Cardiovascular and Renal Drugs
Advisory Committee Briefing Document

Effient (Prasugrel)

Acute Coronary Syndromes Managed by Percutaneous Coronary Intervention

Meeting Date: 03 February 2009

FDA Division of Cardiovascular and Renal Drugs

Eli Lilly and Company

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Executive Summary

Eli Lilly and Company and its development partner Daiichi Sankyo are seeking approval of EFFIENT (prasugrel) for the reduction of cardiovascular (CV) events in acute coronary syndrome (ACS) patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) when managed with percutaneous coronary intervention (PCI) and patients with ST-segment elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

Prasugrel, a thienopyridine adenosine diphosphate (ADP) receptor antagonist, is an orally administered prodrug requiring in vivo conversion to an active metabolite that irreversibly inhibits platelet activation and aggregation mediated by the $P2Y_{12}$ receptor. The absorption and metabolism of prasugrel are rapid. The pharmacokinetics and pharmacodynamics are not prone to clinically relevant drug-drug interactions nor genetic variations in CYP enzymes.

There is a clear medical need for improved therapies in the treatment of patients with ACS. Although clopidogrel is considered a significant advance in the treatment of ACS, it has limitations that clinicians are attempting to address by higher doses and timing of administration. The data supporting EFFIENT's approval demonstrate a further advance in the treatment of ACS patients.

Efficacy Results from TRITON-TIMI 38

TRITON-TIMI 38 was the pivotal study of the efficacy of prasugrel in patients with ACS. This was a double-blind, 13,608-patient trial in which patients were followed for an average of 12 months, randomized either to prasugrel (60-mg loading dose [LD]/10-mg maintenance dose [MD]) or to clopidogrel at the standard, approved dose (300-mg LD/75-mg MD), with aspirin as background therapy in all patients. Prasugrel was superior to clopidogrel across the primary endpoints and all pre-specified secondary endpoints, first in the UA/NSTEMI patient population and then in the All ACS population. Within the STEMI population, the primary and all secondary endpoints also favored prasugrel. Within the All ACS population, prasugrel provided:

- A highly statistically significant 19% reduction in the rate of the primary composite efficacy endpoint of CV death, nonfatal MI, or nonfatal stroke compared with clopidogrel (9.4% versus 11.5%; HR=0.812; p=0.0004). The superior efficacy of prasugrel was apparent within the first 3 days of hospitalization (4.7% versus 5.6%, HR=0.82, p=0.01), and persisted during maintenance dosing (5.6% versus 6.9%; HR=0.80, p=0.003).
- A statistically significant reduction in all pre-specified secondary endpoints, including a reduction in the incidence of stent thrombosis. These reductions were also statistically significant when the UA/NSTEMI and STEMI populations were analyzed separately.

- There was also a significant reduction in the incidence of MI, particularly for myocardial infarctions associated with large degrees of myonecrosis. There was also a significant reduction in the need for urgent target vessel revascularization (UTVR).
- A statistically significant reduction in recurrent primary endpoint events compared to clopidogrel (10.8% versus 15.4%; HR=0.65; p=0.016). There was a reduction in cardiovascular death following a nonfatal primary endpoint in patients treated with prasugrel.
- Beneficial effects across prespecified subgroups based on sex, ethnicity, body weight, geographic regions, adjunctive therapy, and stent type.

Safety Results from TRITON-TIMI 38

The safety profile of prasugrel is consistent with the target pharmacology of thienopyridine therapy.

Bleeding. Antithrombotic advances in the treatment of coronary heart disease (aspirin, anticoagulation, GPIIb/IIIa inhibition, thrombolysis, and earlier thienopyridines) have all been accompanied by an increase in bleeding. Prasugrel continues the pattern seen with earlier antiplatelet agents: Each step, from placebo to aspirin (ATC 2002), from aspirin to clopidogrel (Yusuf et al. 2003), from clopidogrel to clopidogrel-aspirin (CURE 2001; Mehta et al. 2001), and now from clopidogrel-aspirin to prasugrel-aspirin, has provided increased clinical benefit, each time taking into account a large reduction in thrombotic events and a variously smaller increased incidence of major bleeding. In the CURE study, for example, clopidogrel plus aspirin was associated with a 38% increase in the odds of major bleeding events compared with aspirin, but the net benefit was still positive. So as anticipated, treatment with prasugrel had an increased risk of bleeding relative to treatment with clopidogrel.

Since each of the components of the TRITON-TIMI 38 primary endpoint was related to irreversible harm to the heart or to the CNS, the only bleeding that might bear upon prasugrel's net benefit is major or life-threatening bleeding. Bleeding in TRITON-TIMI 38 was characterized as "Major" by established TIMI criteria, and bleeding in the prasugrel group was more common in every subcategory:

- Overall non-CABG-related Major Bleeding 2.17% (prasugrel) versus 1.65% (clopidogrel), HR=1.32, p=0.03);
- Non-CABG-related Life-Threatening Bleeding 1.3% versus 0.8%, HR=1.5, p=0.015;
- Non-CABG-related fatal bleeding (21versus 6).

Hematologic toxicity. Hematologic toxicity, common with ticlopidine and reported (although rarely) with clopidogrel, was seen less frequently in patients treated with prasugrel. No cases of TTP have been observed with prasugrel.

Other Safety Findings. Minor bleeding, like major bleeding, was significantly more common in the prasugrel patients. In other respects, the tolerability of prasugrel was similar to that of clopidogrel, as demonstrated by similar incidences of the following:

- Common treatment-emergent adverse events (TEAEs),
- Serious adverse events,
- Study drug discontinuation,
- Pre-specified, non-hemorrhagic, clinically relevant TEAEs and laboratory values (allergic reactions [including angioedema], abnormal hepatic function, and torsades de pointes/QT prolongation).

Treatment-emergent non-benign neoplasms, mainly adenocarcinomas of the colon, were more common in the prasugrel group than in the clopidogrel group. This difference was not statistically significant and the timing of these findings was not consistent with the known biology of solid tumors. Although a possible causative effect or the play of chance can not be ruled out, the difference may be due to detection/ascertainment bias related to the higher incidence of bleeding observed in prasugrel-treated patients.

Net Benefit of Prasugrel Compared with Clopidogrel

The overall benefit/risk profile for prasugrel compared with clopidogrel is favorable in the setting of ACS managed by PCI as demonstrated by the TRITON-TIMI 38 study results. Even when the composite endpoint was expanded to include all cause death, nonfatal MI or nonfatal stroke, prasugrel demonstrated a clinically relevant and statistically significant beneficial effect (HR=0.83, p=0.0003). This composite endpoint incorporated any fatal hemorrhage and, as the duration of follow-up in TRITON-TIMI 38 was up to 15 months, also incorporated any irreversible ischemic complication of a nonfatal hemorrhage. Even more conservative estimates of net clinical benefit, in which permanent myocardial damage was weighted no more heavily than the largely transient risk of non-CABG TIMI Major bleeding, favored treatment with prasugrel over clopidogrel in each population (all $p<0.05$ for the All ACS, UA/NSTEMI, and STEMI populations). These data indicate that for every 1,000 patients treated with prasugrel, there were 22 fewer patients with MI, and 5 more with non-CABG-related TIMI Major bleeding. The estimated number needed to treat (NNT) with prasugrel, compared to the approved clopidogrel regimen, to prevent one primary efficacy event over 15 months is approximately 46; the number needed to harm (NNH) for one non-CABG-related TIMI Major bleed is approximately 169.

Patient Selection and Dose Adjustment

The favorable net clinical benefit of prasugrel seen in the total TRITON-TIMI 38 study population can be further improved by giving special attention to certain patient populations.

Prasugrel-related major bleeding was especially frequent in patients with prior transient ischemic attack (TIA) or stroke. Prasugrel should not be administered to patients with such histories or to patients with active pathological bleeding.

Patients <60 kg or ≥75 years of age were also at high risk of bleeding. The TRITON-TIMI 38 population pharmacokinetic substudy showed that the special risk in these patients was largely attributable to increased exposure to the prasugrel active metabolite. Results from this substudy and additional information obtained from clinical pharmacology studies support data driven dosing recommendations to improve the expected safety profile of prasugrel in these patient populations. Administration of a lower MD dose (5 mg) to these patients should reliably provide drug exposure similar to that seen in younger, heavier patients who received the 10-mg prasugrel dose studied in TRITON-TIMI 38.

For patients <75 years of age, at least 60 kg, and without prior TIA/stroke, the 10-mg prasugrel maintenance dose provides an acceptable benefit/risk profile and is superior to the 75-mg clopidogrel maintenance dose. These patients were approximately 80% of the TRITON-TIMI 38 study population, and they are a similar portion of the "real-world" ACS/PCI population.

Conclusion

The Sponsor is seeking approval of EFFIENT (prasugrel) for the reduction of CV events in ACS patients when managed with PCI with a 60-mg LD and a 10-mg MD and an additional recommendation for a 5-mg MD in patients ≥75 years of age and <60 kg. The Sponsor has demonstrated that prasugrel is clinically superior to clopidogrel in the reduction of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke in ACS patients undergoing PCI. This new advance in treatment is accompanied by an increase in bleeding events, but there is net clinical benefit in the overall trial population, which includes patients recommended for dose adjustment and the contraindicated TIA/Stroke population. The overall benefit provided by prasugrel can be increased by the contraindication of prasugrel in patients with a prior TIA/stroke and the reduction of the MD dose for patients <60 kg or ≥75 years of age. The Sponsor has proposed a risk-management program to assist in the appropriate management of identified and potential risks associated with prasugrel.

On 18 December 2008, the CMP adopted a positive opinion to recommend granting marketing authorization consistent with the US proposal outlined above. The Sponsor believes the data in this document support a similar recommendation by the FDA Cardio-Renal Advisory Committee.

Table of Contents

Abbreviations and Definitions

AAA	Abdominal aortic aneurysm
ACC/AHA	American College of Cardiology/American Heart Association
ACEI	Angiotensin II converting enzyme inhibitor;
ACS	Acute coronary syndromes
ADP	Adenosine diphosphate
AE	Adverse event
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blockers
ARC	Academic Research Consortium
ARO	Academic Research Organization
ASA	Aspirin
AUC	Area under the plasma concentration-time curve
BMS	Bare metal stent
BT	Bleeding time
CABG	Coronary artery bypass graft (surgery)
CAD	Coronary artery disease
CBC	Complete blood count
CCU	Critical/Coronary care unit
CEC	Clinical Endpoint Committee
CI	Confidence interval
CIE	Cardiac ischemic event
CK-MB	Creatine kinase-myocardial bands
CMH	Cochran-Mantel-Haenszel (test)
CrCL	Creatinine Clearance
CRF	Case report form
CRO	Contract research organization
CS-TEAE	Clinically significant treatment-emergent adverse event
CPR	Cardiopulmonary resuscitation

CV	Cardiovascular
CVA	Cerebrovascular accident
DES	Drug-eluting stent
DM	Diabetes mellitus
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ESC	European Society of Cardiology
GP	Parenteral glycoprotein (GP). Often used with reference to GPIIb/IIIa inhibitors
H_2	Histamine 2 receptor
Hct	Hematocrit
HCRI	Harvard Clinical Research Institute
Hgb	Hemoglobin
HDL	High density lipoprotein
HMG	Co-A 3-hydroxy-3-methylglutaryl coenzyme A
HR	Hazard ratio
IABP	Intraaortic balloon pump
ICH	Intracranial hemorrhage
ICU	Intensive care unit
INFF	Immediate Notification Fax Form
INR	International Normalized Ratio
IPA	Inhibition of platelet aggregation
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
JUMBO-TIMI 26	A study also known as H7T-MC-TAAH
K-M	Kaplan-Meier
LAD	Left anterior descending artery
LCX	Left Circumflex artery
LD	Loading dose

LDL	Low-density lipoprotein
LSS	Lilly Safety System
LY640315	Prasugrel
MD	Maintenance dose
MPA	Maximum Platelet Aggregation
MedDRA	Medical Dictionary of Regulatory Activities (Version 9.1)
MI	Myocardial infarction
MRI	Magnetic resonance imaging
Non-CABG	Non-coronary artery bypass graft (surgery)
NF	Nonfatal
NNH	Number needed to harm
NNT	Number needed to treat
NMSC	Nonmelanotic skin cancers
NSAID	Non-steroidal anti-inflammatory drug
NSTEMI	Non-ST-segment elevation myocardial infarction
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention (which can include balloon angioplasty, coronary artery stenting, and atherectomy)
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	Pharmacokinetic(s)
PPI	Proton pump inhibitor
PT	Prothrombin time
PPMI	Peri-procedural myocardial infarction
Pras-AM	Prasugrel's active metabolite
Prasugrel	Generic name for Effient, LY640315, prasugrel.base, and prasugrel.HCl
PRINCIPLE-TIMI 44	A study also known as H7T-MC-TABL
PRBC	Packed red blood cells
RCA	Right coronary artery

Reporting database	A point-in-time copy of the collection database. The test reporting database is used to ensure that data are valid and sufficient for the intended analyses before creation of the final reporting database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
SAE	Serious adverse event
SAT	Subacute stent thrombosis
SOC	System organ class
Sponsor	Eli Lilly and Company in collaboration with Daiichi Sankyo
STEMI	ST-segment elevation myocardial infarction
TBILI	Total bilirubin
TCIPA	Tumor cell-induced platelet aggregation
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
TIMI	Thrombolysis In Myocardial Infarction study group. Often used with reference to "TIMI bleeding criteria" developed by the TIMI study group.
TRITON-TIMI 38	A study also known as H7T-MC-TAAL
TTP	Thrombotic thrombocytopenic purpura
UA	Unstable angina
UA/NSTEMI	Unstable angina /Non-ST-segment elevation myocardial infarction
UFH	Unfractionated heparin
ULN	Upper limit of normal
UTVR	Urgent target vessel revascularization

Note to the Reader:

- All trademarks used herein are the property of their respective owners
- At the time of issuance of this briefing document, the EFFIENT (prasugrel) application is under review by the Food and Drug Administration. Consequently, some information contained in this document will be subjected to revision. Specifically,
    - The Risk Evaluation and Mitigation Strategies plan described is a proposal that requires finalization with FDA upon its review.
    - The full prescribing information and labeling is under review.

1. Introduction

1.1. Introduction

Eli Lilly and Company, in collaboration with its development partner Daiichi Sankyo, has submitted a New Drug Application (NDA 22-307) for the use of prasugrel in patients with Acute Coronary Syndrome (ACS) undergoing percutaneous coronary intervention (PCI). The Division of Cardiovascular and Renal Products (DCRP) of the US Food and Drug Administration (FDA) has scheduled an Advisory Committee meeting for 3 February 2009 to discuss regulatory considerations surrounding the application.

The Sponsor has prepared this briefing document to summarize key aspects of the prasugrel development program and NDA, including:

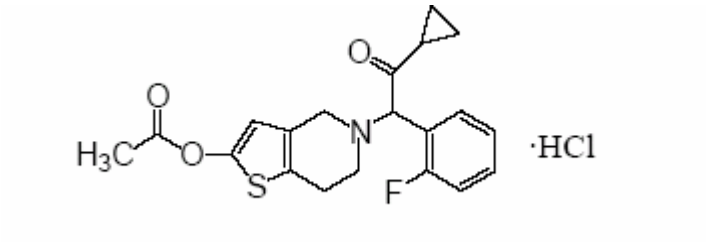
- Need to improve clinical outcomes of patients with ACS undergoing PCI;
- Pharmacokinetics and pharmacodynamics of prasugrel, a new third generation thienopyridine;
- Rationale for the choice of prasugrel loading and maintenance doses in the Phase 3 TRITON-TIMI 38 study;
- Efficacy and safety data from TRITON-TIMI 38 focusing on the overall benefit/risk profile;
- Selected regulatory review topics;
- Risk Management Program and the Risk Evaluation and Mitigation Strategy (REMS).

Much of the development of prasugrel, including the Phase 2 study JUMBO-TIMI 26, and the pivotal Phase 3 study TRITON-TIMI 38, was performed in collaboration between the Sponsor and the Thrombolysis In Myocardial Infarction (TIMI) Study Group (consulting academic research group).

1.2. Pharmacologic Class and Mode of Action

Prasugrel, a thienopyridine adenosine diphosphate (ADP) receptor antagonist, is an orally administered prodrug requiring in vivo conversion to an active metabolite that irreversibly inhibits platelet activation and aggregation mediated by the $P2Y_{12}$ receptor. Once the active metabolite is bound to the $P2Y_{12}$ receptor, platelet activation and aggregation are inhibited for the lifetime of the platelet. After drug discontinuation, platelet activation and aggregation return to baseline, typically over 5 to 9 days, as new platelets are formed.

The chemical structure of prasugrel hydrochloride is:



The proposed US trade name for prasugrel is EFFIENT. Each 10-mg EFFIENT tablet is manufactured with 10.98 mg of prasugrel HCl, equivalent to 10 mg of prasugrel; each 5-mg EFFIENT tablet is manufactured with 5.49 mg of prasugrel HCl, equivalent to 5 mg of prasugrel.

1.3. Proposed Indication and Dose

The indication as proposed in the labeling is:

> *EFFIENT™ (prasugrel) is indicated for the reduction of cardiovascular events in patients with ACS as follows:*
>
> - *Unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) when managed with percutaneous coronary intervention (PCI).*
> - *ST-segment elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.*
>
> *EFFIENT has been shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke.*

The proposed dose regimen of EFFIENT is a single 60-mg loading dose (LD) followed by a 10-mg once-daily maintenance dose (MD), co-administered with ASA (75-325 mg daily). A reduced MD regimen (5 mg once daily) is proposed for patients weighing less than 60 kg and those aged 75 years or older.

1.4. Overview of the Prasugrel Clinical Development Program

The overall objective of the prasugrel clinical development program was to establish the efficacy and safety of prasugrel, in combination with ASA, for treatment of adult patients with ACS at intermediate to high risk for ischemic complications. This NDA seeks to demonstrate the efficacy and safety of prasugrel in ACS patients undergoing PCI, based largely on the TRITON-TIMI 38 trial, which enrolled 13,608 patients worldwide. An additional large clinical trial, currently being conducted in collaboration with the Duke Clinical Research Institute (DCRI), will examine the role of prasugrel in patients with ACS who are managed without an invasive strategy (TRILOGY-ACS). The planned enrollment is 10,300 patients worldwide.

The current application consists of 46 completed placebo-controlled or active-comparator (clopidogrel) controlled studies. Across all studies, 8656 patients received at least 1 dose of prasugrel. After discussion with the Sponsor regarding the prasugrel development program, the FDA and CHMP agreed that a single, large, clinical outcome, superiority study (TRITON-TIMI 38) against the active comparator clopidogrel was adequate to support regulatory filings and registration for the proposed indication.

1.5. Regulatory Background

Eli Lilly, Daiichi Sankyo, and the TIMI Study Group have had numerous interactions with the FDA and global regulatory authorities during the development of prasugrel resulting in agreement that: 1) preclinical studies and clinical pharmacology studies were adequate to support regulatory filing and registration; 2) the definitions for the primary (the composite of CV death, nonfatal MI, or nonfatal stroke) and secondary endpoints of TRITON-TIMI 38 were adequate to demonstrate clinical benefit; and 3) the statistical analysis plan for the primary and secondary endpoints for TRITON-TIMI 38 was acceptable. In addition, a Special Protocol Assessment (SPA) was obtained for TRITON-TIMI 38 and FDA agreed that a single trial is acceptable for registration so long as robust statistical significance is demonstrated and safety is acceptable.

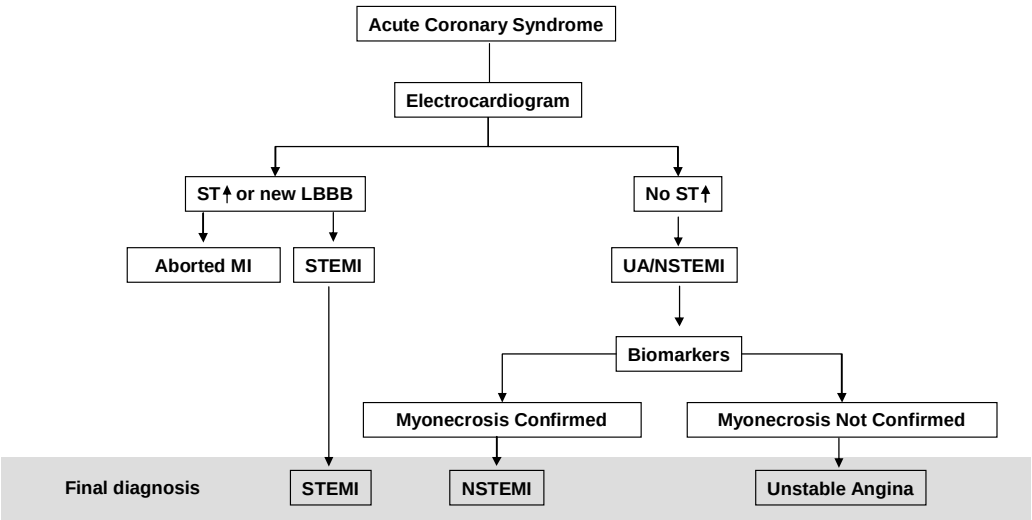
On 26 December 2007, the Sponsor submitted an NDA for prasugrel which received priority review status. The decision to provide priority review status was based on the results of TRITON-TIMI 38, which demonstrated significant improvement over the current standard of care in ACS patients undergoing PCI. The priority review set a 6-month review schedule with an initial PDUFA date of 26 June 2008. The FDA extended the review period by three months based on supplemental information provided by the Sponsor but did not complete its review by the revised PDUFA date of 26 September 2008.

In early February 2008, the Sponsor submitted a marketing authorization application to the European Medicines Agency; the content of this application was essentially identical to that of the US NDA. On 18 December 2008, the CHMP adopted a positive opinion, recommending to grant marketing authorization for prasugrel 5-mg and 10-mg film-coated tablets for prophylaxis against atherothrombotic events in patients with acute coronary syndrome undergoing primary or delayed percutaneous coronary intervention. The recommended dosing is a loading dose of 60 mg and a daily maintenance dose of 10 mg. However, for patients at special risk ($\geq$75 years of age, <60 kg), a dose reduction is strongly recommended. Following the administration of a loading dose of 60 mg, the 5-mg once daily maintenance dose is to be given. Prasugrel will be marketed under the trade name EFIENT in Europe.

2. ACS and Medical Need

2.1. Acute Coronary Syndrome

Acute coronary syndrome (ACS) represents a spectrum of ischemic myocardial events ranging from unstable angina (UA) to non-ST-segment-elevation myocardial infarction (NSTEMI) to ST-segment-elevation myocardial infarction (STEMI). Figure 2.1 displays acute coronary syndrome defined by electrocardiographic criteria and subsequent biomarker evidence of myocardial necrosis (White and Chew 2008). Over 1.4 million hospitalizations for ACS occur in the United States each year (Rosamond et al. 2008). Patients with UA or NSTEMI comprise approximately 70% of the population presenting with ACS (Goldberg et al. 2004).



Source: Adapted from White and Chew 2008.

Figure 2.1. Acute Coronary Syndrome

Most commonly, ACS results from rupture or erosion of an atherosclerotic plaque within an epicardial coronary artery with subsequent platelet activation, aggregation and thrombin generation, which collectively cause intracoronary thrombosis (Mizuno et al. 1992). This thrombotic process diminishes microcirculatory perfusion by reducing coronary blood flow through thrombotic regions, as well as by distal embolization of thrombus. The extent of the intracoronary thrombosis and distal embolization and their location largely determines the clinical presentation.

2.2. Limitations of Current Antiplatelet Therapy in ACS

Management of patients presenting with ACS involves rapid restoration of epicardial and microvascular blood flow by pharmacologic and catheter-based means and suppression of subsequent ischemic events through antiplatelet therapies (White and Chew 2008). Dual

antiplatelet therapy with aspirin (ASA) and a thienopyridine (either ticlopidine or clopidogrel) is currently recommended for the prevention of recurrent atherothrombotic events in patients who present with ACS (AHA/ESC Guidelines). Clopidogrel has largely replaced ticlopidine owing to a higher incidence of life-threatening adverse hematologic reactions with ticlopidine, including neutropenia/agranulocytosis, thrombotic thrombocytopenia purpura, and aplastic anemia (TICLID USPI 2001).

Despite long term therapy with dual anti-platelet therapy, patients with ACS undergoing PCI still suffer substantial morbidity and mortality. Recent clinical trials on a background of clopidogrel plus ASA demonstrate persistently high rates of death, MI or need for coronary revascularization in patients with ACS (Kastrati et al. 2006 [ISAR-REACT 2]; Stone et al. 2006 [ACUITY]) (Table 2.1).

Table 2.1. Clinical Outcomes at 1 Year for Recent ACS Studies.

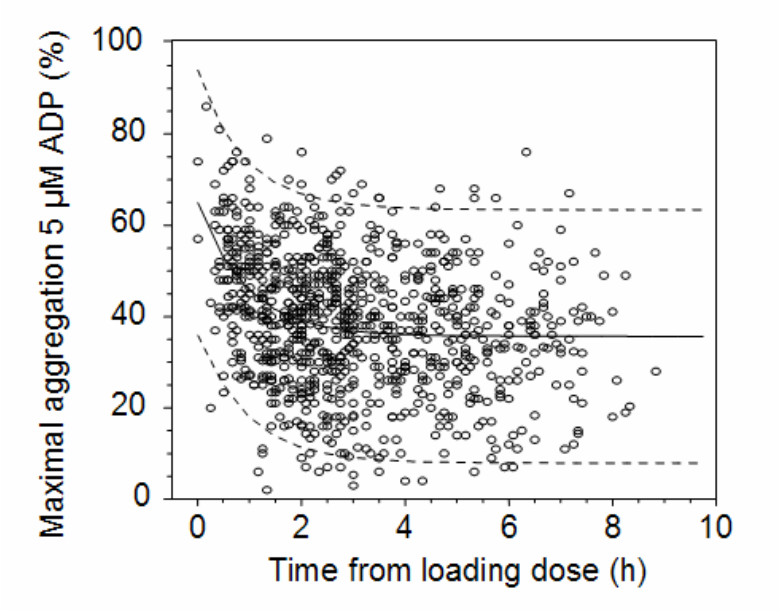
	Total N	D/MI/TVR	Death	MI	TVR
ACUITY	7,789	1,465 (18.8%)	247 (3.2%)	682 (8.8%)	928 (11.9%)[a]
ISAR-REACT 2	2,022	515 (25.5%)	94 (4.6%)	202 (10.0%)	301 (14.9%)[b]

[a] Unplanned revascularization for ischemia.

