/ 128/75 (-1)	No comment/ Not applicable
E3806047	68/ Female/ Romania/ Caucasian	Clopidogrel 75 mg qd/ 188	Yes	No	No	Unstable angina pectoris	No	100 mg	Yes/ 150/80 (-94)	History of.CVA/ Not applicable
E3808006	50/ Male/ Romania/ Caucasian	Clopidogrel 75 mg qd/ 304	No	No	No	Unstable angina pectoris	No	150 mg	Yes/ 140/84 (-21)	No comment/ Not applicable
E3901002	40/ Male/ Russia/ Caucasian	Clopidogrel 75 mg qd/ 173	No	No	No	Unstable angina pectoris	No	100 mg	Yes/ 160/100 (-72)	No comment/ Not applicable
E3927015	45/ Male/ Russia/ Caucasian	Clopidogrel 75 mg qd/ 5	No	No	No	STEMI	No	100 mg	No/ 120/70 (-3)	Ischemic stroke with areas of hemorrhagic transformation/ Not applicable
E4804026	78/ Male/ Thailand/ Caucasian	Clopidogrel 75 mg qd/ 11	No	No	No	NSTEMI	Yes	300 mg	No/ 132/77 (-10)	ICH 6 days after CABG/ Vascular - Stroke

Table 1 Listing of demographic and medical history information (including prior stroke/TIA) for PLATO patients with ICH

Patient number E-code	Age/ gender/ country/ race	Randomized treatment/ Time from first dose to ICH	Prior history of TIA/ stroke	Definite^a history of ICH or probable cerebral hemorrhage component	Fatal ICH	Index event	PPI at random- ization	Median ASA	Hypertension history/ SBP/DBP (days prior to ICH when measurement taken)	AstraZeneca comment from patient narrative review / Cause of death classification
E5102010	71/ Female/ Ukraine/ Caucasian	Clopidogrel 75 mg qd/ 110	No	No	No	STEMI	No	100 mg	Yes/ 132/79 (-11)	No comment/ Not applicable

a Definite: Preferred term of cerebral hemorrhage, cerebral hemorrhage traumatic, hemorrhage intracranial, traumatic intracranial hemorrhage, cerebral hematoma, subdural hematoma, epidural hematoma or subarachnoid hemorrhage. Probable: Preferred term of traumatic brain injury or brain contusion
ASA Acetylsalicylic acid; bid Twice daily; CABG Coronary artery bypass grafting; CVA Cerebrovascular accident; DBP diastolic blood pressure; HTN Hypertension; ICH Intracranial hemorrhage; LMWH Low molecular weight heparin; MRSA Methicillin resistant staphylococcus aureus; N No; NSTEMI Non-ST segment elevation myocardial infarction; PPI Proton pump inhibitor; qd Once daily; SAH Subarachnoid hemorrhage; SBP Systolic blood pressure; SDH Subdural hematoma; STEMI ST segment elevation myocardial infarction; TIA Transient ischemic attack; Y Yes.