[b] Target vessel revascularization = CABG or repeat PCI for symptoms or ischemia.

The risk of mortality is highly correlated to clinical presentation, with patients over the age of 60 years being at highest risk, particularly those that present with ECG changes and elevations of cardiac biomarkers (Ferguson et al. 2004 [SYNERGY]). Diabetes (Beckman et al. 2002) and the clinical presentation of STEMI (Huczek et al. 2007) are also associated with high early and late risk of CV death, MI, and stroke.

Several studies have suggested that the large inter-individual response to clopidogrel, as assessed by ex vivo measurement of residual ADP-inducible platelet aggregation, may contribute to the risk of recurrent ischemic events (Geisler et al. 2006; Hochholzer et al. 2006; Buonamici et al. 2007; Geisler and Gawaz 2007; Geisler et al. 2008). This variability ranges from high residual levels of aggregation (70-80%, i.e., no apparent inhibition of ADP-induced platelet aggregation following clopidogrel dosing) to low residual levels of aggregation (<20%, i.e., high levels of platelet inhibition). Figure 2.2 is one example illustrating considerable variability in maximal platelet aggregation to 5 µmol/L ADP following a 600 mg clopidogrel loading dose in 1,001 patients undergoing cardiac catheterization.



Source: Hochholzer et al. 2005.

Figure 2.2. Variable platelet response to clopidogrel in 1001 patients undergoing cardiac catheterization.

Multiple investigators have dichotomized the patient response to clopidogrel into “poor or non-responders” and “responders”. Although there are various definitions and thresholds for “poor response”, most studies assessing clinical outcomes by response status have demonstrated a high risk of ischemic events for “poor responders” who usually comprise 25-30% of the population (Gurbel and Tantry 2006) (Figure 2.3).

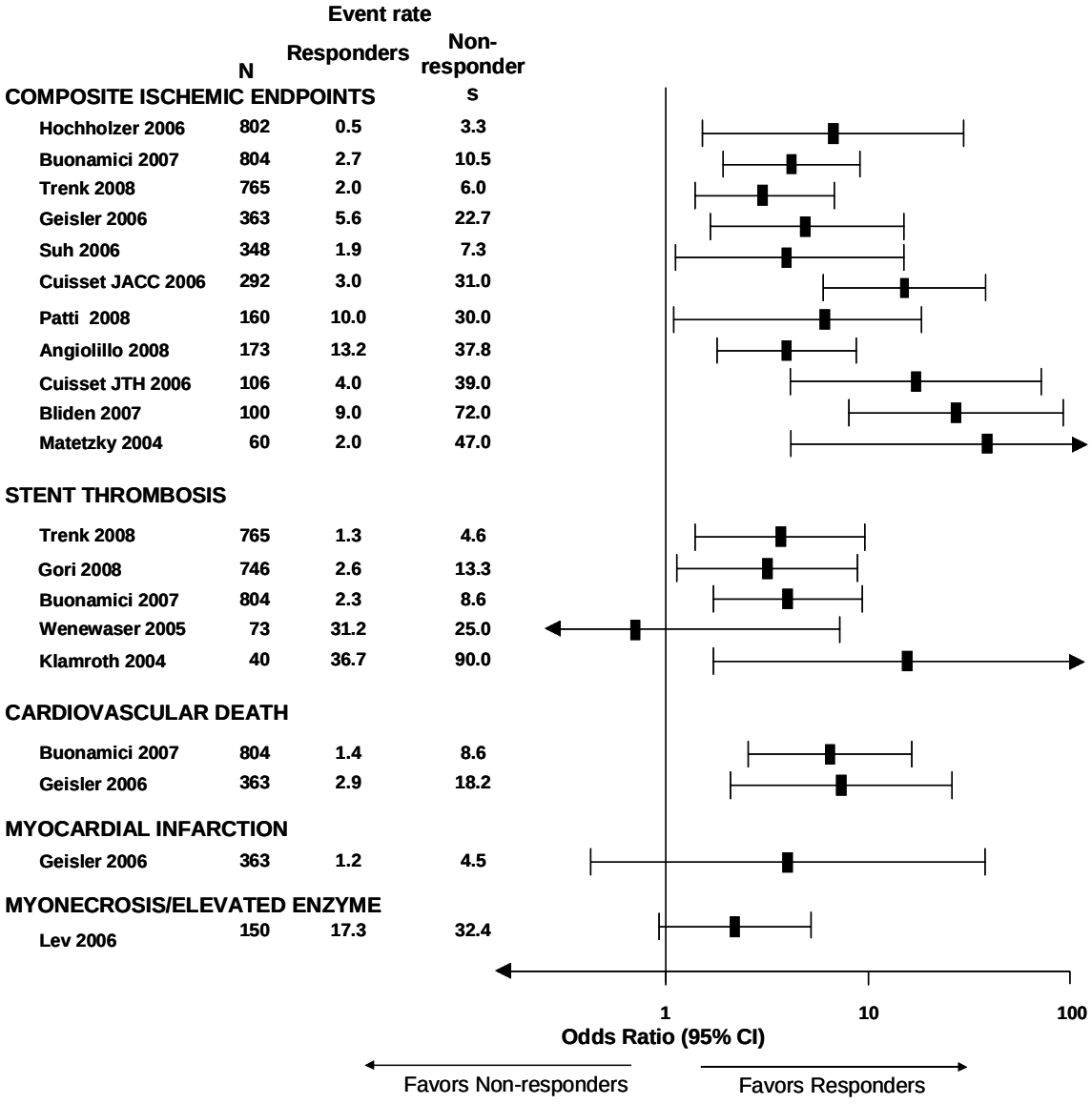
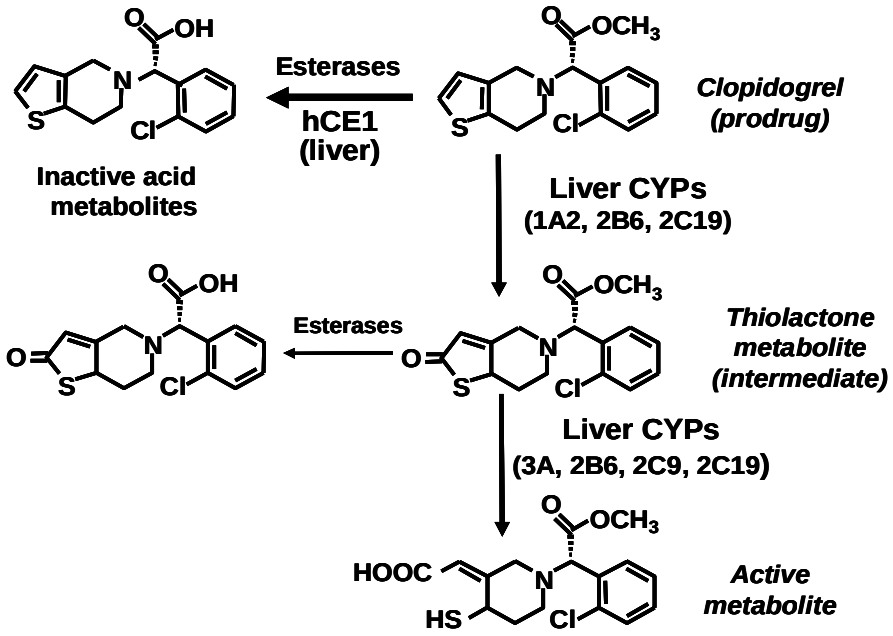


Figure 2.3. **Selected published comparisons of clinical outcomes between clopidogrel responders and non-responders.**

2.3. Clopidogrel Response Variability

The mechanisms leading to a variable antiplatelet response to clopidogrel are multifactorial and not fully understood. In addition to known factors influencing pharmacologic response to therapy such as non-compliance, clinical factors such as age, obesity, diabetes mellitus, initial levels of platelet reactivity, and clinical presentation (UA/NSTEMI versus STEMI) may contribute to the observed variability (Gawaz et al. 1996; Angiolillo et al 2005; Michelson et al 2007; Geisler et al. 2008; Peace et al. 2008).

Recent data suggest that a component of inter-individual variability results from genetic variants that affect the activation of clopidogrel. Like all thienopyridines, clopidogrel is a prodrug that requires in vivo conversion to an active metabolite that irreversibly binds to and inhibits the $P2Y_{12}$ ADP receptor (Figure 2.4). Approximately 85% of the ingested prodrug is metabolized in the liver to inactive metabolites by esterases. The remaining prodrug is converted in the liver to the active metabolite via two successive oxidative steps mediated by the cytochrome P450 (CYP) family of enzymes. Importantly, the CYP2C19 enzyme, encoded by a highly polymorphic gene, is involved in both oxidative steps.



Source: Kurihara et al. 2005; Tang et al. 2006.

Figure 2.4. The metabolic pathway for clopidogrel to its active and inactive metabolites.

Variant alleles of CYP2C19 encode a highly altered or loss-of-function enzyme and occur frequently in Caucasians (approximately 30%), Africans (approximately 40%) and Asians (approximately 60%) (Yamada et al. 1998, Dandara et al. 2001, Myrand et al. 2008). Multiple studies have assessed the impact of CYP2C19 loss-of-function alleles on clopidogrel pharmacokinetics and pharmacodynamics. Subjects with at least one variant allele had increased levels of the unmetabolized clopidogrel prodrug and reduced levels of the active metabolite compared to subjects with no variant alleles (Kim et al. 2008; Umemura et al. 2008). Consistent with the pharmacokinetic effects, presence of at least one variant allele contributes to the variable pharmacodynamic response to clopidogrel (Hulot et al. 2006; Fontana et al. 2007; Giusti et al. 2007; Fontana et al. 2008; Frere et al. 2008; Kim et al. 2008; Trenk et al. 2008; Umemura et al. 2008).

The association of CYP2C19 reduced function with adverse clinical outcomes in clopidogrel-treated patients has been demonstrated recently in several studies. In a study of patients with acute myocardial infarction, those with 2 variant alleles were at higher risk of cardiovascular death, myocardial infarction, or stroke (Simon et al. 2008). In clopidogrel-treated patients with ACS, carriers of at least one variant allele had higher risk of cardiovascular death, nonfatal myocardial infarction or urgent revascularization compared to patients with no variant alleles (Collet et al. 2008). Additionally, carriers of at least one variant allele experienced a higher rate of stent thrombosis than non-carriers (Collet et al. 2008; Gori et al. 2008). Taken together, these results provide strong evidence linking CYP genetic variation to lower active drug metabolite exposure, less platelet inhibition, and less protection from recurrent ischemic events by clopidogrel.

2.4. Conclusion

Thrombosis is central to the pathophysiology of ACS, and thus prevention of platelet-mediated thrombosis is central to therapy. Substantial evidence has validated the platelet $P2Y_{12}$ ADP receptor as a key target for therapy. Treatment with thienopyridines has been shown to reduce ischemic events in large population-based studies of patients with ACS, however, patients continue to suffer morbidity and mortality. Limitations of currently approved thienopyridines include untoward side effects and suboptimal platelet response. Patients with genetic variants of the CYP system may be at particular risk because of the inability to effectively metabolize the prodrug, clopidogrel, to its active moiety. These limitations of current therapy indicate the need to develop additional new therapies to improve outcomes for patients with ACS.

3. Overview of Prasugrel Pre-Clinical Development

An extensive series of pharmacodynamic, pharmacokinetic, and toxicology studies in animals has been conducted with prasugrel. Commonly used nonclinical models for antiplatelet research (primarily rat) and safety assessment (primarily rat and dog) were employed. Doses selected in the pharmacodynamic studies were chosen to evaluate a full range of dose-response activity. The doses for each of the toxicity studies were chosen to provide substantial challenge to the test animals and cause systemic toxic effects; low doses were selected to provide no-observed-effect and/or no-observed-adverse-effect levels (NOEL, NOAEL).

Key findings from the pre-clinical development program are:

- Prasugrel is a prodrug whose active metabolite specifically and irreversibly inhibits the $P2Y_{12}$ class of platelet ADP receptor and consequently inhibits numerous ADP-mediated platelet activities.
- In several species, oral administration of prasugrel resulted in time- and dose-dependent inhibition of ex vivo platelet aggregation and in vivo thrombus formation and prolonged bleeding time; effects were enhanced in the presence of aspirin. At the doses tested, prasugrel was approximately 10- and 100-fold more potent than clopidogrel and ticlopidine, respectively, in inhibiting platelet function as measured in vivo by inhibition of thrombus formation and ex vivo by inhibition of platelet aggregation.
- In vitro, the active metabolites of prasugrel and clopidogrel are approximately equipotent on a molar basis. In vivo, prasugrel is more potent than clopidogrel. This difference is related to the more efficient formation of prasugrel's active metabolite from the prodrug.
- Following oral administration, prasugrel was rapidly absorbed and hydrolyzed by esterases, including carboxylesterases, and then metabolized by cytochrome P450 enzymes to form the active metabolite. The metabolic pathway was similar in mice, rats, dogs, and humans.
- Prasugrel has low toxicity following administration of single or repeated doses. Decreased body weight relative to control was seen in repeat-dose studies in the rodent and dog. Effects on liver were mostly reflective of enzyme induction. Increased alkaline phosphatase (ALP) was observed in the dog.

- In vitro metabolism studies demonstrate that prasugrel's main circulating metabolites are not likely to cause clinically significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A, or induction of CYP1A2 or CYP3A. Prasugrel is a weak inhibitor of CYP2B6. Prasugrel is not anticipated to have a significant effect on the pharmacokinetics of drugs that are primarily metabolized by CYP2B6, such as halothane, cyclophosphamide, propofol, and nevirapine.
- Prasugrel was not genotoxic in two tests in vitro (Ames bacterial gene mutation test, clastogenicity assay in Chinese hamster fibroblasts) and in one test in vivo (micronucleus test by intraperitoneal route in mice).
- No compound-related tumors were observed in a 2-year rat study with prasugrel at oral doses up to 100 mg/kg/day (>100 times the recommended therapeutic exposures in humans [based on plasma exposures to the major circulating human metabolite]). There was an increased incidence of hepatocellular adenomas in mice exposed for 2 years to high doses (>250 times the human metabolite exposure). These tumors are common in mice and are most likely related to chronic enzyme induction and are not considered relevant to human risk.
- Prasugrel had no effect on fertility of male and female rats at oral doses up to 300 mg/kg/day (>80 times the human major metabolite exposure at a daily dose of 10 mg prasugrel).

4. Overview of Prasugrel Development Plan

The prasugrel clinical development program consisted of 46 completed placebo-controlled or active-comparator (clopidogrel) controlled studies. The objectives of the prasugrel clinical program are to:

- Understand prasugrel metabolism and how it impacts pharmacokinetic (PK) and pharmacodynamic (PD) responses.
- Characterize the PK of prasugrel in healthy subjects and the target patient population.
- Characterize the PD response to prasugrel through evaluation of platelet inhibition.
- Identify any intrinsic or extrinsic factors that may affect the PK and/or PD response to prasugrel.
- Identify any potential of prasugrel to affect the PK and/or PD response of other drugs.
- Select a Phase 3 dosing regimen likely to achieve faster onset after a LD with higher and more consistent levels of platelet inhibition than the approved clopidogrel regimen (300-mg/75-mg LD/MD).
- Demonstrate that this dosing regimen results in superior efficacy with an acceptable safety profile in subjects with ACS undergoing PCI.
- Establish criteria for dose-adjustment recommendations based on exposure-efficacy and exposure-safety relationships.

The Sponsor also has a clinical development program to evaluate the safety and efficacy of prasugrel in patients with ACS who are medically managed without an invasive strategy. This program includes the TRILOGY-ACS study and a large observational study in Europe.

Table 4.1 presents a summary of some of the key studies in the prasugrel clinical development program that addressed these objectives. Across all studies, 8656 patients received at least 1 dose of prasugrel. The majority (77.9%) of exposure data are derived from patients in the large, Phase 3 pivotal Study TRITON-TIMI 38 (H7T-MC-TAAL) in patients with ACS managed with PCI. In TRITON-TIMI 38, 6741 patients were exposed for approximately 6483 patient-years. Approximately 60% of these patients were exposed for ≥365 days and 40% were exposed for ≥450 days.

Table 4.1. Overview of Studies in the Prasugrel Development Plan

Study	Treatment duration	# Enrolled [Randomized]	Dose	Study Design and Objectives
H7T-EW-TAAA	up to 21 days	42 [21]	Prasugrel 40 mg LD/7.5 mg MD Prasugrel 60 mg LD/15 mg MD clopidogrel 300 mg LD / 75 mg MD	Phase 1, double-blind, placebo-controlled, randomized, parallel-group study. Primary Objective: To assess the safety and tolerability of prasugrel after multiple dose administration of up to 21 days in healthy subjects.
H7T-EW-TAAE	up to 21 days	45 [32]	Prasugrel 20 mg LD/5 mg MD Prasugrel 30 mg LD/7.5 mg MD Prasugrel 40 mg LD/10 mg MD Prasugrel 60 mg LD/15 mg MD clopidogrel 300 mg LD / 75 mg MD Aspirin 325 mg daily	Phase 1, open-label, randomized, dose escalation study. Primary Objective: To assess the safety and tolerability of prasugrel when co-administered with aspirin.
H7T-EW-TAAJ	up to 21 days	68 [66]	Prasugrel 60 mg LD Clopidogrel 300 mg LD	Phase 1, open-label, randomized, two period crossover study. Primary Objective: To evaluate the inhibition of platelet aggregation.
H7T-EW-TAAD	28 days	101 [78]	Prasugrel 40 mg LD/5 mg MD Prasugrel 40 mg LD/7.5 mg MD Prasugrel 60 mg LD/10 mg MD Prasugrel 60 mg LD/15 mg MD Clopidogrel 300 mg LD/75 mg MD Aspirin 325 mg daily	Phase Ib, randomized, partially blind, parallel-group, multiple-dose study in patients with stable atherosclerosis. Primary Objective: To assess the pharmacodynamic effects (inhibition of platelet aggregation and bleeding times) of prasugrel plus aspirin compared to clopidogrel plus aspirin in patients with stable atherosclerosis.

Table 4.1. Overview of Studies in the Prasugrel Development Plan (continued)

Study	Treatment duration	# Enrolled [Randomized]	Dose	Study Design and Objectives
JUMBO-TIMI 26 [H7T-MC-TAAH]	30-days	905 [904]	Prasugrel 40 mg LD/7.5 mg MD + aspirin Prasugrel 60 mg LD/10 mg MD + aspirin Prasugrel 60 mg/15 mg MD + aspirin Clopidogrel 300 mg LD/75 mg MD + aspirin	Phase 2, randomized, double-blind, active comparator-controlled study. Primary Objectives: (1) Evaluate the safety of increasing doses of prasugrel; (2) Compare the safety of prasugrel to a standard regimen of clopidogrel.
H7T-MC-TABR	28-days	110 [55]	Prasugrel 60 mg LD/10 mg MD Clopidogrel 600 mg LD/75 mg MD Aspirin 75 mg daily	Phase 1b randomized, double-blind, double-dummy, two-arm parallel group study in patients with stable atherosclerosis. Primary Objective: To compare the pharmacodynamic effect of a prasugrel 60 mg LD with a clopidogrel 600 mg LD.
PRINCIPLE-TIMI 44 [H7T-MC-TABL]	30-days	201 [201]	Prasugrel 60 mg LD/10 mg MD + aspirin Clopidogrel 600 mg LD/150 mg MD + aspirin	Phase 2, randomized, parallel, double-blind, double-dummy, crossover, active comparator-controlled study in patients undergoing cardiac catheterization with planned elective PCI with coronary stenting. Primary Objectives: (1) To compare the inhibition of platelet aggregation (IPA) after prasugrel 60-mg LD versus clopidogrel 600-mg LD; (2) To compare the IPA of prasugrel 10-mg daily MD versus the IPA after clopidogrel 150-mg daily MD.
TRITON-TIMI 38 [H7T-MC-TAAL]	Up to 15 months	13,608 [13,457]	Prasugrel 60 mg LD/10 mg MD Clopidogrel 300 mg LD/75 mg MD Aspirin 75-325 mg orally or 250-500 mg IV, single dose within 24 hours prior to index PCI / 75-325 mg daily for remainder of study.	Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study. Primary Objective: To test superiority of prasugrel plus aspirin compared to clopidogrel plus aspirin in patients with ACS undergoing PCI.

Table 4.1. Overview of Studies in the Prasugrel Development Plan (continued)

Study	Treatment duration	# Enrolled [Randomized]	Dose	Study Design and Objectives
H7T-EW-TAAV	31-days	69 [34]	Prasugrel 60 mg LD/10 mg MD with daily 80-mg atorvastatin Clopidogrel 300 mg LD/75 mg MD with daily 80-mg atorvastatin	Phase 1, open-label, two-arm crossover study conducted in parallel. Primary Objective: To assess the effect of atorvastatin on the IPA response to 5 and 20 µM ADP after a 60-mg prasugrel LD and 10-mg MD administration in healthy male subjects.
H7T-EW-TAAI	35-days	24 [25]	Prasugrel: 60 mg single dose with or without 30 mg lansoprazole Clopidogrel: 300 mg single dose with or without 30 mg lansoprazole	Phase 1, single center, open-label, randomized, four-period crossover study. Primary Objective: To investigate the effects of the proton pump inhibitor (PPI) lansoprazole on the pharmacokinetics of prasugrel and clopidogrel.
H7T-EW-TACS	24-days	49 [42]	Prasugrel 60-mg single dose Lansoprazole 30-mg daily doses	Phase 1, three-treatment, three-period, open-label, randomized crossover study. Primary Objective: To determine the effect of salt conversion to base during storage of prasugrel tablets on the pharmacokinetics of prasugrel's active metabolite after a 60-mg loading dose of prasugrel in healthy subjects taking lansoprazole 30-mg once daily for at least a week.
H7T-EW-TACG	25-days	32 [31]	Prasugrel 5- and 10-mg daily MDs Aspirin 75 mg daily	Phase 1, open-label, single-sequence, multiple dose study. Primary Objective: To assess the effect of age on platelet aggregation after administration of prasugrel 5-and 10-mg MDs in the presence of aspirin.

Table 4.1. Overview of Studies in the Prasugrel Development Plan (continued)

Study	Treatment duration	# Enrolled [Randomized]	Dose	Study Design and Objectives
H7T-EW-TACR	24-days	85 [84]	Prasugrel 60-mg single dose	Phase 1, three treatment, three-period, open-label, randomized crossover study in which subjects received 60-mg prasugrel tablets with low (5%), intermediate (58%), and high (70%) extent of conversion of prasugrel HCl to prasugrel base. Primary Objective: To determine the effect of salt conversion to base during storage of prasugrel tablets on the pharmacokinetics of prasugrel's active metabolite after a 60-mg loading dose of prasugrel in healthy subjects.
H7T-EW-TACK	24-days	34 [31]	Prasugrel: 60-mg single dose Lansoprazole: 30-mg daily doses	Phase 1, three treatment, three-period, open-label, randomized crossover study in which subjects taking 30-mg lansoprazole once-daily received 60-mg prasugrel tablets with high (5.4 m^2/g), medium (4.2 m^2/g), and low (3.2 m^2/g) surface areas. Primary Objective: To assess the effect of active pharmaceutical ingredient surface area on the pharmacokinetics of prasugrel's active metabolite in healthy subjects taking lansoprazole 30-mg once daily.
H7T-EW-TABS	up to 30 days	47 [23]	Prasugrel: 60 mg LD/10 mg MD Ranitidine: 150 mg twice daily (bid) dose Clopidogrel: 600 mg LD/75 mg MD	Phase 1, open-label, two-period, two-treatment crossover study conducted in parallel. Primary Objective: To assess the physiological effect of oral ranitidine on the loading and maintenance dose pharmacokinetics of the prasugrel active metabolite, R-138727.

Table 4.1. Overview of Studies in the Prasugrel Development Plan (concluded)

Study	Treatment duration	# Enrolled [Randomized]	Dose	Study Design and Objectives
TRILOGY-ACS [H7T-MC-TABY]	30 months	approx. 10,300 (planned)	Prasugrel: once-daily 5-mg or 10-mg MD or a 30-/ 5- or 10-mg LD/MD Clopidogrel: 300-/75-mg LD/MD or continuation of the once-daily 75-mg MD for patients on commercial clopidogrel at randomization)	Phase 3, multicenter, randomized, parallel group, double-blind, double-dummy, active-controlled study. Primary objective: To test the hypothesis that prasugrel and aspirin is superior to clopidogrel and aspirin in the treatment of medically managed patients enrolled within 7 days of the UA/NSTEMI index event.
H7T-MC-B008	approximately 3 years	To be determined (dependent on the number of prasugrel patients and the number of PCI procedures documented in select EU registries).	Prasugrel 60-mg LD/5 mg or 10 mg MD Clopidogrel 300 mg LD / 75-mg MD	Post-authorization observational study.

5. Prasugrel Clinical Pharmacology and Phase 2

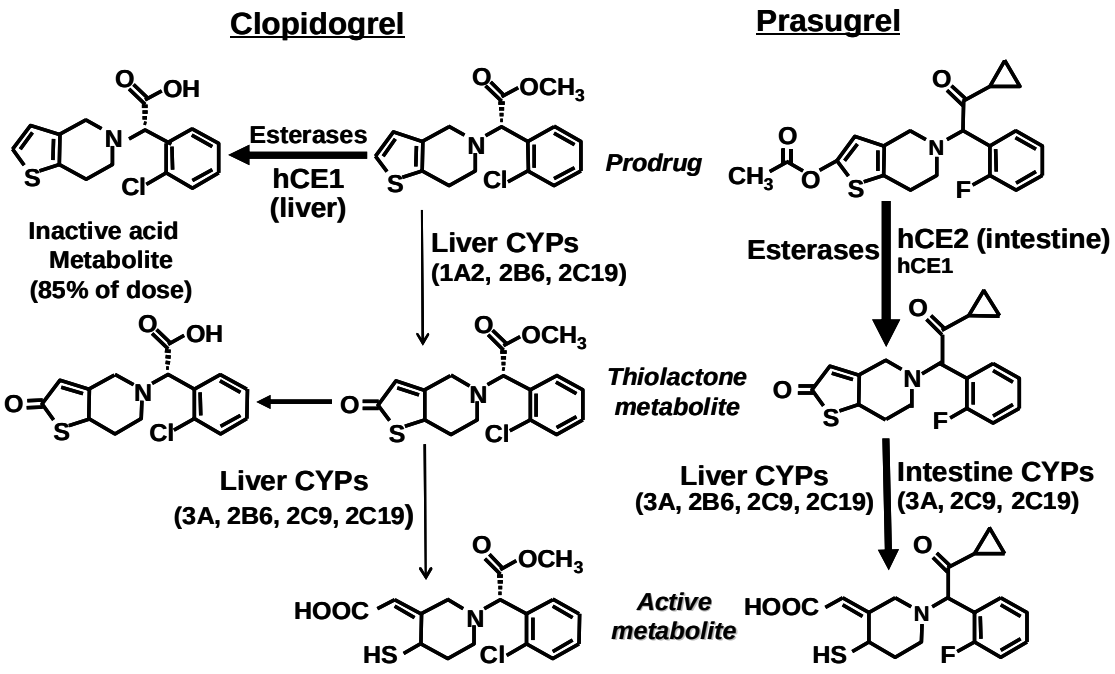
5.1. Overview

The clinical pharmacology program included in vitro studies using human biomaterials and more than 40 clinical pharmacology studies in healthy subjects and patients with stable atherosclerosis or undergoing elective PCI. The program included single prasugrel doses over a range of 2.5 mg to 80 mg, and daily doses of 2.5 mg to 25 mg for up to 10 days, and 5 to 15 mg for approximately 1 month. Prasugrel's PK/PD characteristics reflect its rapid absorption and efficient metabolism to its active metabolite.

The program also included dose-ranging studies to identify a dosing regimen that would provide, when compared to clopidogrel, the best balance of rapid onset, high levels of platelet inhibition, low inter-individual variability in PD response, and acceptable bleeding risk. Ultimately, dose selection was based largely on a Phase 1b PK/PD study (TAAD), and a proof-of-concept Phase 2 study (TAAH, also known as JUMBO-TIMI-26). Together, these studies suggested that a prasugrel loading dose of 60 mg followed by a 10-mg maintenance dose given once daily would produce an adequate PD response in the vast majority of patients while not causing an unacceptable increase in bleeding risk.

5.2. Pharmacokinetics: Absorption, Distribution, Metabolism and Excretion

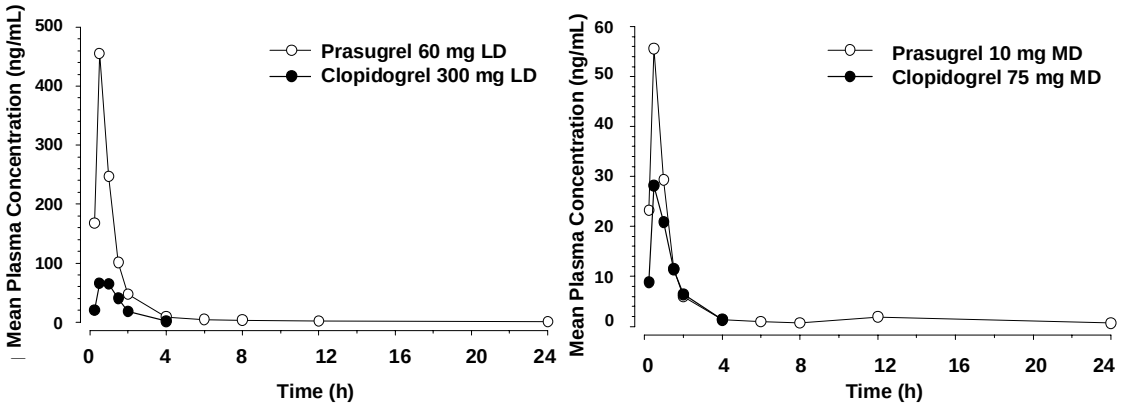
Prasugrel is a prodrug requiring conversion in vivo to an active metabolite, which covalently and irreversibly binds to the $P2Y_{12}$ platelet adenosine diphosphate (ADP) receptor (Niitsu et al. 2005; Algaier et al. 2008). The absorption and metabolism of prasugrel are rapid. The prodrug is not detected in plasma following oral administration owing to its rapid hydrolysis to the thiolactone moiety in the intestine, predominantly by human carboxylesterase 2 (Figure 5.1). Once formed, the thiolactone is metabolized to the active metabolite in the intestine by CYP3A or during its first pass through the liver by CYP3A4/5, CYP2B6, CYP2C9, and CYP2C19.



Prasugrel is rapidly hydrolized to a thiolactone in the intestine and then oxidized to its active metabolite in a single CYP-dependent step. Conversely, esterases shunt the majority of clopidogrel to an inactive pathway with the remaining prodrug requiring 2 separate CYP-dependent oxidative steps to be converted to its active metabolite. Source: Farid et al. 2007b; Kurihara et al. 2005; Rehmel et al. 2006; Tang et al. 2006; Williams et al. 2008.

Figure 5.1. Metabolic pathways of Prasugrel and Clopidogrel to their respective active metabolites.

Peak plasma concentrations (C_{max}) of the prasugrel active metabolite occur approximately 30 minutes after dosing. Representative active metabolite concentration/time profiles in subjects who received 60-mg LD and 10-mg MD prasugrel or 300-mg LD and 75-mg MD clopidogrel are presented in Figure 5.2. Active metabolite that is not bound to platelets has a terminal elimination half-life of about 7 hours. Over a 5-mg to 60-mg range of prasugrel doses, active metabolite exposure increases dose-proportionally with increasing prasugrel dose.



Source: Data from Study TAAV.

Figure 5.2. Prasugrel and clopidogrel active-metabolite concentration/time profiles in healthy subjects, after loading doses (left) and at steady state (right).

Prasugrel has no clinically relevant interaction with inducers or inhibitors of cytochrome P450 (CYP) enzymes (Rehmel et al. 2006; Farid et al. 2007a; Farid et al. 2007b). Pharmacogenetic analyses of data obtained from several clinical pharmacology studies showed no relevant effect of genetic variation in CYP2C19, CYP2C9, CYP3A5, or CYP2B6 on exposure to prasugrel's active metabolite, or accordingly, on its effect on platelet inhibition (Section 7.3). Administration of prasugrel with food reduces C_{max} of the active metabolite by approximately 50% but does not change AUC. Similar to the effect of food, elevated gastric pH does not affect the extent of absorption (i.e., AUC) but decreases C_{max} by nearly 30% (Section 7.4).

5.2.1. Pharmacokinetics in Special Populations

Prasugrel's pharmacokinetic profile is similar in healthy males and females, smoking or non-smoking patients, patients with stable atherosclerosis, and patients undergoing percutaneous coronary intervention.

Effect of Weight

Results from the integrated clinical pharmacology analysis in 506 healthy subjects indicated that active metabolite exposure, represented by the AUC, increases with decreasing body weight.

Individuals with lower body weight have higher prasugrel active metabolite exposure. In the TRITON-TIMI 38 pharmacokinetics substudy of 1159 prasugrel-treated patients, body weight had a statistically significant effect on exposure ($p<0.0001$) (Wrishko et al. 2008). Analyses stratified by body weight indicated that prasugrel's active metabolite exposure in patients weighing <60 kg was 30% higher (90% CI, 16% to 45%) compared to patients ≥60 kg. In addition, mean exposure in patients weighing <60 kg was 42%

higher (90% CI: 27% - 58%) than those weighing ≥85 kg (approximate median weight in TRITON-TIMI 38). This finding is consistent with the results from clinical pharmacology studies described above.

Effect of Age

In a clinical pharmacology study (Study TACG) of 32 healthy subjects between the ages of 20 and 80 years (4 subjects were ≥75 years of age), neither the pharmacokinetics of prasugrel's active metabolite, nor its effect on inhibition of platelet aggregation, was affected by age.

In the TRITON-TIMI 38 pharmacokinetics substudy of 1159 prasugrel-treated patients, elderly patients trended toward higher exposure of active metabolite compared with the younger patients. Analyses stratified by discrete age groups indicated that prasugrel active metabolite exposures for the patients ≥75 years of age were 19% higher (90% CI: 10% to 27%) compared to patients <75 years of age. In addition, the exposure was 25% higher (90% CI: 16% to 34%) compared to patients <60 years, which was the approximate median age in TRITON-TIMI 38.

Effect of Race

In the integrated clinical pharmacology analysis in 506 healthy subjects, exposure in subjects of African and Hispanic descent was similar to that of Caucasians. After adjusting for body weight, the mean AUC of the active metabolite was 19% higher (90% CI: 11% to 28%) in Chinese, Japanese, and Korean subjects compared to Caucasian subjects. This ethnic difference appears to be influenced by a disproportionately greater exposure difference in subjects <60 kg. In subjects ≥60 kg, the difference between Asian and Caucasian populations can be accounted for by differences in body weight. Therefore, the exposure in Asian patients ≥60 kg would be expected to be within the exposure range of Caucasian patients ≥60 kg.

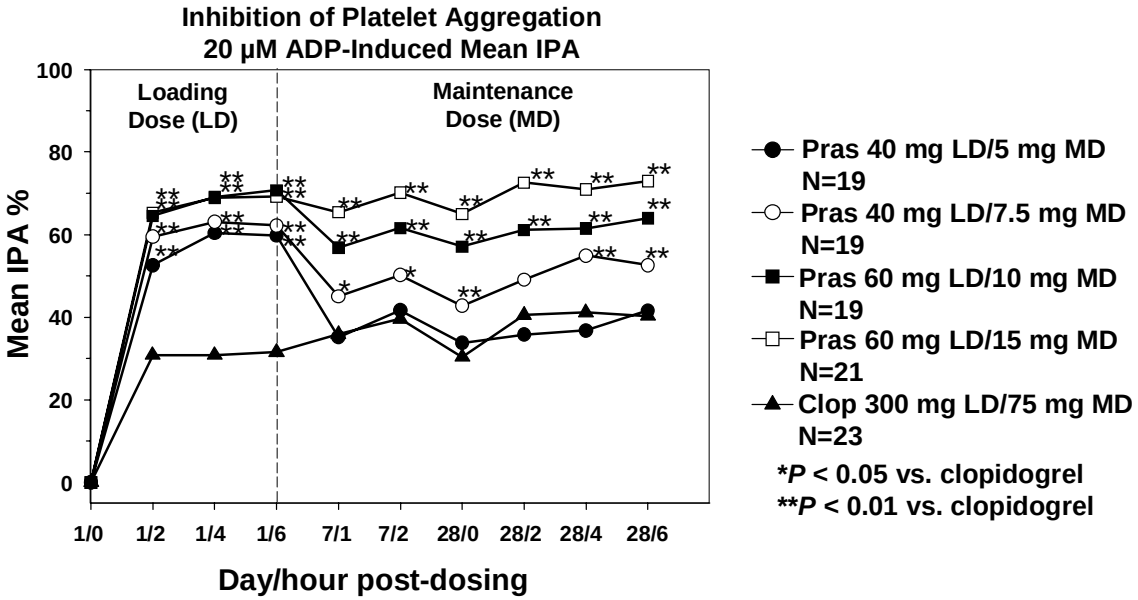
Effect of Impaired Renal and Hepatic Function

Prasugrel's pharmacokinetics and ability to inhibit platelet aggregation are similar in patients with moderate renal impairment (CrCL=30 to 50 mL/min) and healthy subjects. Prasugrel's active metabolite C_{max} and AUC were decreased by about 40% in patients with end stage renal disease (ESRD) compared to those in healthy controls and patients with moderate renal impairment, but this exposure did not cause a difference in pharmacodynamic response between these populations.

Prasugrel's pharmacokinetics and platelet inhibition response were similar in patients with mild to moderate hepatic impairment compared to healthy subjects. Pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic disease have not been studied.

5.3. Pharmacodynamics

Study TAAD assessed the pharmacodynamic effects (percent inhibition of platelet aggregation; IPA) of prasugrel compared to clopidogrel in patients with stable atherosclerosis. Figure 5.3 displays the dosing regimens studied and the pharmacodynamic results through the 28-day treatment period. A prasugrel 60-mg LD had an 8-10 percentage point higher mean IPA ($p<0.02$) over the first 6 hours compared to a prasugrel 40-mg, and both the 40-mg and 60-mg LDs produced significantly higher IPA ($p<0.0001$) than did the clopidogrel 300-mg LD. The 7.5-, 10-, and 15-mg prasugrel MDs achieved significantly greater IPA than the 75-mg clopidogrel MD. Mean IPA was similar for prasugrel 5-mg MD and clopidogrel 75-mg MD.



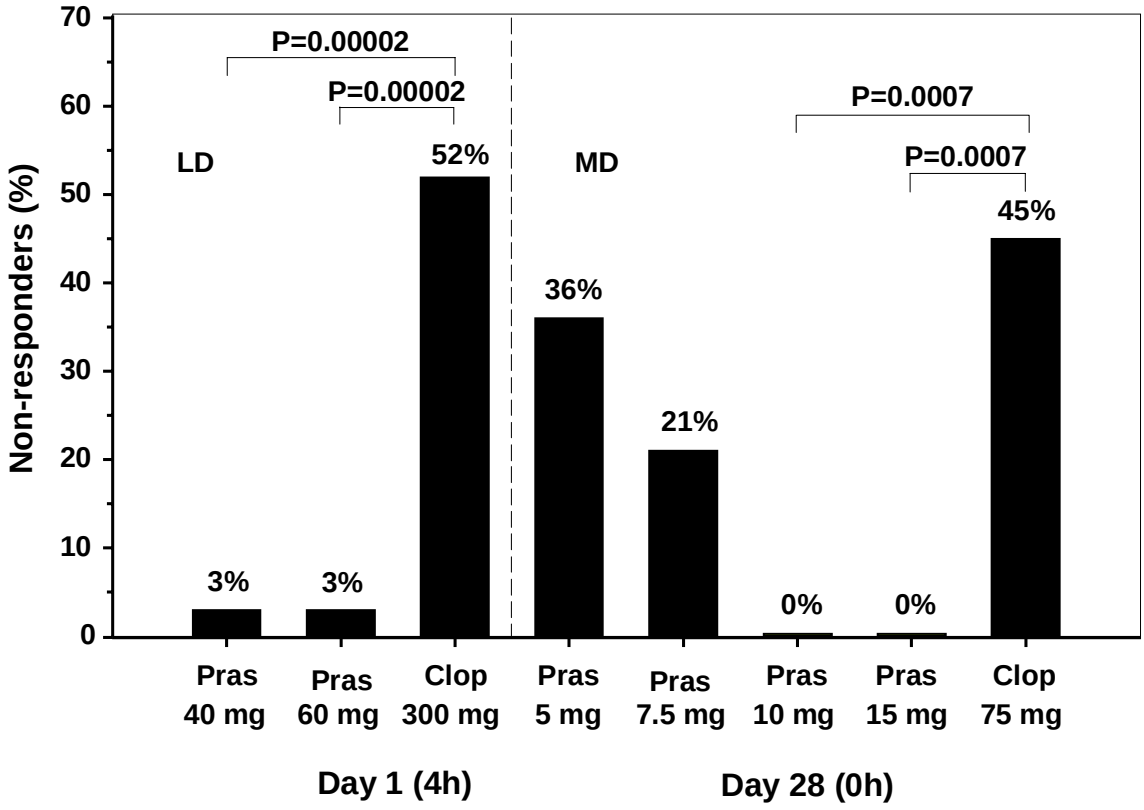
Abbreviations: ADP = adenosine diphosphate; Clop = clopidogrel; IPA = inhibition of platelet aggregation; LD = loading dose; MD = maintenance dose; Pras = prasugrel.
Source: Jernberg et al. 2006.

Figure 5.3. Study TAAD comparison of IPA (20 µM ADP) between prasugrel and clopidogrel LDs and MDs.

Patients were classified as "non-responders" to the LD if their IPA to 20 µM ADP measured 4 hours post-dose was <20% (Jernberg et al. 2006; Weerakkody et al. 2007). Patients were classified as "non-responders" to the MD if their IPA to 20 µM ADP measured pre-dose on day 28 was <20%.

Only 3% of subjects were classified as "non-responders" to the prasugrel 40- and 60-mg LD compared to approximately 52% of subjects who were "non-responders" to the clopidogrel 300-mg LD (Figure 5.4). There were no "non-responders" to the prasugrel 10- and 15-mg MDs. Thirty-six percent and 21% of subjects were "non-responders" to

the prasugrel 5- and 7.5-mg MDs, respectively. Forty-five percent of subjects were "non-responders" to the clopidogrel 75-mg MD.



Source: Jernberg et al. 2006.

Figure 5.4. **Percentage of non-responders on Day 1 at 4 hours post-LD, and on day 28 at pre-MD – Study TAAD.**

5.4. Dose Selection for the Pivotal Phase 3 Study

The choice of the prasugrel dosing regimen studied in TRITON-TIMI 38 was based primarily on platelet aggregation and safety data from Study TAAD (discussed above) and on safety data from JUMBO-TIMI 26 (Study TAAH). JUMBO-TIMI 26 compared 3 prasugrel dosing regimens to the approved dose of clopidogrel in 904 patients undergoing elective PCI. Seventy-seven percent (n=699) of these patients had taken aspirin daily for at least 7 days before enrollment. Treatment duration was 30 to 35 days. The primary endpoint was the safety of increasing prasugrel doses, as indicated by the development of non-CABG related TIMI Major or Minor bleeding through 30 to 35 days after PCI.

In both TAAD and JUMBO-TIMI 26, bleeding was similar in patients treated with either the 40-or 60-mg loading doses (Table 5.1).

Table 5.1. Number of Bleeding Events after a Loading Dose Study TAAD and JUMBO-TIMI 26

	Prasugrel				Clopidogrel
Event	40-mg LD/ 5-mg MD	40-mg LD/ 7.5-mg MD	60-mg LD/ 10-mg MD	60-mg LD/ 15-mg MD	300-mg LD/ 75-mg MD
Study TAAD	N=19	N=19	N=19	N=21	N=23
Bleeding	1	0	0	3	0
Study TAAH	N/A	N=199	N=200	N=251	N=254
Bleeding		6	6	10	7

Source: Figure TAAD.12.1, Table TAAH.11.11

In TAAD, there were similar numbers of bleeding events in patients taking the 7.5- or 10-mg MDs (Table 5.2). In JUMBO-TIMI 26, patients taking the 7.5- or 10-mg MDs had similar numbers of GI hemorrhage and CEC adjudicated TIMI bleeding events. Additionally, in JUMBO-TIMI 26, 5.2% of patients treated with the 15-mg prasugrel MD experienced non-CABG related TIMI Major or Minor bleeding compared to 3.5% on the 10-mg MD and 3.5% on the 7.5-mg MD. Patients in the combined prasugrel groups had a similar bleeding rate as patients in the clopidogrel group (4.2% prasugrel, 3.5% clopidogrel).

Table 5.2. Number of Bleeding Events during the Maintenance Dose Period - Study TAAD and JUMBO-TIMI 26

	Prasugrel				**Clopidogrel**
Event	**40-mg LD/ 5-mg MD**	**40-mg LD/ 7.5-mg MD**	**60-mg LD/ 10-mg MD**	**60-mg LD/ 15-mg MD**	**300-mg LD/ 75-mg MD**
Study TAAD	N=19	N=19	N=19	N=21	N=23
Bleeding	2	4	3	9	7
JUMBO-TIMI 26	N/A	N=199	N=200	N=251	N=254
Epistaxis		2	9	12	1
GI Hemorrhage*		1	0	3	1
Adjudicated CEC Bleed		2	1	4	2
DC due to Bleed		1	0	3	0
Hematuria		0	0	3	1

* Number of patients.

Source: Figure TAAD.12.1, Table TAAH.14.191, Table TAAH.14.17, Table TAAH.12.8.

5.4.1. Summary of Dose Selection for the Pivotal Phase 3 Study

The goal of the prasugrel LD is to achieve maximum inhibition of platelet aggregation as quickly as possible following oral administration of the drug. The 60-mg prasugrel LD produced more rapid and higher levels of platelet inhibition compared to the 40-mg LD without an observed increase in risk of bleeding. Therefore, the 60-mg LD dose was recommended for testing in TRITON-TIMI 38.

The goal of the prasugrel MD is to maintain the level of platelet inhibition as high as possible without subjecting patients to excessive bleeding risk. Although the 15- mg

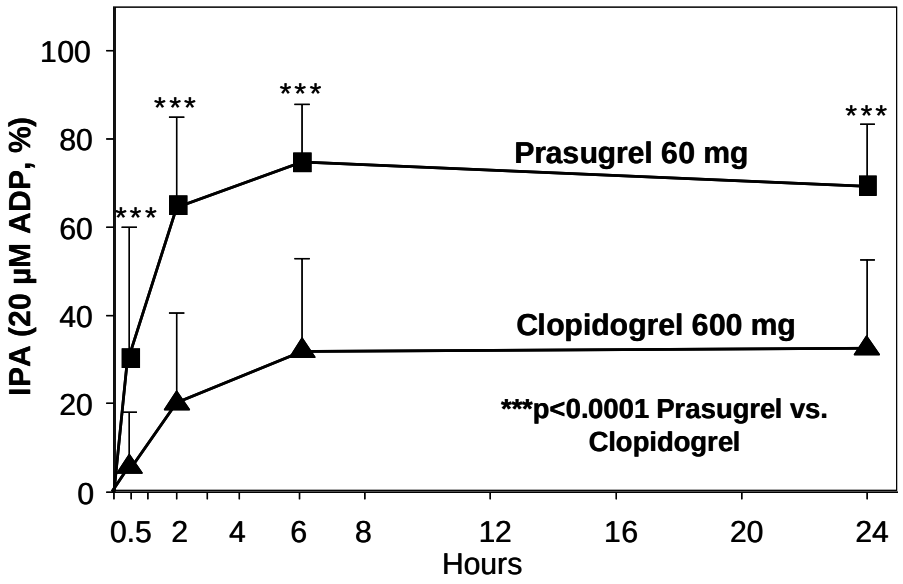
prasugrel MD produced a higher mean IPA compared to lower doses of prasugrel and the clopidogrel 75-mg MD, the 15-mg dose was associated with higher rates of bleeding including bleeding resulting in discontinuation of study drug. Similar rates of bleeding were observed for the 7.5- and 10-mg prasugrel doses and both doses produced higher mean IPA compared to the 75-mg clopidogrel dose. However, 21% of patients taking the 7.5-mg dose were classified as "non-responders" on study Day 28. None of the patients taking the 10-mg prasugrel dose were classified as "non-responders". Although IPA is not a surrogate for efficacy, low IPA is associated with recurring cardiovascular events in patients taking clopidogrel. Therefore, the 10-mg prasugrel MD was recommended for testing in TRITON-TIMI 38.

5.5. Comparison of Prasugrel 60 mg to Clopidogrel 600 mg

Although the only FDA-approved loading dose of clopidogrel is 300 mg, use of a 600-mg LD of clopidogrel has become common in clinical practice, and recent guidelines support this use in selected patients (Silber et al. 2005, Smith et al. 2006). The TRITON-TIMI 38 trial was designed and initiated before use of this clopidogrel LD was widespread. In consultation with the FDA, the approved 300-mg clopidogrel loading dose was considered the appropriate comparator. It would have been difficult to use a non-approved regimen of clopidogrel in a large registration study.

The Sponsor investigated the pharmacodynamic response to the 60-mg prasugrel LD compared to the 600-mg clopidogrel LD in PRINCIPLE-TIMI 44 (TABL). This study was a randomized, cross-over double-blind study in patients undergoing cardiac catheterization with planned elective PCI and coronary stenting. Of 201 patients randomized, 102 received prasugrel LD (55 underwent PCI) and 99 received clopidogrel (57 underwent PCI). The primary efficacy endpoint was to compare the inhibition of platelet aggregation (IPA) with 20 µM ADP after prasugrel 60 mg LD versus clopidogrel 600-mg LD at 6 hours. The second primary efficacy endpoint was to compare prasugrel 10-mg daily MD versus the IPA after clopidogrel 150-mg daily MD. Only patients who received a PCI had further pharmacodynamic data (>6 hours). For all laboratory-derived endpoints, the efficacy analysis included measurements that were deemed evaluable by an independent blinded laboratory reviewer. A patient was excluded if all measurements for the relevant timepoint(s) were not present or were deemed to be non-evaluable, including measurements that were known to be unreliable, which would have potentially diluted any treatment effect.

As seen in Figure 5.5, the levels of IPA achieved by prasugrel were significantly higher than those achieved by clopidogrel.



Source : Wiviott et al. 2007.

Figure 5.5. Loading dose phase inhibition of platelet aggregation (20 µM ADP) – PRINCIPLE-TIMI 44.

5.6. Conclusions Regarding Clinical Pharmacology

Prasugrel is a prodrug requiring conversion in vivo to an active metabolite, which covalently and irreversibly binds to the $P2Y_{12}$ platelet adenosine diphosphate (ADP) receptor. The absorption and metabolism of prasugrel are rapid. The prodrug is not detected in plasma following oral administration owing to its rapid hydrolysis to the thiolactone moiety and oxidation to the active metabolit in the intestine and liver by CYPs. Peak plasma concentrations (C_{max}) of the prasugrel active metabolite occur approximately 30 minutes after dosing.

Prasugrel has no clinically relevant drug-drug interactions. Genetic variations in CYP2C19, CYP2C9, CYP3A5, or CYP2B6 do not affect exposure to prasugrel's active metabolite, or accordingly, on its effect on platelet inhibition.

The C_{max} and t_{max} of the prasugrel active metabolite are relevant parameters for the loading dose, as they determine the rate of platelet inhibition following dosing. These parameters are not relevant to the maintenance dose because, at steady state, each maintenance dose typically increases IPA by less than 10 percentage points from the trough. The rate at which this incremental increase in IPA occurs after each maintenance dose is unimportant because the increment is so small. The AUC of the active metabolite is a relevant parameter for both the loading dose and the maintenance dose. AUC determines the maximum extent of platelet inhibition following dosing, but not the time required to reach it..

Dose ranging studies demonstrated that the 60-mg LD produced more rapid and higher levels of platelet inhibition compared to the 40 mg dose without an observed increase in

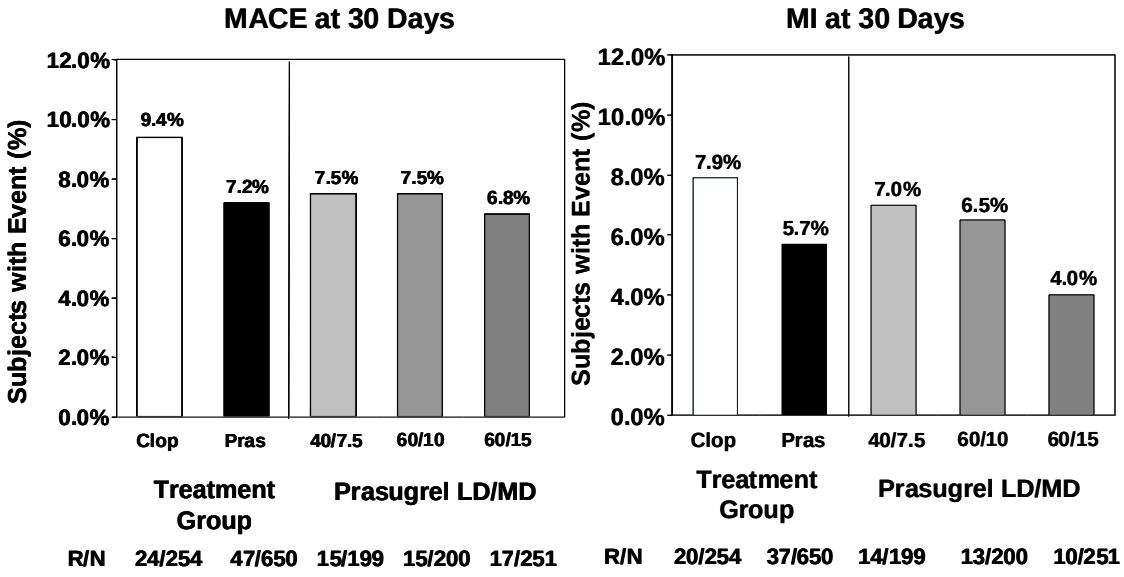
bleeding. The 60-mg LD was recommended for testing in TRITON-TIMI 38. Four maintenance doses (5, 7.5, 10, and 15 mg/day) were studied in comparison to the approved 75-mg clopidogrel MD. From these, the 10-mg dose was recommended for testing in TRITON-TIMI 38 because it was associated with a higher level of platelet inhibition compared to clopidogrel, had no observed pharmacodynamic "non-response", and had similar bleeding risk as the 7.5 mg dose. The 15-mg dose was associated with excessive bleeding while the 5- and 7.5-mg doses did not differentiate pharmacodynamically from the 75-mg clopidogrel dose or were associated with an unacceptable level of "non-response".

6. Clinical Efficacy and Safety

The efficacy and safety of prasugrel were established in a single Phase 3 clinical study (TRITON-TIMI 38) with supporting data from a single Phase 2 clinical study (JUMBO-TIMI 26).

6.1. JUMBO-TIMI 26 Study

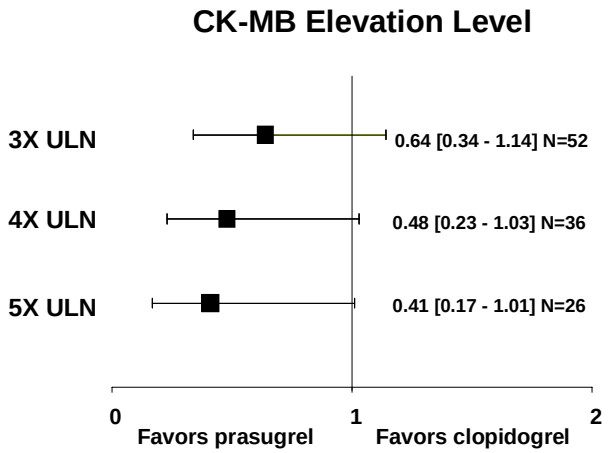
The design and results of safety analyses of JUMBO-TIMI 26 [TAAH] are presented in Section 5.4. The study also evaluated the composite endpoint (death, MI, stroke, clinical target vessel thrombosis, or recurrent myocardial ischemia requiring hospitalization) through 30 days. Study results are presented in Figure 6.1. There were fewer events observed in prasugrel-treated patients than in clopidogrel-treated patients (p=0.260), resulting predominantly from fewer MIs.



Source: Wiviott et al. 2005.

Figure 6.1. Rate of the composite of death, myocardial infarction [MI], stroke, clinical target vessel thrombosis, and recurrent myocardial ischemia through 30 days (left) and rate of MI through 30 days (right).

Figure 6.2 shows hazard ratios and confidence intervals for MI measured by increasing levels of CK-MB. There were fewer MIs associated with large degrees of myonecrosis in prasugrel-treated patients.



Source: Wiviott et al. 2005.

Figure 6.2. Hazard ratio and CI for MI at 30 days.

Although JUMBO-TIMI 26 was predominantly designed to assess the safety of increasing doses of prasugrel, the incidence of the primary composite endpoint was lower in prasugrel-treated patients than in clopidogrel-treated patients. More importantly, as would be observed in TRITON-TIMI 38, there were fewer MIs in prasugrel-treated patients, particularly MIs associated with larger degrees of myocardial necrosis.

6.2. TRITON-TIMI 38 Study

The clinical efficacy of prasugrel was demonstrated in the 13,608 patient, Phase 3 TRITON-TIMI 38 study. The study was a global, multicenter, randomized, double–blind, double-dummy comparison between prasugrel and the active control clopidogrel in the treatment of patients across the spectrum of ACS (UA/NSTEMI and STEMI) undergoing PCI. The primary objective of TRITON-TIMI 38 was to test the hypothesis that prasugrel is superior to clopidogrel in the reduction of the primary composite efficacy endpoint of CV death, nonfatal MI, or nonfatal stroke.

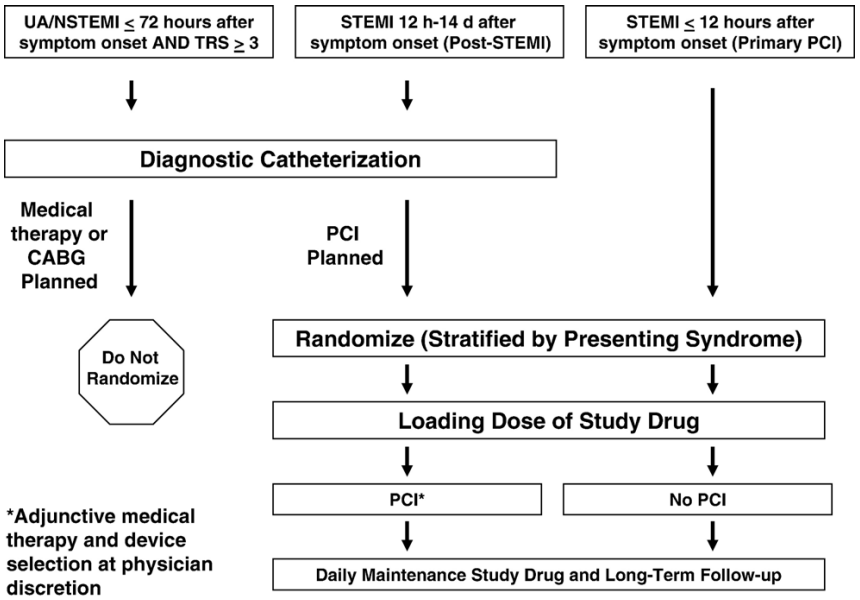
Patients were recruited between 5 November 2004 and 17 January 2007, at 725 study centers in 30 countries. Database lock occurred on 22 September 2007. After database lock, a copy of the full database was transferred to the TIMI Study Group. Independent analyses were performed by the Sponsor and the TIMI Study Group. Major analyses performed by each group were validated by the other. In publications, the TIMI Study Group generally reports Kaplan-Meier (K-M) estimates at 450 days, while in regulatory submissions, the Sponsor reports observed event rates. In the current document, both K - M estimates and observed rates are reported for many analyses. Where only observed rates are reported, the percentages may differ slightly from those presented at scientific meetings or published in manuscripts by the TIMI Study Group.

6.2.1. TRITON-TIMI 38 Study Plan and Design

TRITON-TIMI 38 was an event-driven study. Enrollment was estimated at 13,000 ACS patients including 3500 patients with STEMI. The study was to continue until the following were attained: 1) Each patient completed at least 6 months of follow-up, and the median follow-up had become at least 12 months; 2) At least 875 UA/NSTEMI patients were thought to have had primary endpoint events.

Figure 6.3 shows the study design. Briefly, patients were randomly assigned in a blinded fashion either to a 60-mg loading dose (LD) of prasugrel at the time of PCI, followed by a 10-mg daily maintenance dose (MD) of prasugrel, or to the approved clopidogrel 300-/75-mg LD/MD. All patients were concomitantly treated with 75 mg to 325 mg aspirin once daily.

Patients were eligible to be included in the study if they presented with moderate-to-high-risk ACS and were to undergo PCI. The inclusion criteria for patients with UA/NSTEMI were ischemic symptoms lasting 10 minutes or more and occurring within 72 hours before randomization, a TIMI risk score of 3 or more, and either ST-segment deviation of 1 mm or more or elevated levels of a cardiac biomarker of necrosis. Patients with STEMI could be enrolled within 12 hours after the onset of symptoms if primary PCI was planned or within 14 days after receiving medical treatment for STEMI. Full exclusion criteria have been published previously. Key exclusion criteria included an increased risk of bleeding, anemia, thrombocytopenia, a history of pathologic intracranial findings, or the use of any thienopyridine within 5 days before enrollment.



Source: Wiviott et al. 2006.

Diagnostic angiography was not required for patients presenting with STEMI ≤12 hours. In all cases, randomization was to occur prior to the onset of PCI and study drug was to be administered as soon as possible after randomization.

Figure 6.3. TRITON-TIMI 38 study design.

Diagnostic angiography was required prior to randomization in all patients with UA/NSTEMI and in those >12 hours following STEMI. This approach is consistent with practice patterns in the United States; recent data from the CRUSADE registry show that approximately 40-50% of ACS patients do not receive thienopyridine prior to coronary angiography (Roe et al. 2007).

Section 5.4 provides the rationale for the dose selection of prasugrel (60-/10-mg LD/MD) administered in TRITON-TIMI 38. Patients who had a nonfatal event were to remain in the study and on study drug. Patients who permanently discontinued from study drug remained in the study and were observed for endpoints and adverse events until the completion of the study or to the maximum duration of follow-up of 15 months, whichever came first.

6.2.2. Efficacy Endpoint Collection and Analytical Plan

The primary endpoint of the study was the time of first occurrence of any element of the composite of CV death, nonfatal MI, or nonfatal stroke. A death was considered to be a CV death unless it was clearly attributable to a non-CV cause. Bleeding death that was classified as CV death included death from intracranial hemorrhage (ICH) and bleeding death associated with a cardiac procedure. To be considered an endpoint, myocardial infarction had to be distinct from the index event. Myocardial infarction was defined by symptoms suggestive of ischemia/infarction, electrocardiographic data, cardiac biomarkers, or pathologic evidence of infarction using criteria adapted from the definition developed by the American College of Cardiology (Bethesda, MD). Stroke was defined as the rapid onset of new neurologic deficit lasting at least 24 hours (or resulting in death before 24 hours).

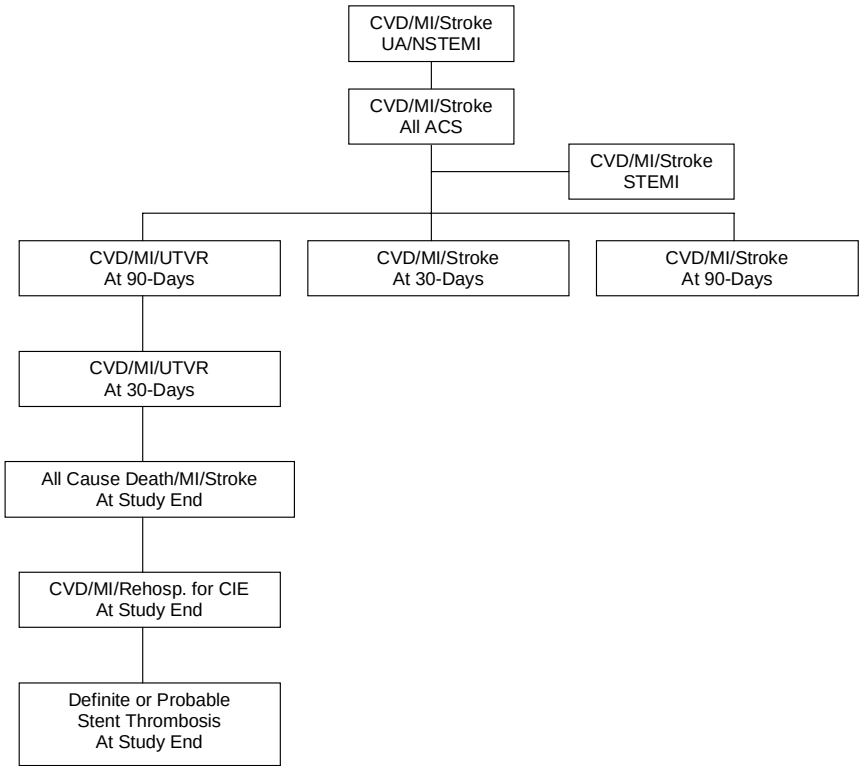
All components of the primary and secondary efficacy endpoints were adjudicated by the clinical events committee (CEC) who were blinded to treatment assignment. To ensure comprehensive evaluation of endpoints and potential endpoints, events to be sent for adjudication were collected in several ways:

- Investigator reported endpoints.
- A programmatic search of cardiac biomarker data for possible MIs requiring adjudication.
- A programmatic search of the adverse events database for adverse events consistent with efficacy endpoints or site-reported procedures requiring adjudication.
- A search by the CEC of source documents for unreported events.

The study provided 90% power to establish superiority of prasugrel over clopidogrel, relative to the primary composite efficacy endpoint for a relative risk reduction of 20% in the UA/NSTEMI cohort. The primary analysis was based on the time from randomization to the first occurrence of any one of the components of the primary

efficacy endpoint using the Gehan-Wilcoxon test (Collett 1994) as the hazard ratio (HR) was not expected to be constant over time. The primary endpoint was also verified by the log rank test. All secondary and other endpoint analyses were analyzed using the log rank test.

Efficacy analyses were carried out in a hierarchical manner. The analysis of the primary endpoint was first carried out at a two-sided test ($p \leq 0.05$) in the UA/NSTEMI patient population, and then in the All ACS population ($p \leq 0.05$). In the latter analysis, ACS classification (UA/NSTEMI or STEMI) was used as a stratification factor. Secondary endpoints are listed in Figure 6.4.



Abbreviations: CVD = cardiovascular death. CIE = cardiad ischemic event; UTVR = urgent target vessel revacularization.

Figure 6.4. Endpoint testing hierarchy.

6.2.3. Safety Endpoint Collection

The primary safety analysis was based on the incidence of non-CABG related TIMI Major bleeding between treatment groups. TIMI Major bleeding was defined as any ICH or clinically overt bleeding with a fall in hemoglobin (Hgb) of ≥ 5 gm/dL from baseline adjusted for transfusion.

TIMI Life-Threatening bleeding was a subset of TIMI Major bleeding that:

- was fatal,

- led to hypotension that required treatment with intravenous inotropic agents,
- required surgical intervention for ongoing bleeding,
- necessitated the transfusion of 4 or more units of blood (whole blood or packed RBC) over a 48-hour period,
- was a symptomatic intracranial hemorrhage.

TIMI Minor bleeding was defined as clinically overt bleeding with a fall in Hgb of ≥3 gm/dL but <5 g/dL from baseline adjusted for transfusion.

TIMI Minimal bleeding was defined as clinically overt bleeding that required medical attention but did not meet the criteria for TIMI Major or TIMI Minor.

All bleeding events requiring medical attention were reported as endpoints and adjudicated by the CEC. To ensure comprehensive evaluation of endpoints and potential endpoints, events to be sent for adjudication were collected in several ways:

- Investigator-reported endpoints.
- A programmatic search of hematology data to identify possible unreported bleeds requiring adjudication.
- A programmatic search of the adverse events database for adverse events consistent with safety endpoints requiring adjudication.
- A search by the CEC of source documents for unreported events.

Bleeding events meeting serious criteria were also reported as serious adverse events (SAEs) on a SAE form.

6.2.4. TRITON-TIMI 38 Study Conduct

Protocol Amendment

There was one amendment to the TRITON-TIMI 38 (Study H7T-MC-TAAL) protocol. This amendment was approved and implemented prior to the first interim analysis conducted by the data monitoring committee (DMC). The modifications to the protocol were: 1) to include in the definition of peri-procedural MI (PPMI) an elevation of CK-MB >5×ULN in one sample, if it was the last available sample and was drawn ≥12 hours after PCI; and 2) to allow patients who could not return to the study site to have visits conducted by other means, such as via telephone. The rationale for the first modification was that analysis of blinded study data by the TRITON-TIMI 38 Study Operations Committee revealed that in several patients, central lab CK-MB elevations had been noted only in the last available sample. Some of these last-sample values were greater than 5×ULN, and a few were greater than 20×ULN. These elevations did not meet the strict criteria of the protocol definition for MI, but the Study Operations Committee felt that they were clinically meaningful.

Sensitivity analyses of the primary endpoint were performed using the definition of PPMI prior to the protocol amendment (Section 6.4.1.1). The results of these analyses were consistent with the primary analysis reported in Table 6.2.

Interim Analyses

Periodic safety monitoring was conducted for TRITON-TIMI 38 under the auspices of an independent, external DMC. The DMC conducted 3 safety interim analyses after 161, 433, and 589 UA/NSTEMI patients reached the primary endpoint. In addition, the DMC chairperson conducted periodic multiple safety reviews prior to the first interim analysis.

All 3 interim DMC analyses were conducted for safety, the latter two assessed futility, and the last analysis assessed for overwhelming efficacy. Prespecified stopping criteria were not met at any of the interim analyses. Because of the stringent criteria for the efficacy stopping, the alpha penalty was negligable.

Sample Size

When 589 patients with UA/NSTEMI were confirmed to have reached the primary endpoint, the Study Operations Committee conducted a blinded review of the aggregated event rate. This review indicated that there had been a slightly lower than anticipated aggregated event rate in Study TAAL, and the size of the UA/NSTEMI population was increased to 10,100 patients to meet the protocol target of 875 events.

6.3. Baseline Characteristics and Disposition in TRITON-TIMI 38

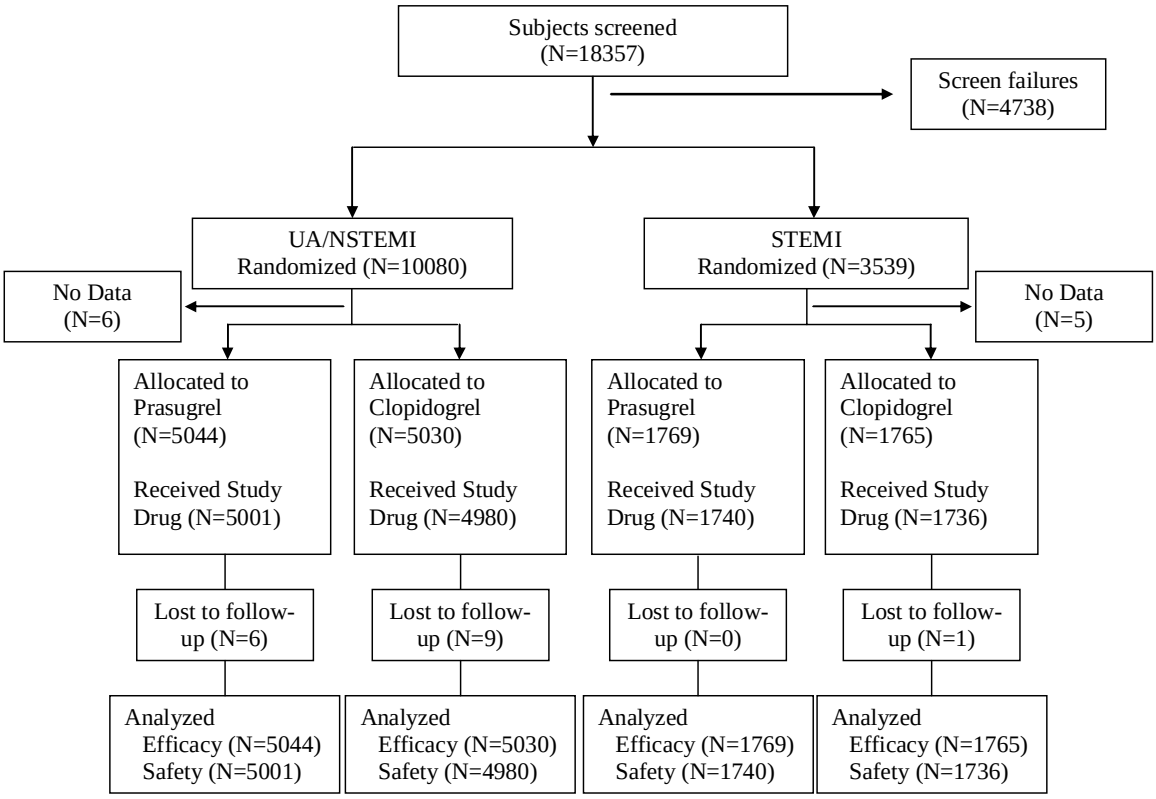
6.3.1. Patient Disposition

Figure 6.5 shows that 18,357 patients were screened. There were 4738 screen failures. Of the remaining 13,619 patients, 11 withdrew consent both for participation in the study and for the use of any of their data. The remaining 13,608 patients were stratified by clinical presentation (UA/NSTEMI: 10,074; STEMI: 3534) and randomly assigned to prasugrel (6813 patients) or to clopidogrel (6795 patients). At database lock, vital status was ascertained for 13,594 of the 13,608 patients who underwent randomization (99.9 %). At database lock, 16 patients were lost to follow-up. After database lock, vital status was determined for 2 additional patients (one subject had been randomly assigned to prasugrel and had a positively adjudicated MI; the remaining subject was randomly assigned to clopidogrel and did not have a primary efficacy event).

Overall, the study population was representative of the population of patients with ACS undergoing PCI (Goldberg et al. 2007; Roe et al. 2007). The average patient in the TRITON study was a male Caucasian, 61 years old, with a mean weight of 83 kg (Table 6.1). The majority of patients had multiple CV risk factors, including hypertension and hypercholesterolemia. Many patients also had a prior history of coronary artery disease (CAD), including prior MI, prior PCI, and prior CABG. In addition, 23% of the patients had diabetes mellitus and approximately 4% had a prior history of TIA or stroke.

Pharmacotherapy on admission reflected current treatment patterns with the majority of patients taking statins, β-blockers, ACEI, and/or angiotensin receptor blockers. Approximately 34% were taking aspirin at the time of presentation with the index event.

Nearly all patients had PCI at the time of randomization, with most receiving at least 1 stent and nearly half receiving a drug-eluting stent. Slightly more than half of the patients received a GPIIb/IIIa inhibitor during the index procedure.



Source: Q3165, Q946, IVR database.

Figure 6.5. Patient disposition at end of study.

Table 6.1. Summary of Baseline Characteristics

Characteristic	Prasugrel	Clopidogrel
Clinical Presentation	N=6813	N=6795
	n (%)	n (%)
UA/NSTEMI	5044 (74.0)	5030 (74.0)
STEMI	1769 (25.9)	1765 (26.0)
STEMI ≤12 hours [a]	1203 (17.7)	1235 (18.2)
STEMI >12 hours [a]	564 (8.3)	530 (7.8)
Age (Years)	N=6813	N=6795
Overall Mean (SD)	60.9/11.2	60.9/11.4
≥75 Years n (%)a	901/13.2	908/13.4
Sex n (%a)	N=6813	N=6795
	n (%)	n %)
Female	1705 (25.0)	1818 (26.8)
Region of Enrollment	N=6813	N=6795
	n (%)	n (%)
North America	2164 (31.8)	2146 (31.6%)
United States	2039 (29.9)	2020 (29.7%)
Europe	3436 (50.4)	3439 (50.6%)
Eastern Europe	1657 (24.3)	1665 (24.5%)
Western Europe	1779 (26.1)	1774 (26.1%)
South America	270 (3.96)	264 (3.9%)
Rest of World	943 (13.8)	946 (13.9%)
Body Weight (kg)	N=6722	N=6715
Mean (SD)	83.6 (16.8)	83.2 (16.9)
Creatinine Clearance	N=6699	N=6681
	n (%)	n (%)
<60 ml/min	717 (10.7%)	774 (11.6%)
Index Procedure(s)	N=6813	N=6795
	n (%)	n (%)
PCI	6715 (98.6)	6698 (98.6%)
Multivessel PCI	967 (14.7)	946 (14.4%)
CABG	25 (0.37)	23 (0.3%)
Any Stent	6018 (95.7)	6004 (96.1%)
Bare Metal Stent	3190 (51.0)	3185 (51.0%)
Drug Eluting Stent	2860 (45.5)	2872 (46.0%)
GPIIb/IIIa inhibitor use	3670 (53.9)	3733 (55.0%)
Medical History	N=6813	N=6795
	n (%)	n (%)
Diabetes Mellitus	1576 (23.1)	1570 (23.1%)
Hypertension	4370 (64.1)	4371 (64.3%)
Hypercholesterolemia	3790 (55.6)	3790 (55.8%)
Prior MI	1226 (18.0)	1208 (17.8%)
Prior PCI	904 (13.3)	926 (13.6%)
Prior CABG	541 (7.94)	497 (7.3%)
Prior TIA	94 (1.4)	117 (1.7%)
Prior Stroke	181 (2.7%)	160 (2.3%)

Table 6.1. Summary of Baseline Characteristics (concluded)

Characteristic	Prasugrel	Clopidogrel
Therapy at Index Visit	N=6813	N=6795
	n (%)	n (%)
Statins	5372 (78.9)	5340 (78.5%)
ACE Inhibitors	3541 (51.97)	3356 (49.4%)
Beta-blocker	5042 (74.0%)	5023 (73.9%)
Aspirin within 7 days	2326 (34.1%)	2333 (34.3%)

Source: Q151; Q2421; Q156

6.4. Overview of Efficacy in TRITON-TIMI 38

The efficacy endpoint analyses were carried out using the intent-to-treat (ITT) data set, consisting of all randomized patients. All efficacy endpoints that occurred through a patient's study termination or 464 days from randomization, whichever was earlier, were included in the analyses. The analyses were conducted according to the treatment group to which a patient was assigned by random allocation, even if the patient was not treated with study drug, received the incorrect study drug, prematurely discontinued study drug, prematurely discontinued from the study, or otherwise did not follow the protocol.

Efficacy analyses were carried out in a hierarchical manner. The analysis of the primary endpoint was first carried out in the UA/NSTEMI patient population, which demonstrated a reduction in the primary endpoint ($p=0.002$), and then in the All ACS population, which also demonstrated a reduction ($p=0.0004$). In the UA/NSTEMI population, each of the prespecified secondary endpoints favored prasugrel (all $p<0.02$). Each of the prespecified endpoints was assessed in the All ACS population, and again found to favor prasugrel (all $p<0.001$). Within the STEMI population, the primary and all secondary endpoints also favored prasugrel (all $p<0.05$). Therefore, the All ACS population was considered the primary population of interest.

6.4.1. Primary Composite Efficacy Endpoint

In the UA/NSTEMI population, the incidence of the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke was statistically significantly lower in patients treated with prasugrel compared to clopidogrel (Table 6.2). After superiority of prasugrel was established in the UA/NSTEMI population, the primary endpoint was tested and shown to be statistically significantly lower in both the All ACS and the STEMI populations (Table 6.2).

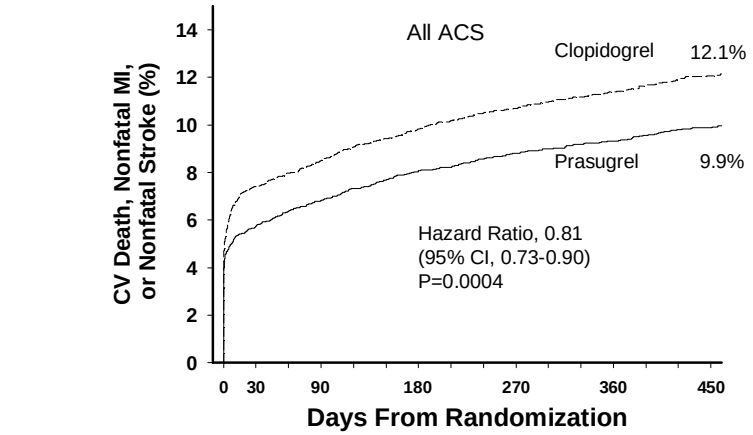
Table 6.2. TRITION-TIMI 38 Composite Efficacy Endpoint (CV Death, Nonfatal MI, Nonfatal Stroke)

Population	Prasugrel n (%)[a] [%][b]	Clopidogrel n (%)[a] [%][b]	HR (95% CI)	p-value
	N=5044	**N=5030**		
UA/NSTEMI	469 (9.30) [9.88]	565 (11.23) [12.06]	0.820 (0.726, 0.927)	0.002
	N=6813	**N=6795**		
All ACS	643 (9.44) [9.89]	781 (11.49) [12.05]	0.812 (0.732, 0.902)	0.0004
	N=1769	**N=1765**		
STEMI	174 (9.84) [9.99]	216 (12.24) [12.37]	0.793 (0.649, 0.968)	0.019

[a] Observed rate; [b] KM estimate at 450 days

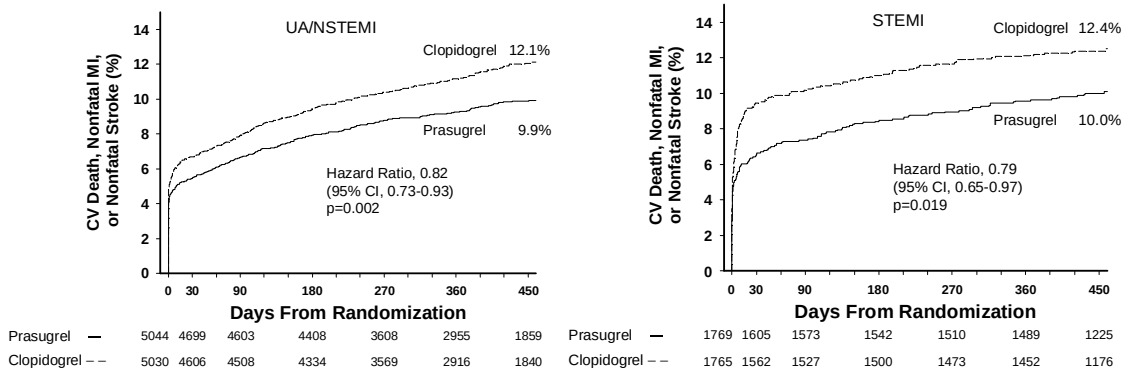
Source: Q176, Q197

In the All ACS population (Figure 6.6a) and in the UA/NSTEMI and STEMI subsets separately (Figure 6.6b), the Kaplan-Meier curves showed early separation in favor of prasugrel that was sustained throughout the study. In the All ACS population and in the UA/NSTEMI subset, the curves continued to diverge throughout the period of observation (Figure 6.6b).



Source: Q3405

Figure 6.6a. Kaplan-Meier estimates of the incidence of the primary composite endpoint—All ACS patients.

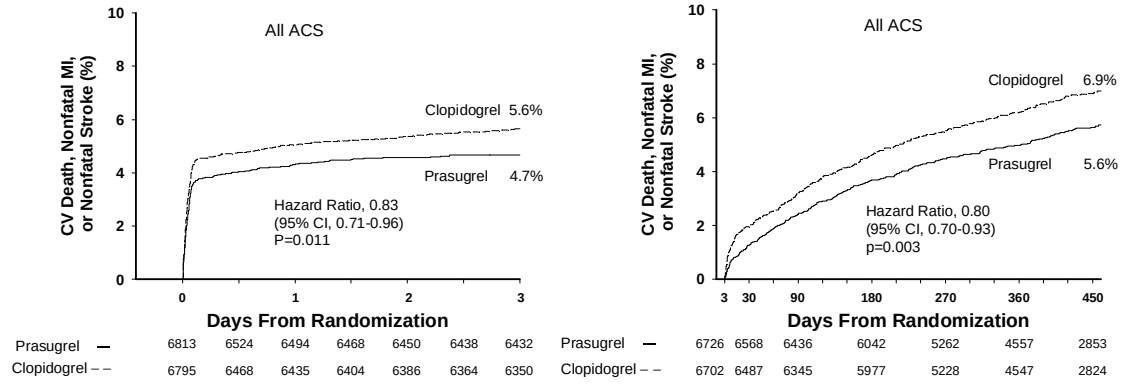


Source: Q3395, Q0181. Source: Q3400, Q186.

Figure 6.6b. Kaplan-Meier estimates of the incidence of the primary composite endpoint—UA/NSTEMI patients (left) and STEMI patients (right).

Figure 6.7, (left) shows that the treatment benefit of prasugrel was evident within the first 24 hours following PCI and was statistically significant at the first prespecified timepoint (Day 3) in patients treated with prasugrel compared to clopidogrel in the All ACS population.

The long-term treatment benefit of prasugrel compared to clopidogrel is evidenced by a continued reduction in the incidence of the primary composite efficacy endpoint beyond 3 days through study completion (Figure 6.7, right). The continued divergence of the event curves demonstrates the reduction in subsequent ischemic events with prasugrel during both the acute loading dose and chronic maintenance dose phases.



Source: Q7010. Source: Q7205.

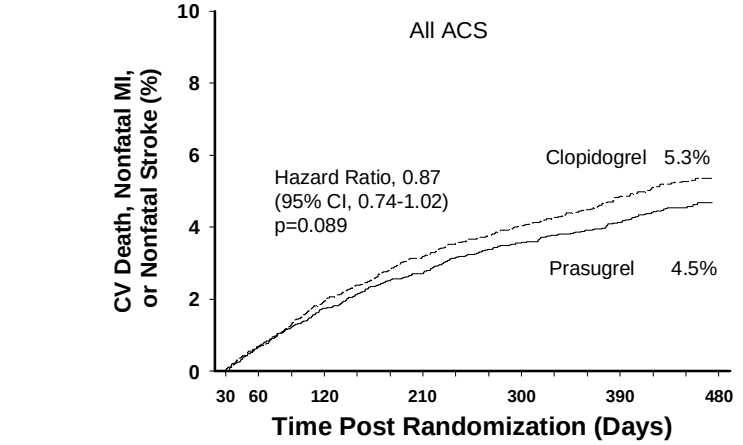
Figure 6.7. Cumulative incidence of the composite endpoint from randomization through 3 days (left) from 3 days to 15 months (right) — All ACS patients.

The benefit of prasugrel was seen through 30 days after randomization and from 30 days after randomization to the end of follow-up. In both analyses, the incidence of the primary composite endpoint was lower in patients treated with prasugrel than in patients treated with clopidogrel (Table 6.3). The Kaplan-Meier curves for the incidence of the primary composite endpoint more than 30 days after randomization begin to separate in favor of prasugrel 90 days after randomization and continue to separate through the end of follow-up (Figure 6.8).

Table 6.3. TRITON-TIMI 38 Primary Efficacy Endpoint through 30 days and after 30 days

	Prasugrel n (%)[a] [%][b]	Clopidogrel n (%)[a] [%][b]	HR (95% CI)	p-value
Patients randomized	**N=6813**	**N=6795**		
CV Death, Nonfatal MI, or Nonfatal Stroke through 30 days	389 (5.71) [5.73][c]	502 (7.39) [7.42][c]	0.77 (0.67, 0.88)	0.00008
Patients in study at day 30	**N=6623**	**N=6585**		
CV Death, Nonfatal MI, or Nonfatal Stroke after 30 days	274 (4.14) [4.54][d]	314 (4.77) [5.27][d]	0.87 (0.74, 1.02)	0.089

[a] Observed rate; [b] KM estimate; [c] at 30 days; [d] from 30 days to 450 days
Source: Q8318, Q401, Q197, Q8150b



Source: Q8150.

Figure 6.8. Kaplan-Meier estimates of the incidence of the primary composite endpoint more than 30 days after randomization.

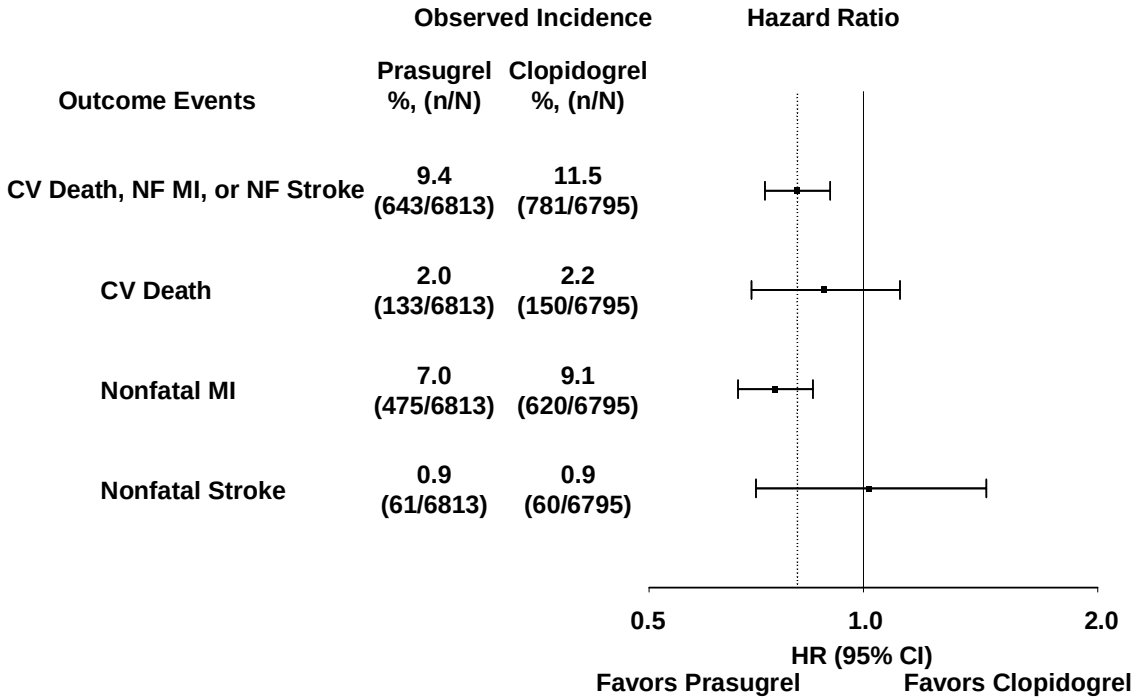
6.4.1.1. Sensitivity Analyses of Primary Efficacy Endpoint

As mentioned in Section 6.2.4, the TRITON-TIMI 38 protocol was amended to include an expanded definition of PPMI within 48 hours of the PCI procedure. The expanded

definition was used for the primary analysis (Table 6.2). All PPMIs were adjudicated by the CEC using both the definition of PPMI prior to and after the protocol amendment. The reduction of the primary endpoint using the definition of PPMI prior to the protocol amendment was consistent with the primary analysis reported in Table 6.2, with significantly fewer events in patients randomized to prasugrel compared to clopidogrel (All ACS population 8.88% versus 10.85%, HR=0.810, p<0.001; UA/NSTEMI 8.78% versus 10.66%, HR=0.817, p=0.002; STEMI 9.16% versus 11.39%, HR=0.793, p=0.024).

6.4.2. Components of the Primary Endpoint

Figure 6.9 shows the hazard ratio and confidence interval for the primary endpoint and its components in the All ACS population.



Source: Q176, Q231.

Figure 6.9. Hazard ratio and 95% confidence interval for the primary endpoint components — All ACS patients.

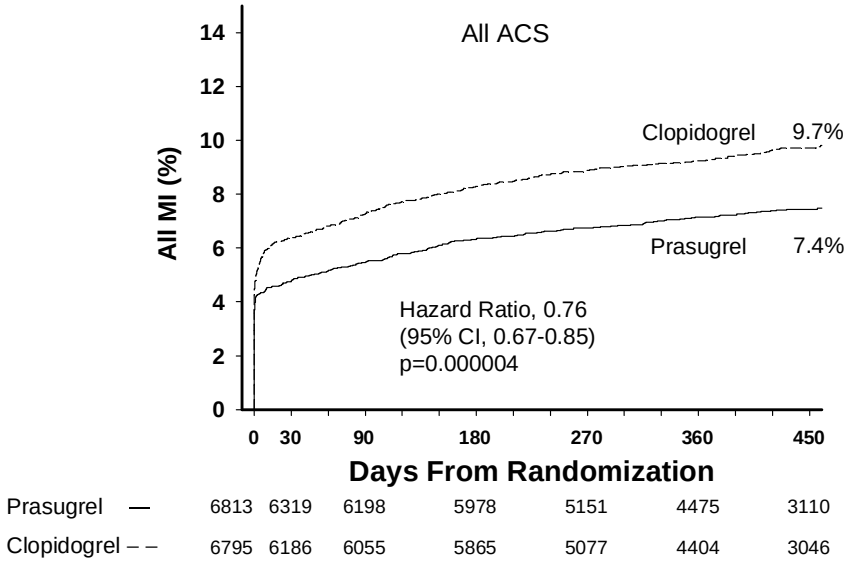
6.4.2.1. Death

Cardiovascular (CV) deaths include those adjudicated to cardiovascular causes as well as those due to uncertain causes. Bleeding death that was classified as CV death included death from intracranial hemorrhage (ICH) and bleeding death associated with a cardiac procedure. The incidence of CV death (prasugrel 1.95% [133/6813] versus clopidogrel 2.21% [150/6795], HR=0.886, p=0.307) and all-cause death (prasugrel 2.76% [188/6813]

versus clopidogrel 2.90% [197/6795], HR=0.953, p=0.639) at a median of 14.5 months follow-up were low and similar in each treatment group.

6.4.2.2. Myocardial Infarction

The treatment benefit of prasugrel in TRITON-TIMI 38 was primarily related to a significant reduction in MI as demonstrated in the Kaplan-Meier curve of the incidence of MI (Figure 6.10). Table 6.4 shows that the reduction in MI with prasugrel was seen across types and timing of MI. In addition, prasugrel treatment was associated with a statistically significant reduction in cardiovascular death following MI.



Source: Q306.

Figure 6.10. Incidence of MI— All ACS Patients.

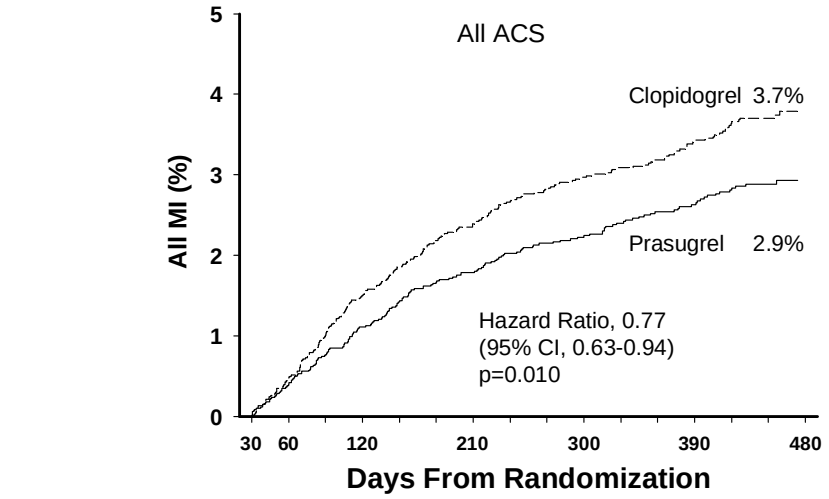
Table 6.4. TRITON-TIMI 38 Incidence of MI

	Prasugrel n (%)[a] [%][b]	Clopidogrel n (%)[a] [%][b]	HR (95% CI)	p-value
	N=6813	N=6795		
All MI (fatal and nonfatal)	485 (7.12) [7.44][c]	633 (9.32) [9.72] [c]	0.76 (0.67, 0.85)	0.000004
Biomarker MI[e] ≤ 3 days	240 (3.52) [3.52]	273 (4.02) [4.02]	0.87 (0.74, 1.04)	0.129
Clinical MI[f] ≤ 3 days	51 (0.75) [0.75]	83 (1.22) [1.23]	0.61 (0.43, 0.87)	0.005
CV Death post MI	29 (0.43) [0.44] [c]	55 (0.81) [0.86] [c]	0.53 (0.34, 0.83)	0.004
Patients in study at Day 3	N=6726	N=6702		
All MI > 3 days	208 (3.09) [3.40][d]	297 (4.43) [4.79] [d]	0.69 (0.58, 0.83)	0.00005

[a] Observed rate; [b] KM estimate; [c] at 450 days; [d] from 3 days to 450 days, [e]detected by elevation in biomarker only, [f] reported by investigator

Source: Q8134, Q7335, L0568, Q8007b, Q8428b, Q8429b, Q8430b

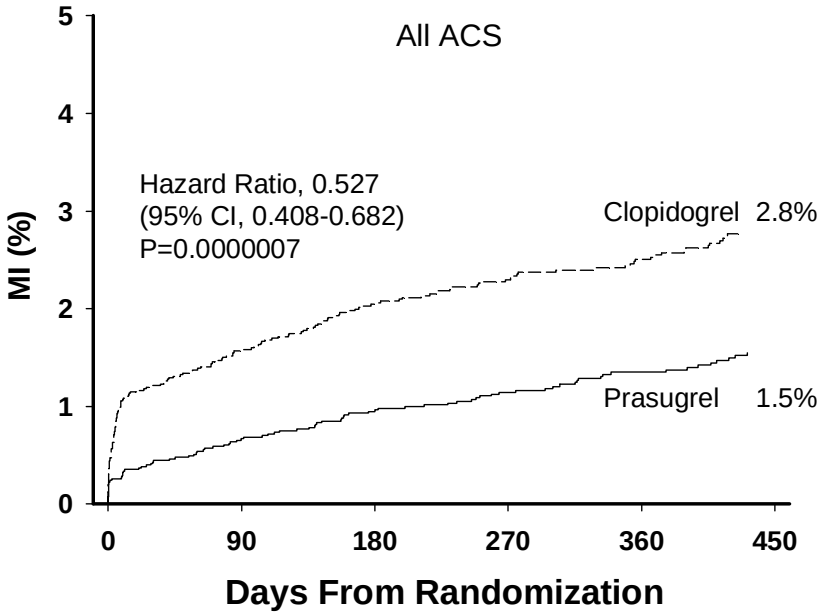
During chronic therapy, prasugrel was associated with a statistically significant reduction in late MI. Figure 6.11 shows the Kaplan-Meier curves of MIs occurring more than 30 days after randomization. The curves separate approximately 75 days after randomization and continue to diverge through the end of follow-up.



Source: Q8126

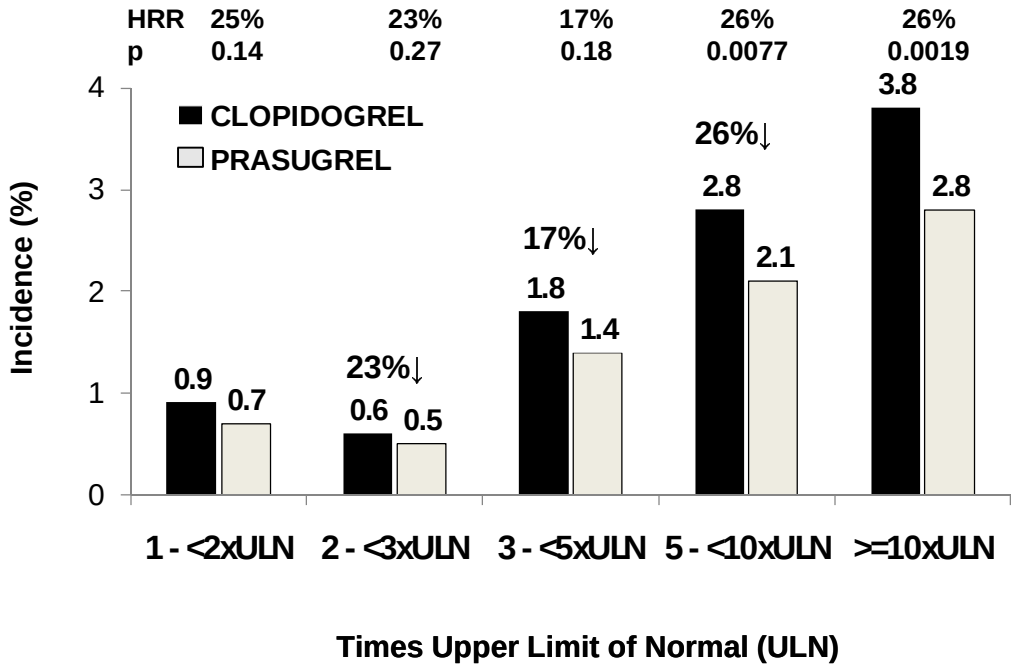
Figure 6.11. Kaplan-Meier estimates of the incidence of myocardial infarction more than 30 days after randomization All ACS Patients.

Prasugrel treatment was associated with a reduction in large, clinically significant MIs. As shown in Figure 6.12, there was a statistically significant reduction associated with prasugrel compared to clopidogrel for MI defined by the presence of all 3 criteria of biomarker elevation, ECG changes, and ischemic symptoms. The Kaplan-Meier curves separate early in favor of prasugrel and continue to diverge over time. Figure 6.13 shows that the consistent reduction in relative risk of MI with prasugrel was noted for MI of every size as measured by biomarker elevation, with the greatest absolute reduction seen in those MIs associated with the greatest extent of myocardial necrosis. Thus, reduction in MI, regardless of classification, represents an important benefit of prasugrel treatment.



Source: L0493

Figure 6.12. **Kaplan-Meier estimates of the incidence of MI accompanied by ischemic symptoms, ECG changes, and biomarker elevations - All ACS Patients.**



Source: Morrow et al. 2008.

Figure 6.13. Incidence of MI categorized by infarct size.

6.4.2.3. Stroke

No statistically significant differences were observed in all transient ischemic attack (TIA) or all stroke between patients randomized to prasugrel and clopidogrel in the UA/NSTEMI, STEMI, or All ACS populations (Table 6.5). The number of patients experiencing ischemic or hemorrhagic stroke was similar in each treatment group. Based on the Rankin Scale, there was no increase in the number of patients with moderate to severe disability following nonfatal stroke (hemorrhagic or ischemic) in prasugrel-treated patients compared to clopidogrel-treated patients (41% [25/61] versus 50% [30/60]).

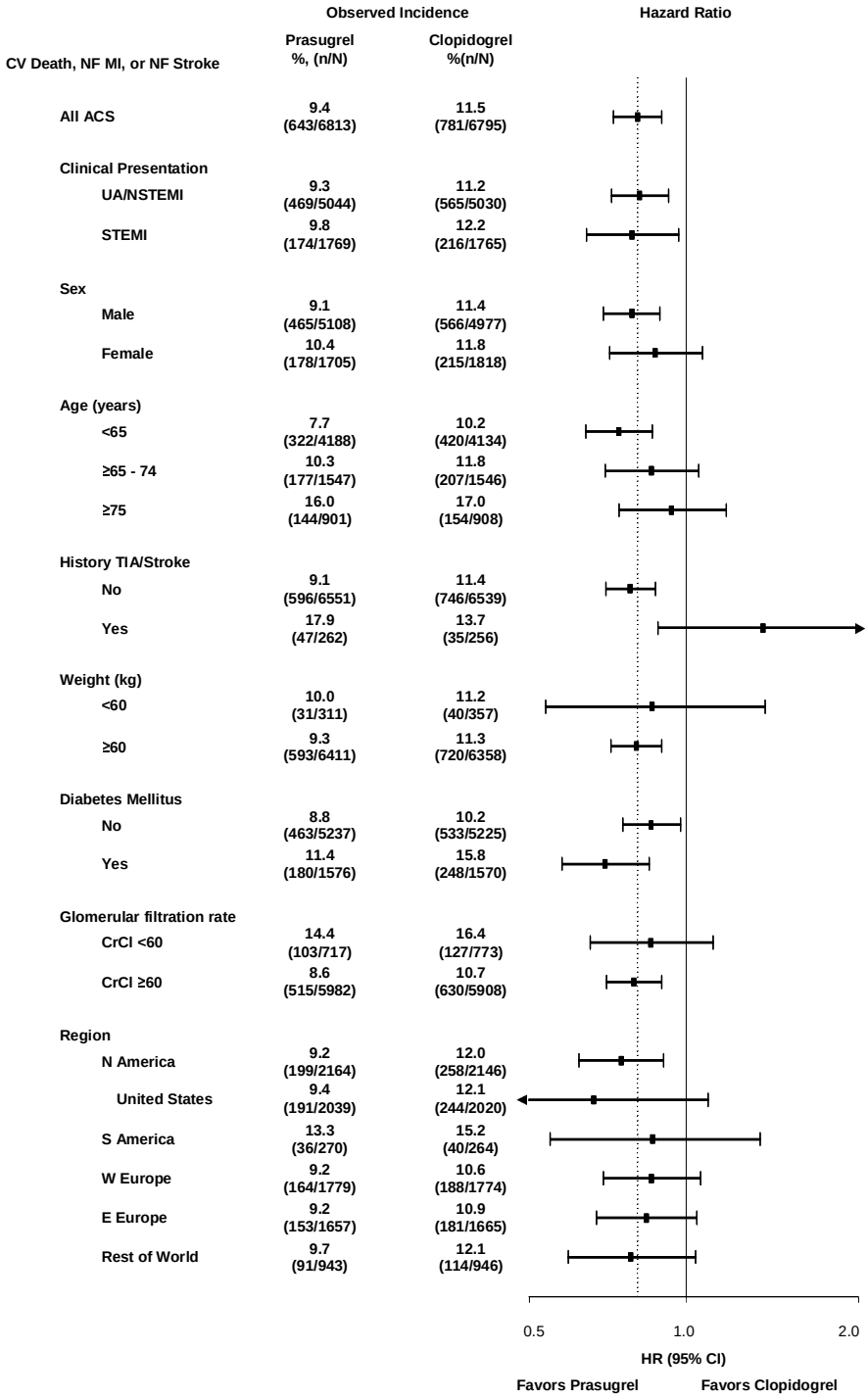
Table 6.5. Summary of Cerebrovascular Events All Randomized All ACS Patients

	Prasugrel N = 6813 n (%)	Clopidogrel N = 6795 n (%)	p-value
All TIA	25 (0.37)	29 (0.43)	0.582
All Stroke	75 (1.10)	71 (1.04)	0.745
Ischemic	54 (0.79)	54 (0.79)	
Hemorrhagic	20 (0.29)	16 (0.24)	
Unspecified	1 (0.01)	1 (0.01)	

Based on observed rates.
Source: Q736.

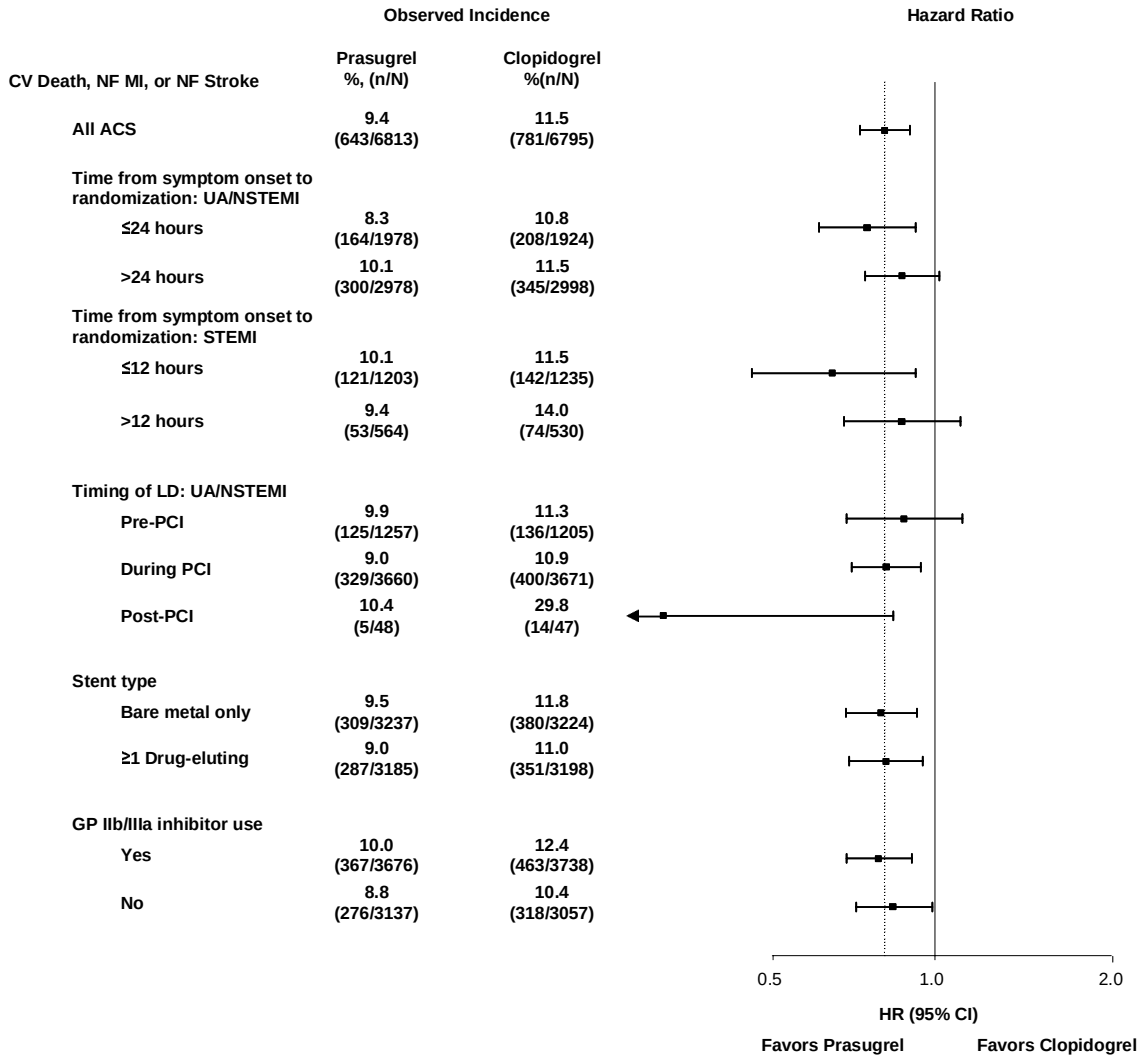
6.4.3. TRITON-TIMI 38 Efficacy in Subgroups

The treatment benefit associated with prasugrel was consistent across major prespecified subgroups (Figures 6.14a and 6.14b) except that there was a lack of treatment benefit with regard to the composite efficacy endpoint for prasugrel compared to clopidogrel in patients with a history of prior TIA or stroke.



Source: Q176, Q441, Q641,Q 3970, Q7055.

Figure 6.14a. **Observed incidence and hazard ratios for primary composite endpoint (CV death, Nonfatal MI, or Nonfatal Stroke) for selected demographic and baseline characteristics - All ACS Patients.**



Source: Q176, Q441, Q641,Q 3970, Q7055.

Figure 6.14b. Observed incidence and hazard ratios for primary composite endpoint (CV death, Nonfatal MI, or Nonfatal Stroke) for selected procedure characteristics and concomitant medications - All ACS Patients.

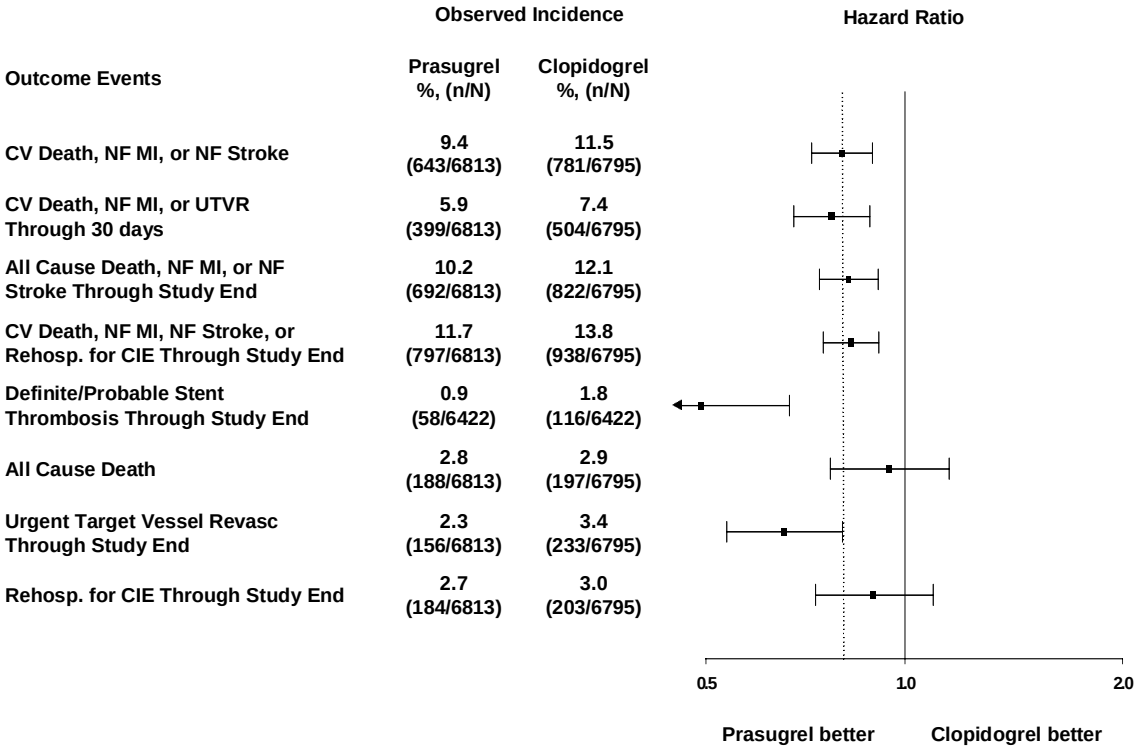
6.4.4. Secondary Efficacy Outcomes

Figure 6.15 displays prespecified secondary endpoints and components for the All ACS population. The prespecified secondary endpoints in the hierarchy were all statistically significantly lower in patients treated with prasugrel (Figure 6.15), including:

- The composite endpoint of CV death, nonfatal MI, or UTVR at 30 days;
- The composite endpoint of all-cause death, nonfatal MI, or nonfatal stroke;

- The composite endpoint of CV death, nonfatal MI, nonfatal stroke, or rehospitalization for cardiac ischemic event; and
- Definite or probable stent thrombosis.

For the individual components of the secondary efficacy endpoints, prasugrel was associated with a statistically significantly lower incidence of UTVR. The incidence of all-cause death and rehospitalization for cardiac ischemic events was similar in each treatment group (Figure 6.15).

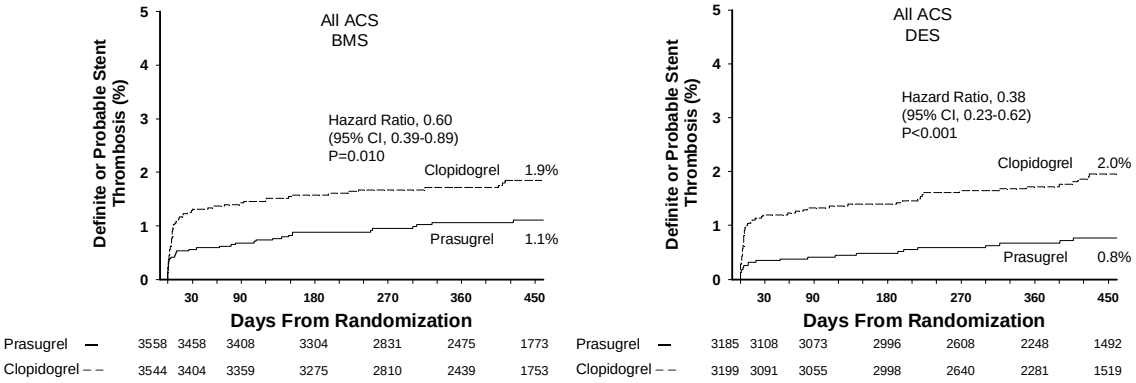


Source: Q176, Reg Response 080321 PPMI.doc, Q231, Q3460.

Figure 6.15. Incidence of primary and secondary endpoint components - All ACS Patients.

Stent Thrombosis

In TRITON–TIMI 38, 12,844 of 13,608 patients received at least one stent during the index procedure. Treatment with prasugrel resulted in a significant reduction in the prespecified endpoint of stent thrombosis compared with clopidogrel in patients with ACS in both drug-eluting stents (DES) and bare metal stents (BMS) (Figure 6.16).

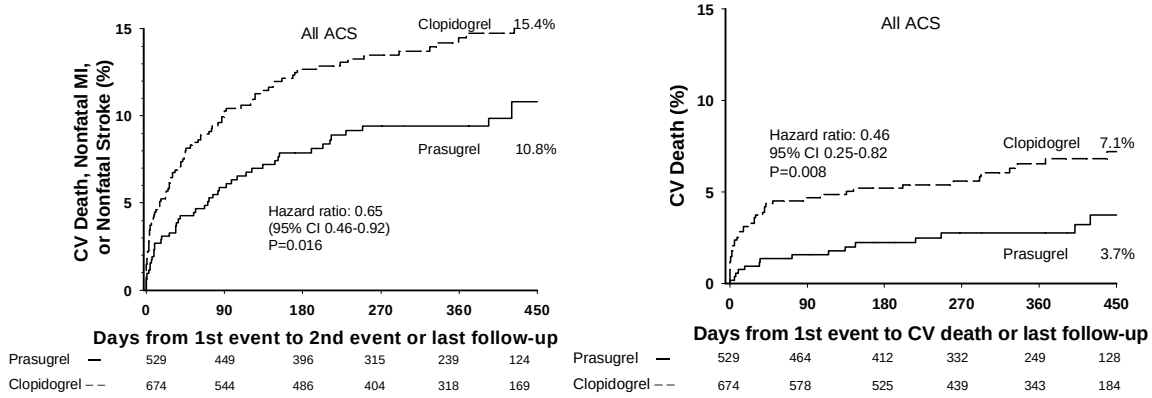


Source: Q8095. Source: Q8090.

Figure 6.16. Kaplan-Meier estimates of the incidence of definite or probable thrombosis (Academic Research Consortium definition) in stents placed at index PCI—CEC adjudicated - showing results in Bare Metal Stent (left)and Drug Eluting Stent (right)
All ACS Patients.

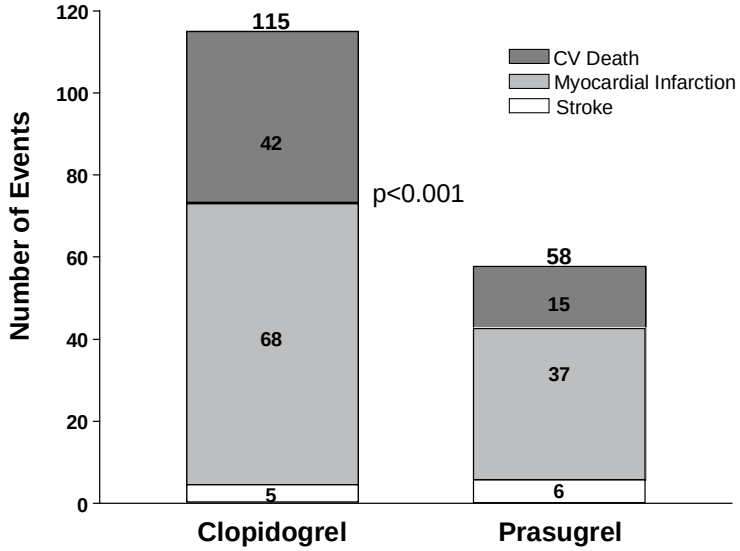
6.4.5. Prevention of Recurrent Events

For the preceding analyses, a patient experiencing more than one endpoint event was counted only once. As a further assessment of the durability of prasugrel's treatment benefit, a prespecified analysis was performed of multiple occurrences of the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke. In addition to the statistically significant reduction in the first occurrence of the primary endpoint (Table 6.2), the incidence of recurrent primary endpoint events was also statistically significantly reduced in patients treated with prasugrel compared to clopidogrel (Figure 6.17 left). The Kaplan-Meier curves separate early and diverge during chronic follow-up. Figure 6.18 shows the individual components of the recurrent composite primary endpoint. In the prasugrel treatment group compared to clopidogrel, fewer patients experienced the composite of CV death, nonfatal MI, or nonfatal stroke after a nonfatal primary endpoint. Figure 6.17 (right) shows the risk of CV death over time following a nonfatal primary event. The Kaplan-Meier curves separate early and diverge during follow-up.



Source: Murphy et al. 2008.

Figure 6.17. Kaplan-Meier estimates of the incidence of the second primary endpoint (left) and CV death (right).



Source: Murphy et al. 2008.

Figure 6.18. Number and type of endpoint events occurring after the first non-fatal primary event.

6.4.6. Net Clinical Benefit

The reduction in the incidence of CV death, nonfatal MI, nonfatal stroke associated with prasugrel treatment represents a substantial improvement in outcome for patients with ACS undergoing PCI. However, this reduced risk of irreversible cardiovascular events (i.e., those events associated with cell death) must be balanced against any increased risk for adverse events that may also result in irreversible morbidity or mortality. For the

thienopyridine class of drugs, these adverse events include ICH, fatal hemorrhage, bone marrow suppression (neutropenia), and thrombotic thrombocytopenic purpura (TTP). In TRITON-TIMI 38, there was less neutropenia reported as a serious adverse event (0 versus 7) and TTP (0 versus 1) in prasugrel-treated patients compared to clopidogrel-treated patients. There was a higher incidence of non-CABG related TIMI Major bleeding, non-CABG related TIMI Life-Threatening bleeding, and fatal bleeding in prasugrel-treated patients compared to clopidogrel-treated patients (Table 6.6). See Section 6.5.1 for further analyses of non-CABG related TIMI Major bleeding.

The absolute risk of non-CABG related TIMI Major bleeding is small in comparison to the absolute benefit in the reduction of the composite endpoint of CVD, nonfatal MI, or nonfatal stroke associated with prasugrel (Figure 6.20).

Table 6.6. Incidence of TIMI Major Bleeding Events All Treated Patients

Non-CABG-related Bleeding Events	Prasugrel n (%)[a] [%][b]	Clopidogrel n (%)[a] [%][b]	HR (95% CI)	p-value
	N=6741	N=6716		
TIMI Major	146 (2.17) [2.43]	111 (1.65) [1.84]	1.32 (1.03, 1.68)	.029
Life-Threatening	85 (1.26) [1.44]	56 (0.83) [0.94]	1.52 (1.08, 2.13)	.015
Fatal[c]	21 (0.31) [0.36]	5 (0.07) [0.09]	4.19 (1.58, 11.11)	.002

[a] Observed rate

[b] K-M estimate at 450 days

[c] Six clopidogrel patients experienced non-CABG related fatal bleeding events during the safety reporting period. One of these patients died before a Hgb measurement could be obtained, so did not meet strict criteria for TIMI Major bleeding and is not included here. This patient is included in discussion of all fatal bleeding events.

Source: Q951, Q7265

The balance between benefit and risk can be assessed by various measures of relative and absolute differences between treatments. Net clinical benefit using the prespecified secondary composite endpoint of all-cause death, nonfatal MI, or nonfatal stroke brings all fatal bleeding (not just fatal ICH-related or cardiac procedure-related bleeding, as in the primary endpoint) into the calculation. Because of the long duration of the TRITON trial, this endpoint also captures any potential late consequences of bleeding episodes. As shown in Table 6.7 and Figure 6.19, the benefit associated with prasugrel was essentially unchanged by broadening the endpoint to include all-cause death. The incidence of the composite endpoint of all-cause death, nonfatal MI, or nonfatal stroke was statistically significantly lower in patients randomized to prasugrel compared to clopidogrel in the UA/NSTEMI, STEMI, and All ACS populations (Table 6.7) just as it had been with the primary endpoint (Table 6.2). This benefit is shown in the early separation in favor of prasugrel and continued divergence of the Kaplan-Meier curves for the All ACS populations (Figure 6.19).

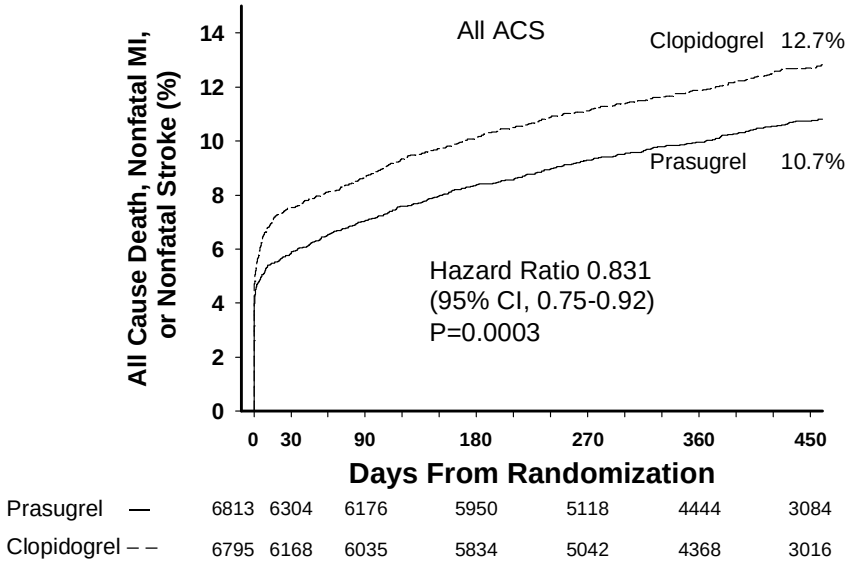
Table 6.7. All-Cause Death, Nonfatal MI, Nonfatal Stroke All Randomized Patients

All-Cause Death, Nonfatal MI, Nonfatal Stroke	Prasugrel n (%)[a] [%][b]	Clopidogrel n (%)[a] [%][b]	Hazard Ratio (95% CI)	p-value
	N=6813	N=6795		
All ACS	692 (10.16) [10.73]	822 (12.10) [12.70]	0.83 (0.75, 0.92)	0.0003
	N=5044	N=5030		
UA/NSTEMI	504 (9.99) [10.70]	590 (11.73) [12.66]	0.84 (0.75, 0.95)	0.005
	N=1769	N=1765		
STEMI	188 (10.63) [10.82]	232 (13.14) [13.18]	0.80 (0.66, 0.97)	0.020

[a] Observed rate

[b] K-M estimate at 450 days

Source: Q231, Q7335, l568



Source: Q261.

Figure 6.19. Kaplan-Meier estimates of the incidence of the composite endpoint of all-cause death, nonfatal MI, or nonfatal stroke- All Randomized All ACS Patients.

Two additional post hoc approaches to net clinical benefit illustrated in Table 6.8 show that even when non-CABG related TIMI Major and non-CABG related TIMI Life-Threatening bleeding are counted equal to events associated with irreversible cell death, the significant superiority of prasugrel persists in the All ACS population, and separately in the UA/NSTEMI and STEMI populations.

Table 6.8. Net Clinical Benefit TRITON-TIMI 38 Endpoints All Randomized Patients

All-Cause Death, Nonfatal MI, Nonfatal Stroke, or Non-CABG related TIMI Major Bleed

Population	Prasugrel n (%)[a] [%][b] N=6813	Clopidogrel n (%)[a] [%][b] N=6795	Hazard Ratio (95% CI)	p-value
All ACS	784 (11.51) [12.14]	893 (13.14) [13.80]	0.87 (0.79, 0.95)	0.003
UA/NSTEMI	N=5044 573 (11.36) [12.15]	N=5030 637 (12.66) [13.67]	0.89 (0.80, 1.0)	0.043
STEMI	N=1769 211 (11.93) [12.15]	N=1765 256 (14.50) [14.57]	0.81 (0.67, 0.97)	0.022

All-Cause Death, Nonfatal MI, Nonfatal Stroke, or Non-CABG related TIMI Life-Threatening Bleed

Population	Prasugrel n (%)[a] [%][b] N=6813	Clopidogrel n (%)[a] [%][b] N=6795	Hazard Ratio (95% CI)	p-value
All ACS	733 (10.76) [11.38]	853 (12.55) [13.18]	0.85 (0.77, 0.94)	0.001
UA/NSTEMI	N=5044 535 (10.61) [11.38]	N=5030 610 (12.13) [13.08]	0.87 (0.77, 0.97)	0.016
STEMI	N=1769 198 (11.19) [11.40]	N=1765 243 (13.77) [13.82]	0.80 (0.66, 0.97)	0.020

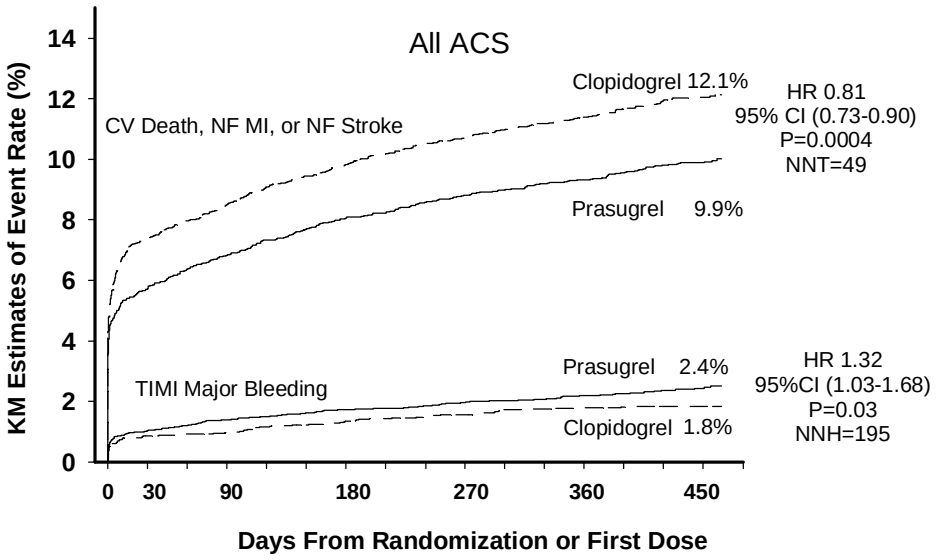
[a] Observed rate

[b] K-M estimate at 450 days

Source: Q8403, Q8183b, Q8245b, Q8431b, Q8404b, Q8405b, Q8406b

Additional net clinical benefit analyses compare the absolute reduction in the ischemic endpoints associated with prasugrel with the absolute increase in non-CABG related TIMI Major or Life-Threatening bleeding, although the majority of bleeding is not associated with irreversible outcomes. These analyses do not include reduction in recurrent events following a non-fatal primary endpoint. Figure 6.20 displays the overall benefit of the reduction of irreversible cardiovascular events relative to the increase in the incidence of non-CABG related TIMI Major bleeding. The absolute reduction in irreversible cardiovascular events exceeds the absolute increase in non-CABG-related TIMI Major bleeding.

Using observed rates of myocardial infarction (Table 6.4), the absolute risk reduction with prasugrel is 2.2%. For every 1000 patients treated, 22 myocardial infarctions were prevented with prasugrel compared to clopidogrel. The corresponding comparison using observed rates for non-CABG TIMI Major bleeding (absolute increase of 0.5%; Table 6.6) is an excess of 5 Major bleeding events are caused prasugrel compared to clopidogrel for every 1000 patients treated



Source: Q8292

Figure 6.20 **Balance of efficacy and safety in TRITON-TIMI 38 – All ACS Patients.**

The benefit/risk profile for prasugrel compared with clopidogrel can be assessed by the number needed to treat (NNT), the number of patients treated to prevent one ischemic event, versus the number needed to harm (NNH), the number of patients treated to cause one major bleeding event. As shown in Table 6.9, the benefit of prasugrel (small NNT, large NNH) was evident in each population (All ACS, UA/NSTEMI, STEMI), regardless of the endpoint (using CV mortality or all-cause mortality), and regardless of the definition of important bleeding (TIMI Major or TIMI Life-Threatening).

Table 6.9. **NNT (Primary Efficacy Outcome) and NNH (TIMI Major Bleeds) - Study TAAL; All Randomized Patients**

Subgroup	Efficacy Sample size	NNT[a] (Primary efficacy)	NNT[a] (All death, MI, Stroke)	NNH[a] (TIMI Major[b])	NNH[a] (TIMI Life-Threatening[b])
All ACS	13608	46	51	169	200
UA/NSTEMI	10074	46	51	143	159
STEMI	3534	42	42	323	714

[a] Values were calculated using K-M estimates.

[b] Non-CABG-related.

Source: NNT NNH using K-M estimates.xls.

Thus, regardless of the approach used to characterize net clinical benefit, the treatment benefit with prasugrel versus clopidogrel was maintained in patients across the spectrum of ACS managed by PCI.

6.4.7. Efficacy Conclusions

TRITON-TIMI 38 was a superiority trial that compared prasugrel to clopidogrel as therapy for patients with ACS undergoing PCI. Clopidogrel, itself, has been shown to be a highly effective therapy. The study employed the primary efficacy endpoint of CV death, nonfatal MI, or nonfatal stroke, which is a measure of irreversible ischemic events associated with both short- and long-term morbidity and mortality.

In TRITON-TIMI 38, the administration of prasugrel to patients with ACS undergoing PCI was associated with a clinically relevant and highly statistically significant 19% relative risk reduction in this primary endpoint compared to treatment with clopidogrel. The beneficial effect of prasugrel in reducing ischemic events was evident in patients presenting with either UA/NSTEMI or STEMI. For both clinical presentations, there was a statistically significant reduction in all prespecified secondary endpoints including clinically important reductions in the incidence of endpoints associated with morbidity or mortality, UTVR, and stent thrombosis. There was a consistent beneficial treatment effect across all major prespecified subgroups in the All ACS population, except for those patients with prior TIA/stroke. The reduction in ischemic events with prasugrel was also evident regardless of the adjunctive therapy (e.g., with or without IIb/IIIa inhibitors, mono- or multi-antithrombin therapy, and dose of aspirin).

As important, the reduction in ischemic events with prasugrel was larger when the analyses focused on myocardial infarctions associated with large degrees of myonecrosis. There were clinically relevant reductions in the risk of early and late stent thrombosis as well as early and late symptomatic myocardial infarctions. The reduction in the risk of stent thrombosis was observed regardless of the stent type selected during PCI (BMS or DES).

The beneficial effect associated with prasugrel treatment appeared early and increased throughout the entire study period. Prespecified analyses demonstrated a clinically relevant reduction in the risk of the primary endpoint from 30 days following the first dose of study drug through to the end of the study. This benefit was primary driven by a statistically significant reduction in late myocardial infarctions. For those patients who experienced a nonfatal primary event, prasugrel treatment was associated with a reduction in risk for recurrent ischemic events. There was a significant reduction in CV death following myocardial infarction in prasugrel treated patients.

Prasugrel treatment was associated with an unanticipated increased risk of life-threatening and fatal hemorrhage. Therefore, the prespecified secondary composite endpoint of all cause death, nonfatal MI or nonfatal stroke was used to assess the overall impact of prasugrel on clinical outcomes. This composite endpoint incorporates any fatal hemorrhage and, as the duration of follow-up in TRITON-TIMI 38 was up to 15 months, also incorporates any irreversible ischemic complication of a nonfatal hemorrhage. When assessed by the composite endpoint of all cause death, nonfatal MI, or nonfatal stroke, prasugrel again demonstrated a clinically relevant and statistically significant

beneficial effect. Even more conservative estimates of net clinical benefit, which incorporated the incidence of non-CABG TIMI Major bleeding, favored treatment with prasugrel in each population (All ACS, UA/NSTEMI, STEMI).

6.5. Overview of Safety in TRITON-TIMI 38

In TRITON-TIMI 38, a total of 6741 patients were exposed to at least 1 dose of prasugrel. Of these, 5782 were exposed to prasugrel for at least 6 months and 4015 were exposed to prasugrel for at least 12 months. The population sample included older (≥65 years, 39% of patients), very elderly (≥75 years, 13% of patients), and female patients (25%), and is representative of the target population with ACS managed by PCI.

The overall tolerability of prasugrel was comparable to clopidogrel as demonstrated by a similar incidence of study drug discontinuation between treatment groups (17.91% versus 17.32%). However, prasugrel was associated with a greater incidence of study drug discontinuation for hemorrhagic TEAE (2.51% versus 1.35%). There was a similar incidence of non-hemorrhagic TEAEs and non-hemorrhagic SAEs between treatment groups. These topics are further discussed in Section 6.5.4.

In TRITON-TIMI 38, the key safety finding associated with prasugrel treatment was an increased risk of non-CABG related TIMI bleeding (Section 6.5.1) and CABG-related TIMI bleeding (Section 6.6).

6.5.1. Non-CABG related TIMI Major Bleeding Events (CEC Adjudicated)

Table 6.10 summarizes the adjudicated non-CABG related TIMI Major bleeding events for all treated patients.

The incidence of non-CABG related TIMI Major bleeding and its associated subgroup of non-CABG related TIMI Life-Threatening was statistically significantly higher in patients treated with prasugrel compared to clopidogrel. There was a similar incidence of TIMI Major bleeding due to instrumentation between treatment groups. There was a statistically significantly higher rate of spontaneous TIMI Major bleeding in patients treated with prasugrel compared to clopidogrel.

Non-CABG related fatal bleeding events were also statistically significantly higher in prasugrel (n=21) compared to clopidogrel (n=6; 1 patient who experienced fatal bleeding without measurement of hemoglobin was adjudicated as TIMI Minimal - see footnote to Table 6.10). More information on the factors contributing to fatal bleeding is provided in Section 6.5.1.2.

Table 6.10. Incidence of TIMI Major Bleeding Events All ACS Patients

Non-CABG related Bleeding Events[a]	Prasugrel N=6741 n (%)[d] [%][e]	Clopidogrel N=6716 n (%)[d] [%][e]	HR (95% CI)	p-value
TIMI Major	146 (2.17) [2.43]	111 (1.65) [1.84]	1.315 (1.028, 1.683)	0.029
Life-Threatening	85 (1.26) [1.44]	56 (0.83) [0.94]	1.517 (1.083, 2.126)	0.015
Fatal[c]	21 (0.31)	5 (0.07)	4.191 (1.580, 11.113)	0.002
Symptomatic ICH	19 (0.28)	17 (0.25)	1.119 (0.582, 2.152)	0.736
Inotrope Required	21 (0.31)	8 (0.12)	2.617 (1.159, 5.908)	0.016
Surgery Required	19 (0.28)	19 (0.28)	0.998 (0.528, 1.885)	0.995
Transfusion ≥4 Units	45 (0.67)	30 (0.45)	1.499 (0.945, 2.379)	0.084
Non Life-Threatening	63 (0.93) [1.03]	56 (0.83) [0.92]	1.124 (0.784, 1 .611)	0.524
Provocation of Non-CABG related TIMI Major Bleeding[b]				
Instrumented	45 (0.67) [0.72]	38 (0.57) [0.59]	1.182 (0.767, 1.820)	0.447
Spontaneous	92 (1.36) [1.55]	61 (0.91) [1.05]	1.508 (1.091, 2.085)	0.012

[a] Patients experiencing multiple bleeding events may be included in more than one category.

[b] Provocation of bleeding is as reported by the investigator-reported bleeding endpoint form.

[c] A total of 6 clopidogrel patients experienced non-CABG related fatal bleeding events. One patient died before a hemoglobin measurement could be obtained, and did not meet strict criteria for TIMI Major bleeding.

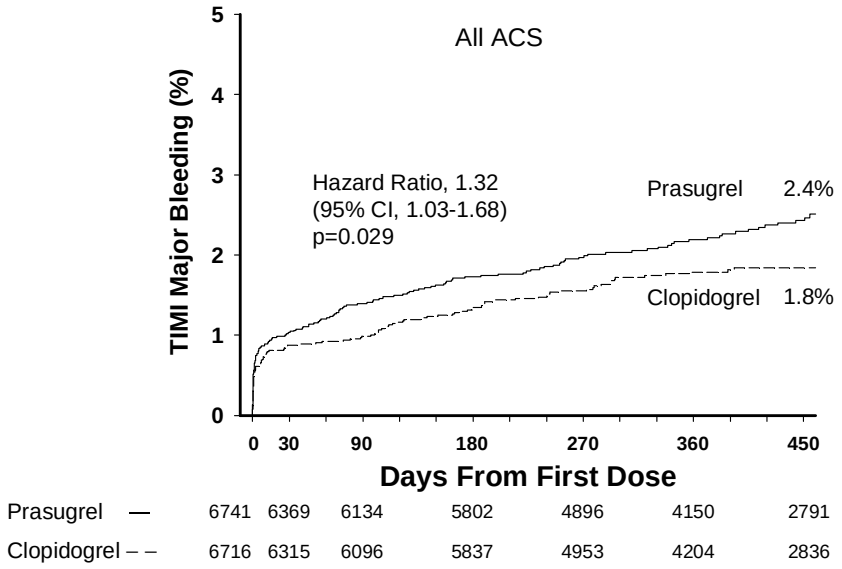
[d] Observed rate

[e] K-M estimate at 450 days

Source: Q951, Q7265, Q8359, Q8362b.

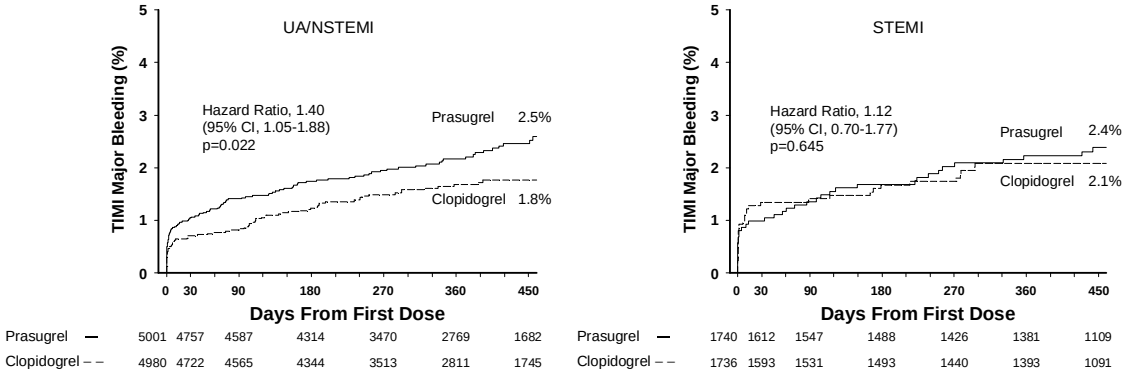
The Kaplan-Meier curve for non-CABG related TIMI Major bleeding is shown in Figure 6.21. The curves separated early in favor of clopidogrel and remained parallel between 90 and 360 days. Beyond 360 days, events continued to accrue in patients treated with prasugrel, while a diminished accrual rate was seen in patients treated with clopidogrel.

The Kaplan-Meier curves for TIMI Major bleeding for the UA/NSTEMI and STEMI populations are displayed in Figure 6.22. There was no separation observed in the curves for the STEMI population.



Source: Q966.

Figure 6.21. Kaplan-Meier estimates of the incidence of Non-CABG related TIMI major bleeding events while at risk—All ACS patients.



Source: Q956. Source: Q961.

Figure 6.22. Kaplan-Meier estimates of the incidence of Non-CABG related TIMI major bleeding events while at risk—UA/NSTEMI patients (left) and STEMI patients (right).

6.5.1.1. Multivariable Analyses for non-CABG related TIMI Major Bleeding

Multivariable analyses including treatment assignment and treatment-by-risk factor interactions were conducted to identify independent factors associated with a differential risk for TIMI Major bleeding between treatment groups (Table 6.11). The following patient characteristics were statistically significant independent risk factors for the increased occurrence of non-CABG related TIMI Major bleeding: prasugrel treatment,

weight <60 kg, age ≥75 years, history of hypertension, history of prior TIA/stroke, and use of GPIIb/IIIa inhibitor from symptom onset through 3 days after randomization.

In addition, there was a significant interaction between weight and age indicating that the effect of body weight <60 kg was more pronounced in patients <75 years of age than in patients ≥75 years of age. There was also a significant interaction between age and history of prior TIA/stroke indicating that the effect of a prior TIA/stroke was more pronounced in patients aged ≥75 years of age than in patients <75 years of age. Finally, the use of GPIIb/IIIa inhibitors from symptom onset through 3 days after randomization was a factor influencing the incidence of non-CABG related TIMI Major bleeding differentially for prasugrel and clopidogrel. For those patients treated with a GPIIb/IIIa inhibitor, the risk of having a bleed on prasugrel was similar to that of clopidogrel (OR=1.09, p=0.591), while for those patients not treated with a GPIIb/IIIa inhibitor, the risk of having a bleed on prasugrel was higher compared to clopidogrel (OR=1.81, p=0.004). This was due to the fact that the bleeding rate for clopidogrel was higher in patients receiving GPIIb/IIIa inhibitor while the rate in prasugrel was similar in patients receiving or not receiving a GPIIb/IIIa inhibitor.

Table 6.11. Statistically Significant Risk Factors for Non-CABG-Related TIMI Major Bleeding With Prasugrel and Clopidogrel

Variable	Estimate	Standard Error	Wald Chi-Square	p-value
Intercept	-3.2012	0.1589	406.0919	<.0001
Treatment	0.1708	0.0669	6.5248	0.0106
Weight (<60 kg)	0.3569	0.1190	8.9897	0.0027
AGE (≥75 years)	0.3049	0.1531	3.9676	0.0464
Hypertension	0.1362	0.0720	3.5795	0.0585
TIA/stroke	0.3908	0.1241	9.9078	0.0016
GPIIb/IIIa	0.1459	0.0672	4.7194	0.0298
Weight*age	-0.2338	0.1188	3.8744	0.0490
Age*TIA/stroke	0.2450	0.1235	3.9352	0.0473
Treatment*GPIIb/IIIa	-0.1255	0.0669	3.5220	0.0606

Source: l0047_lgsafj11_multivariate.rtf (Table APP.2.7.4.174).

Multivariable analyses were also conducted within each treatment arm to identify independent factors associated with an increased risk for TIMI Major bleeding (Table 6.12). Factors indicating a higher absolute risk for patients treated with prasugrel were: age ≥75 years, weight <60 kg, and prior TIA/stroke. Among patients treated with clopidogrel, the factors were weight <60 kg, history of diabetes, baseline TIMI risk index in the 5th quintile, and use of GPIIb/IIIa inhibitor through 3 days from randomization. The clinical presentations of UA/NSTEMI and STEMI were not independent risk factors for non-CABG related TIMI Major bleeding in either treatment group.

Table 6.12. Odds Ratio for Statistically Significant Risk Factors of Non-CABG-Related TIMI Major Bleeding with Prasugrel and Clopidogrel

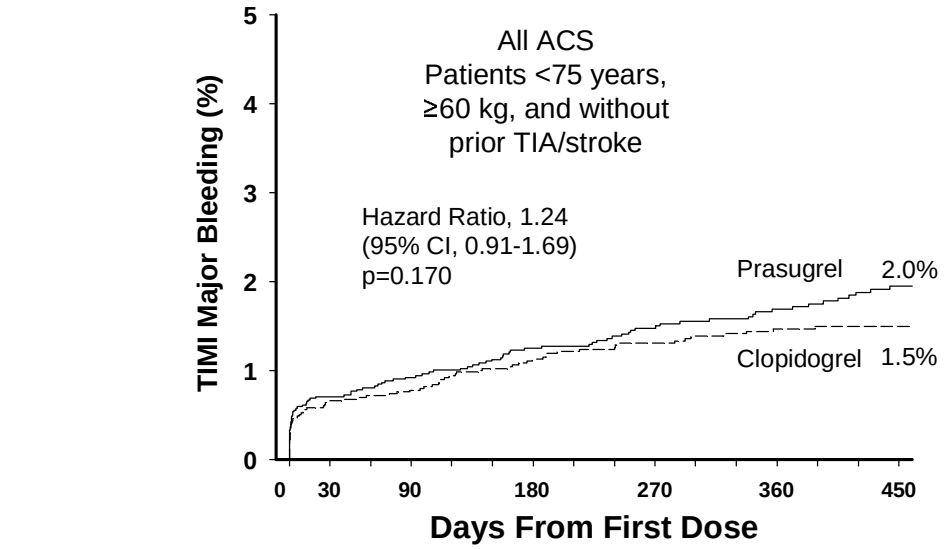
	Prasugrel			Clopidogrel		
	Point estimate	95% Wald Confidence Limits	p-value	Point estimate	95% Wald Confidence Limits	p-value
Weight <60 kg	2.768	1.652, 4.640	0.0001	2.008	1.054, 3.825	0.0340
Diabetes				1.563	1.032, 2.367	0.0348
TIMI Risk Index Q5				1.688	1.107, 2.574	0.0151
GPIIb/IIIa				1.647	1.101, 2.463	0.0153
Age ≥75 years	1.805	1.205, 2.704	0.0042			
Prior TIA/Stroke	2.623	1.480, 4.649	0.0010			

Source: l0047_lgsafj11_multivariate.rtf (Table APP.2.7.4.179).

Population pharmacokinetic analyses indicated that low body weight and increasing age are associated with increased exposure to prasugrel's active metabolite (Section 8.3). Additionally, increased exposure to prasugrel's active metabolite is associated with an increased risk of bleeding (Section 8.5). Therefore, there is strong biologic plausibility that the identification of weight <60 kg and age ≥75 years as independent risk factors for increased risk of bleeding in patients treated with prasugrel observed in TRITON-TIMI 38 is unlikely to be a chance finding.

There is also strong biologic plausibility that the observed increased risk of bleeding in patients with prior TIA/stroke treated with prasugrel is unlikely to be a chance finding. Prior studies of dual antiplatelet therapy with clopidogrel and aspirin compared to monotherapy in patients with prior TIA/stroke have demonstrated an increased risk of major bleeding, including intracranial hemorrhage (Diener et al. 2004; Soman et al. 2006). It follows that a more potent dual antiplatelet regimen could be associated with an increased risk of major bleeding compared to a less potent dual antiplatelet regimen in these patients.

When the populations with independent risk factors for non-CABG related TIMI Major bleeding with prasugrel treatment were removed from the analysis, the incidence of non-CABG related TIMI Major bleeding was similar in each treatment group through approximately 360 days (Figure 6.23). Thereafter, the bleeding rate in the prasugrel arm remained constant while there were no further events observed in clopidogrel-treated patients.



Source: Q8146.

Figure 6.23. Kaplan-Meier estimates of the incidence of non-CABG-related TIMI major bleeding for ACS patients who are less than 75 years of age, equal to or greater than 60 kg, and without prior TIA/stroke.

6.5.1.2. Contributing Factors to Fatal Bleeding

The overall incidence of non-CABG-related fatal bleeding events was 0.31% (n=21) in the prasugrel treatment group and 0.09% (n=6) in the clopidogrel treatment group (Table 6.10). This observation was an unexpected finding as the Sponsor had anticipated the fatal bleed rate associated with prasugrel treatment to be similar to that seen in previous studies of clopidogrel plus aspirin (Table 6.13). Although the rate of fatal hemorrhage for prasugrel-treated patients in TRITON-TIMI 38 was comparable to that seen in CURE (and comparable to rates published in subsequent studies of clopidogrel plus aspirin), the observed fatal bleeding rate for clopidogrel was less than expected.

Table 6.13. Fatal Bleeding in Studies of Clopidogrel plus Aspirin

Study (Median follow-up)	Population	Fatal Bleeding % (n/N) Clopidogrel + ASA	ASA
CURE (9 months)	UA/NSTEMI	0.2 (11/6259)	0.2 (15/6303)
CLARITY[b] (1 month)	STEMI – with lytic	0.8 (14/1733)	0.6 (10/1719)
COMMIT[a] (< 1 month)	STEMI – without lytic	0.3 (73/22961)	0.3 (74/22891)
MATCH (18 months)	patients with TIA/stroke	0.4 (16/3759)	0.3 (clopidogrel alone) (11/3781)

[a] Data on fatal bleedings are limited to the time of hospital discharge.

[b] Back calculated using data provided in clopidogrel's summary basis of approval (SBA).

Source: Chen et al. 2005; [CURE] 2001; Diener et al. 2004; Sabatine et al. 2005, PLAVIX USPI 2008.

Nonetheless, TRITON-TIMI 38 was a randomized comparison of prasugrel treatment to clopidogrel and the observed increased risk of fatal hemorrhages with prasugrel is unlikely to be a chance finding. Table 6.14 lists the fatal bleeding events by type (i.e., spontaneous, procedure-related, traumatic) and by site.

Table 6.14. Fatal Bleeding by Provocation and Location

	Fatal Hemorrhages	
	Prasugrel N=6741 n (%)	**Clopidogrel N=6716 n (%)**
Overall	**21 (0.31)**	**6[a] (0.09)**
Spontaneous	**13 (0.19)**	**5 (0.07)**
ICH	8 (0.12)	4 (0.06)
Gastrointestinal	4 (0.06)	1[a] (0.01)
Ruptured AAA	1 (0.01)	0
Procedural-Related	**7 (0.10)**	**0**
PCI Related	5 (0.07)	0
Access site (groin)	3 (0.04)	0
Aortic tear with IABP	1 (0.01)	0
Hemopericardium post PCI	1 (0.01)	0
Non-CABG Surgery	2 0.03)	0
Traumatic	**1 (0.01)**	**1 (0.01)**
ICH	1 (0.01)	1 (0.01)

[a]One patient counted here died of a GI bleed, but hemoglobin level was not determined. Therefore, this bleeding event was adjudicated as a TIMI Minimal bleed and this patient is not included in tables of non-CABG related TIMI Major bleeding.

Source: Table TAAL.12.13a, Table TAAL.12.13b, l0598_lsbldc13_allfatalbld.xls.

The primary risk factor for spontaneous fatal hemorrhage associated with prasugrel treatment was age ≥75 years. Of the 13 spontaneous events occurring in prasugrel-treated patients, 9 occurred in patients ≥75 years of age (4 ICH, 4 GI, 1 AAA). None of the spontaneous bleeding events in clopidogrel treated patients occurred in patients ≥75 years of age. Conversely, for patients <75 years of age, there were 4 prasugrel-treated and 5 clopidogrel-treated patients who experienced spontaneous fatal hemorrhage. Table 6.15 lists additional characteristics for patients experiencing fatal hemorrhage.

There were 7 procedure-related fatal bleeding complications in prasugrel-treated patients. Three of these were access site complications; all from the femoral artery approach and 2 of the 3 events occurred in obese patients (≥130 kg). The remaining two PCI-related events were an aortic tear at the level of the bifurcation associated with placement of an intra-aortic balloon pump and hemopericardium associated with coronary intervention leading to tamponade. Non-CABG-related surgical complications occurred in one patient who underwent surgery without discontinuation of study drug and in one patient who experienced dehiscence of a gastric anastomosis 16 days post surgery and 6 days after restarting study drug.

Review of the treatment regimens employed to manage fatal bleeding complications revealed that relatively few patients experiencing fatal bleeding received platelet transfusions to minimize the extent of bleeding. For example, of the 27 non-CABG-related fatal bleeds, only 4 patients received more than 1 unit of platelets to treat the bleed, suggesting that there is a lack of understanding that thienopyridine-induced inhibition of platelet aggregation is irreversible. Platelet administration may reverse the platelet inhibitory effect in the setting of major bleeding. Therefore, the Sponsor recommends incorporating the following language into the Warnings and Precautions:

For patients with active bleeding for whom reversal of the pharmacological effects of EFFIENT is required, platelet transfusion may be appropriate.

Conclusions Regarding Fatal Bleeding

Fatal bleeding is a known and catastrophic complication of anti-platelet therapy. There was an increased fatal bleeding risk with prasugrel compared to clopidogrel in TRITON. The risk of procedural-related bleeding may be modulated by access site selection and management and discontinuation of therapy prior to surgical intervention. The risk of spontaneous fatal bleeding with prasugrel is not uniform across populations and appears to be higher in the very elderly. Identification of patients at increased risk should further diminish the risk of fatal bleeding with prasugrel. In patients age <75 years, no difference the incidence of spontaneous fatal bleeding was observed between treatment groups.

Table 6.15. Summary of Non-CABG-Related Fatal Hemorrhages by Demographics and Selected Medical History

	All Fatal Hemorrhages		Fatal Intracranial Hemorrhages		Fatal Gastrointestinal Hemorrhages	
	Prasugrel n (%)	Clopidogrel n (%)	Prasugrel n (%)	Clopidogrel n (%)	Prasugrel n (%)	Clopidogrel n (%)
Overall	21	6***	9	5	6	1
Sex						
Male (N=9975)	15 (0.30)	2 (0.04)	7 (0.14)	2 (0.04)	4 (0.08)	0
Female (N=3482)	6 (0.36)	4 (0.22)	2 (0.12)	3 (0.17)	2 (0.12)	1 (0.06)
Age						
<75 years (N=11672)	12 (0.21)	5 (0.09)	5 (0.08)	4 (0.07)	2 (0.03)	1 (0.02)
≥75 years (N=1785)	9 (1.01)	1 (0.11)	4 (0.44)	1 (0.11)	4 (0.44)	0
Weight						
<60 kg (N=664)	0*	1 (0.28)	0	1 (0.28)	0**	0
≥60 kg (N=12672)	18 (0.28)	5 (0.08)	9 (0.14)	4 (0.06)	5 (0.08)	1 (0.02)
History of TIA or Stroke						
Yes (N=509)	3 (1.17)	0	2 (0.78)	0	1 (0.39)	0
No (N=12948)	18 (0.28)	6 (0.09)	7 (0.11)	5 (0.08)	5 (0.08)	1 (0.02)
Geographic Region						
North America (N=4252)	4 (0.19)	2 (0.09)	3 (0.14)	2 (0.09)	0	0
US (N=4005)	3 (0.15)	2 (0.10)	2 (0.01)	2 (0.10)	0	0
South America (N=533)	1 (0.37)	0	1 (0.37)	0	0	0
Western Europe (N=3505)	7 (0.40)	3 (0.17)	4 (0.23)	3 (0.17)	0	0
Eastern Europe (N=3300)	4 (0.24)	0	1 (0.06)	0	3 (0.04)	0
Rest of World (N=1867)	5 (0.54)	1 (0.11)	0	0	3 (0.32)	1 (0.11)

*Weight measurement unavailable for 3 patients.

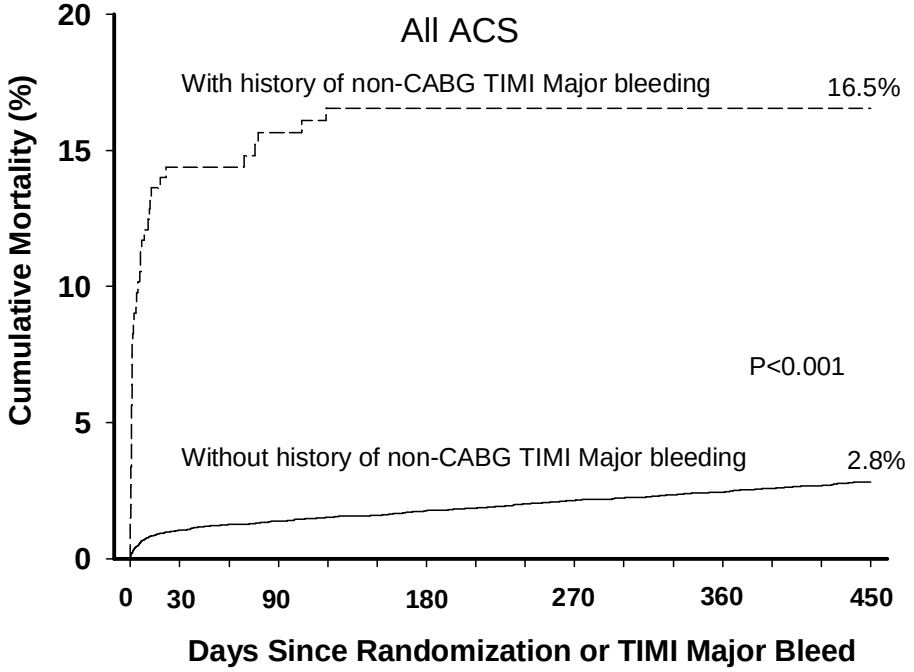
**Weight measurement unavailable for 1 patient.

***One patient died of a GI hemorrhage. However the event was adjudicated as a TIMI Minimal bleed due to the absence of laboratory hemoglobin values.

Source: l0598_lsbldc13_allfatalbld.xls, Q1166, Q1206, Q3815, Q3820.

6.5.1.3. Clinical Outcomes after non-CABG related TIMI Major Bleeding Events

Because the duration of treatment in TRITON-TIMI 38 was a median of 14.5 months with a planned minimum of 6 months, the duration of follow-up in TRITON-TIMI 38 was adequate to capture any irreversible outcomes and any long-term CV sequelae associated with ischemic and hemorrhagic events. Figure 6.24 provides a Kaplan-Meier estimate for all cause death after a non-CABG related TIMI Major bleed by patient group. Non-CABG related TIMI Major bleeding was associated with increased risk of death primarily during the 30 days after the bleeding event. However, after 30 days the risk of all-cause mortality was similar for those patients who did or did not experience a non-CABG related TIMI Major bleeding event.



Source: L0604.

Figure 6.24 **Risk of all cause death after a non-CABG-related TIMI Major bleeding event - through study end.**

6.5.2. Non-CABG related TIMI Major or Minor Bleeding Events

The incidence of non-CABG related TIMI Major or Minor bleeding was statistically significantly higher in patients treated with prasugrel compared to clopidogrel in the UA/NSTEMI and All ACS populations, but not in the STEMI population. In the All ACS population, this difference is primarily due to a statistically significant higher incidence of spontaneous bleeding (2.39% versus 1.62%; p=0.002; Table 6.16) associated with prasugrel compared to clopidogrel. Instrumented bleeding, which primarily reflects

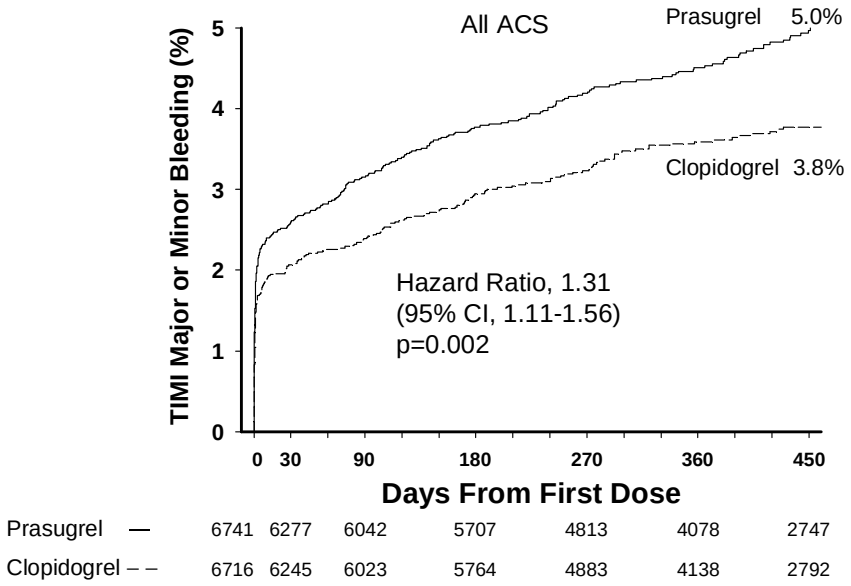
the effect of the LD, was increased to a lesser degree that did not reach statistical significance.

Table 6.16. Incidence of TIMI Major or Minor Bleeding Events

Non-CABG-related Bleeding Events[a]	Prasugrel N=6741 n (%)[b] [%][c]	Clopidogrel N=6716 n (%)[b] [%][c]	HR (95% CI)	p-value[d]
TIMI Major or Minor	303 (4.49) [4.97]	231 (3.44) [3.77]	1.314 (1.107, 1.559)	.002
Provocation of Non-CABG-related TIMI Major or Minor Bleeding[e]				
Instrumented	114 (1.69) [1.78]	95 (1.41) [1.47]	1.198 (0.913, 1.573)	.191
Spontaneous	161 (2.39) [2.71]	109 (1.62) [1.87]	1.478 (1.159, 1.885)	.002

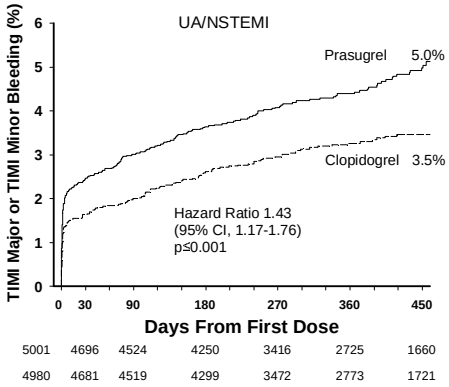
a Patients experiencing multiple bleeding events may be included in more than one category.
b Observed rate
c K-M estimate at 450 days
d Two-sided log-rank p-value based on time to first event analysis compares the event free survival distributions for prasugrel and clopidogrel. Clinical presentation, UA/NSTEMI versus STEMI, was used as a stratification factor in analyses of All ACS patients.
e Provocation of Bleeding is as reported by the investigator reported bleeding endpoint form.
Source: Q951, Q7265, Q8432b, 8433b

These differences are reflected by the separation favoring clopidogrel in the Kaplan-Meier curves for TIMI Major or Minor bleeding in UA/NSTEMI patients and in All ACS patients (Figure 6.25 and Figure 6.26). However, there was no separation in the curves for the STEMI population.

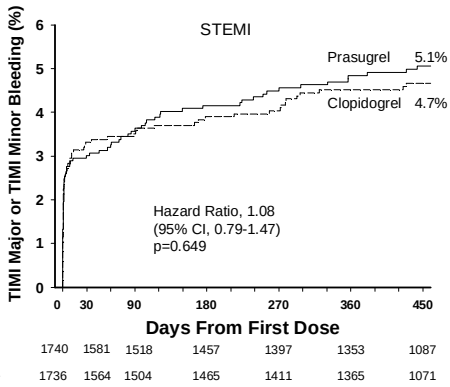


Source: Q8070.

Figure 6.25. Kaplan-Meier estimates of the incidence of non-CABG-related TIMI major or TIMI minor bleeding while at risk —all ACS patients.



Source: Q1005



Source: Q1006.

Figure 6.26. Kaplan-Meier estimates of the incidence of non-CABG-related TIMI major or minor bleeding events while at risk—UA/NSTEMI patients (left) and STEMI patients (right).

6.5.2.1. Bleeding Events in Subgroups

Multivariable subgroup analyses within treatment groups were performed for non-CABG related TIMI Major bleeding as noted in Section 6.5.1.1. For non-CABG related TIMI Major or Minor bleeding, univariate subgroup analyses were performed to assess the risk of individual patient characteristics. In these analyses, a characteristic was considered potentially significant if the interaction p-value was <0.1.

Demographics and Baseline Characteristics

No treatment interaction reached statistical significance for the demographic and baseline characteristic subgroups analyzed. When absolute differences in risk are compared, in both treatment groups a higher absolute incidence of non-CABG-related TIMI Major or Minor bleeding events was noted in patients with the following characteristics: female sex, advanced age, or low body weight (Table 6.17). Compared to the complementary subgroup, these patients also demonstrated a greater absolute increase in non-CABG related TIMI Major or Minor bleeding within the prasugrel treatment group. In the multivariable analysis of non-CABG TIMI Major bleeding (Section 6.5.1.1), female sex was not an independent risk factor.

Table 6.17. Patients with Non-CABG-Related TIMI Major or TIMI Minor Bleeding Events While at Risk - Subgroup Analysis by Demographics and Baseline Characteristics

	Prasugrel n (%)	Clopidogrel n (%)	Absolute Risk Difference %	HR (95% CI)
Sex				
Female (N=3482)	123 (7.30)	97 (5.39)	1.91	1.379 (1.057, 1.799)
Male (N=9975)	180 (3.56)	134 (2.72)	0.84	1.308 (1.046, 1.635)
Age (years)				
<75 (N=11672)	223 (3.81)	169 (2.90)	0.91	1.320 (1.081, 1.612)
≥75 (N=1785)	80 (8.98)	62 (6.94)	2.04	1.346 (0.966, 1.877)
Geographic Region				
North America (N=4252)	112 (5.23)	84 (3.98)	1.25	1.309 (0.987, 1.737)
United States (N=4005)	108 (5.35)	79 (3.98)	1.37	1.341 (1.003, 1.792)
South America (N=533)	9 (3.35)	11 (4.17)	-0.82	0.820 (0.340, 1.979)
Western Europe (N=3505)	77 (4.38)	61 (3.49)	0.89	1.262 (0.902, 1.765)
Eastern Europe (N=3300)	69 (4.20)	44 (2.66)	1.54	1.595 (1.093, 2.328)
Rest of World (N=1867)	36 (3.86)	31 (3.32)	0.54	1.181 (0.731, 1.910)
Ethnicity				
Caucasian (N=12396)	281 (4.54)	217 (3.50)	1.04	1.302 (1.091, 1.555)
African (N=386)	10 (4.98)	7 (3.78)	1.2	1.341 (0.510, 3.528)
Hispanic (N=524)	10 (3.72)	6 (2.35)	1.37	1.551 (0.563, 4.273)
Asian (N=123)	2 (3.33)	1 (1.59)	1.74	-
Other (N=28)	0	0	0	-
Weight (kg)				
≤60 (N=664)	31 (10.06)	23 (6.46)	3.6	1.570 (0.915, 2.694)
>60 (N=12672)	268 (4.21)	206 (3.27)	0.94	1.293 (1.078, 1.551)

Source: Q1166, Q3815, Q3820.

Medical History

No treatment interaction reached statistical significance for the medical history subgroups analyzed. For absolute rates of risk, in both treatment groups a higher incidence of non-CABG related TIMI Major or Minor bleeding events was noted in patients with the following characteristics: history of hypertension, congestive heart failure, atrial fibrillation, peripheral artery disease, and renal impairment (Table 6.18). For prior TIA/stroke, a higher incidence was noted in the prasugrel group alone. Compared to the complementary subgroup, patients with the following medical histories also demonstrated a greater absolute increase in non-CABG related TIMI Major or Minor bleeding within the prasugrel treatment group: prior TIA/stroke, atrial fibrillation, and renal impairment. Of these risk factors, only prior TIA/stroke was an independent risk factor for non-CABG related TIMI Major bleeding. Patients with atrial fibrillation who were at risk for bleeding were also very elderly (age ≥75 years), and have a history of TIA/stroke. Patients with renal impairment who were at risk for bleeding were also very elderly (age ≥75 years). Patients with atrial fibrillation or renal impairment without these other risk factors were not at increased risk of bleeding with prasugrel compared to those without atrial fibrillation or renal impairment.

Table 6.18. Patients with Non-CABG-Related TIMI Major or TIMI Minor Bleeding Events While at Risk - Subgroup Analysis by Medical History

	Prasugrel n (%)	Clopidogrel n (%)	Absolute Risk Difference %	HR (95% CI)
Diabetes				
Yes (N=3108)	76 (4.89)	59 (3.80)	1.09	1.297 (0.923, 1.822)
No (N=10349)	227 (4.38)	172 (3.33)	1.05	1.320 (1.083, 1.609)
Hypertension				
Yes (N=8645)	212 (4.91)	168 (3.89)	1.02	1.270 (1.037, 1.555)
No (N=4812)	91 (3.76)	63 (2.63)	1.13	1.437 (1.042, 1.982)
Prior TIA/Stroke				
Yes (N=509)	20 (7.78)	10 (3.97)	3.81	2.082 (0.972, 4.456)
No (N=12948)	283 (4.36)	221 (3.42)	0.94	1.282 (1.076, 1.529)
CHF				
Yes (N=504)	15 (5.73)	14 (5.79)	-0.06	0.932 (0.449, 1.934)
No (N=7121)	288 (4.45)	217 (3.35)	1.10	1.335 (1.120, 1.593)
Atrial Fibrillation				
Yes (N=416)	16 (7.69)	9 (4.33)	3.36	1.782 (0.788, 4.034)
No (N=13041)	287 (4.39)	222 (3.41)	0.98	1.296 (1.087, 1.544)
Peptic Ulcer				
Yes (N=809)	18 (4.51)	13 (3.17)	1.34	1.422 (0.696, 2.903)
No (N=12648)	285 (4.49)	218 (3.46)	1.03	1.308 (1.096, 1.560)
PAD				
Yes (N=706)	21 (6.05)	16 (4.46)	1.59	1.350 (0.704, 2.587)
No (N=12751)	282 (4.41)	215 (3.38)	1.03	1.312 (1.099, 1.567)
Hepatic Impairment[a]				
Yes (N=69)	2 (6.25)	3 (8.11)	-1.86	-
No (N=13388)	301 (4.49)	228 (3.41)	1.08	1.321 (1.112, 1.569)
Renal Impairment[b]				
Yes (N=125)	10 (16.67)	5 (7.69)	8.98	2.114 (0.716, 6.247)
No (N=13332)	293 (4.39)	226 (3.40)	0.99	1.298 (1.091, 1.544)
Creatinine Clearance[c]				
<30 (N=104)	9 (18.00)	5 (9.26)	8.74	1.466 (0.469, 4.577)
30-60 (N=1372)	58 (8.83)	47 (6.57)	2.26	1.373 (0.934, 2.017)
>60 (N=11833)	232 (3.89)	175 (2.98)	0.91	1.312 (1.078, 1.596)

a Hepatic impairment based on pre-existing conditions or Hy's Rule at baseline.

b Renal impairment based on creatinine ≥2mg/dL at baseline.

c Creatinine clearance using Cockroft-Gault formula (mL/min).

Source: Q1206.

Antithrombotics and Related Medications Through 3 Days

Table 6.19 shows non-CABG-related TIMI Major or Minor bleeding events through 3 days while at risk. There was a higher incidence of bleeding in patients treated with prasugrel compared to clopidogrel. There was a higher incidence of bleeding in patients receiving a GPIIb/IIIa inhibitor in each treatment group. The incidence of bleeding events in patients receiving a GPIIb/IIIa inhibitor was similar in patients treated with prasugrel or clopidogrel. There was a higher incidence of bleeding events in patients treated with prasugrel compared to clopidogrel in the absence of a GPIIb/IIIa inhibitor. These results indicate that prasugrel can be used with GPIIb/IIIa inhibitor without substantial increased risk of bleeding. In contrast, bleeding was higher with clopidogrel treatment in the presence of GPIIb/IIIa inhibitors, demonstrating the greater bleeding risk associated with higher levels of platelet inhibition when clopidogrel is co-administered with GPIIb/IIIa inhibitors.

There was a significant treatment-by-subgroup interaction for antithrombin therapy (monotherapy versus multiple therapies). In patients receiving monotherapy, the incidence of non-CABG related TIMI Major or Minor bleeding events was higher in patients treated with prasugrel compared to clopidogrel. Conversely, in patients receiving multiple anti-thrombin therapies, the incidence of non-CABG related TIMI Major or Minor bleeding events was lower in patients treated with prasugrel compared patients treated with clopidogrel. There were no other treatment-by-subgroup interactions for anti-thrombotic treatments. These results suggest that prasugrel can be used with multiple anti-thrombin agents in the management of patients with ACS undergoing PCI without higher risk of bleeding events.

Table 6.19. Patients with non-CABG-related TIMI Major or Minor Bleeding Events Through 3 Days While at Risk – Subgroup Analysis by Antithrombotics Through 3 Days

	Prasugrel n (%)	Clopidogrel n (%)	Absolute Risk Difference %	HR (95% CI)
Total (N=13457)	138 (2.05)	113 (1.68)	0.37	1.22 (0.95, 1.56)
GPIIb/IIIa Use				
Any Use (N=7349)	98 (2.68)	90 (2.43)	0.25	1.10 (0.83, 1.47)
Never Used (N=6108)	40 (1.29)	23 (0.76)	0.53	1.71 (1.02, 2.85)
Anti-thrombin Use				
Monotherapy (N=8398)	97 (2.30)	60 (1.43)	0.87	1.60 (1.16, 2.21)
Multiple Therapies (N=4788)	39 (1.64)	52 (2.16)	-0.52	0.75 (0.50, 1.14)

Source: Q1031, Q8418.

Aspirin Use

In patients who received concomitant aspirin therapy, there was no correlation between aspirin dose and higher risk for non-CABG related TIMI Major or Minor bleeding.

6.5.3. Adverse Events

In the discussion that follows, the common hemorrhagic TEAEs are presented followed by the common non–hemorrhagic TEAEs. Unless otherwise noted, the discussion will focus on TEAE preferred terms that were identified as common (i.e., with an incidence of at least 1% of the treated patients during the while at risk period) in the All ACS population.

6.5.3.1. Hemorrhagic Adverse Events

A statistically significantly higher percentage of patients treated with prasugrel reported ≥1 hemorrhagic TEAE than patients treated with clopidogrel (29.7% [2002/6741] prasugrel versus 22.0% [1480/6716] clopidogrel; p<0.001). Contusion, hematoma, epistaxis, ecchymosis, puncture site hemorrhage, and GI hemorrhage were common (≥1%) hemorrhagic TEAEs that had a statistically significantly higher incidence in patients treated with prasugrel compared to clopidogrel (Table 6.20).

Table 6.20. Common (greater than or equal to 1%) Hemorrhagic Treatment-Emergent Adverse Events All ACS Patients

Preferred Term	Prasugrel N=6741 n (%)	Clopidogrel N=6716 n (%)	OR[a]	p-value[a]
Contusion	468 (6.9)	262 (3.9)	1.84	<.001
Haematoma	441 (6.5)	374 (5.6)	1.19	.018
Epistaxis	415 (6.2)	219 (3.3)	1.95	<.001
Ecchymosis	149 (2.2)	116 (1.7)	1.29	.044
Vessel puncture site haemoatoma	135 (2.0)	109 (1.6)	1.24	.099
Puncture site hemorrhage	124 (1.8)	87 (1.3)	1.43	.011
Haematuria	104 (1.5)	86 (1.3)	1.21	.197
Gastrointestinal Hemorrhage	102 (1.5)	64 (1.0)	1.6	.003

a The p-value is obtained from a 2-sided CMH general association test where clinical presentation, UA/NSTEMI versus STEMI, was used as a stratification factor. Odds ratio (OR) is based on the frequency procedure.

Source: Q1686.

6.5.3.2. Non-Hemorrhagic Adverse Events

6.5.3.2.1. Non-Hemorrhagic Serious Adverse Events

The rate of non-hemorrhagic SAEs was similar in each treatment group (21.6% [1453/6741] prasugrel versus 22.0% [1478/6716] clopidogrel; p=0.525). The rates of the commonly reported SAEs in both treatment groups (non-cardiac chest pain, coronary

artery restenosis, chest pain, and angina pectoris) were similar in each of the 2 treatment groups. These SAEs represent symptoms that are commonly experienced by patients with coronary artery disease (CAD).

The percentage of non-hemorrhagic TEAEs was similar for the prasugrel- and clopidogrel-treated groups (77.3% versus 77.9%; p=0.494). Of common (occurring at an incidence of ≥1% in either treatment group) non-hemorrhagic TEAEs, 2 had a statistically significantly higher incidence in patients treated with prasugrel than in patients treated with clopidogrel, while 6 had a statistically significantly higher incidence in patients treated with clopidogrel than in those treated with prasugrel (Table 6.21).

Table 6.21. Non-Hemorrhagic TEAEs Occurring greater than or equal to 1% and Differentially (p-value less than 0.05) Between Prasugrel or Clopidogrel While at Risk All ACS Patients

Preferred Term	Prasugrel N=6741 n (%)	Clopidogrel N=6716 n (%)	OR[a]	p-value[a]
Coronary Revascularization	313 (4.6)	390 (5.8)	0.79	.002
Fatigue	249 (3.7)	325 (4.8)	0.75	.001
Pyrexia	185 (2.7)	147 (2.2)	1.26	.037
Myocardial Infarction	108 (1.6)	162 (2.4)	0.66	<.001
Musculoskeletal Pain	92 (1.4)	122 (1.8)	0.75	.036
Constipation	91 (1.4)	131 (2.0)	0.69	.006
Increased tendency to bruise	82 (1.2)	49 (0.7)	1.68	.004
Cardiac Failure	62 (0.9)	89 (1.3)	0.69	.026

a The p-value is obtained from a 2-sided CMH general association test where clinical presentation, UA/NSTEMI versus STEMI, was used as a stratification factor. Odds ratio (OR) is based on the frequency procedure.

Source: Q3005.

In TRITON-TIMI 38, a higher number of prasugrel-treated patients (173/6741, 2.60%) compared to clopidogrel-treated patients (138/6716, 2.05%) experienced an adverse event coded to the "Neoplasms Benign, Malignant, and Unspecified (including Cysts and Polyps)" system organ class (HR=1.26; p=0.043). Of these, the incidence of new non-benign neoplasms diagnosed during the study was not statistically significantly different between treatment groups (Table 6.22).

Colorectal neoplasms accounted for the majority of the difference in new non-benign neoplasms between treatment groups. Gastrointestinal bleeding or anemia, which were higher in prasugrel-treated patients, led to the detection of colorectal neoplasm in a high percentage of cases in each treatment group (prasugrel: 16 of 19, clopidogrel: 8 of 10). Excluding colorectal neoplasms, the absolute difference of new non-benign neoplasms between treatment groups is reduced from 14 to 5 patients (Table 6.22). This topic is further discussed in Section 7.1.

Table 6.22. Number and Percentage of Patients with a New Diagnosis of Non-Benign Neoplasm, Including and Excluding Colorectal Neoplasm
All ACS Patients

	Prasugrel N=6741 n (%)	Clopidogrel N=6716 n (%)	HR (95% CI)	p-value
First New Diagnosis	94 (1.39)	80 (1.19)	1.172 (0.870, 1.579)	.295
First New Diagnosis Excluding Colorectal Neoplasm	75 (1.11)	70 (1.04)	1.069 (0.772, 1.481)	.687

Source: l3543_kmcanl14_spfda_hemteae.rtf.

Table 6.23 shows the number of patients in TRITON-TIMI 38 experiencing clinically significant adverse events. Clinically significant adverse events were a set of prospectively defined adverse events based on knowledge of adverse reactions to thienopyridines and medications in general. There were fewer prasugrel-treated patients with neutropenia or abnormal hepatic function reported as a serious adverse event.

Table 6.23 also shows the number of patients in TRITON-TIMI 38 experiencing selected adverse drug reactions that have been associated with clopidogrel as reported in the PLAVIX label (2008), CDER (2002) medical review, or medical literature. Aside from taste disorders (dysgeusia or ageusia) which occurred at a statistically significantly higher incidence in clopidogrel- compared to prasugrel-treated patients, no other statistically significant differences in reported adverse events were observed between the 2 treatment groups.

Table 6.23. Patients Experiencing Clinically Significant Adverse Events or Adverse Events That Have Been Associated with Clopidogrel
All ACS Patients

	Prasugrel N=6741 n (%)	Clopidogrel N=6716 n (%)	OR	p-value
Clinically Significant Adverse Events[a]				
Thrombocytopenia	20 (0.30)	21 (0.31)	0.95	0.867
Reported as an SAE	17 (0.25)	18 (0.27)	0.94	0.857
Thrombotic Thrombocytopenia Purpura	0	1 (0.01)	-	NE
Reported as an SAE	0	0	-	NE
Neutropenia	2 (0.03)	10 (0.15)	0.20	0.021
Reported as an SAE	0	7 (0.10)	-	NE
Leukopenia	187 (2.77)	236 (3.51)	0.79	0.014
Reported as an SAE	0	0	-	NE
Abnormal Hepatic Function	15 (0.22)	18 (0.27)	0.83	0.59
Reported as an SAE	8 (0.12)	15 (0.22)	0.53	0.14
Adverse Events Associated with Clopidogrel				
Gastrointestinal Events				
Patients with one or more of the following	316 (4.69)	305 (4.54)	1.03	0.686
Dysgeusia or Ageusia	6 (0.09)	15 (0.22)	0.40	0.048
Nausea	311 (4.61)	291 (4.33)	1.07	0.431
Skin Reactions				
Patients with one or more of the following	13 (0.19)	14 (0.21)	0.92	0.839
Steven Johnson Syndrome (SJS)[b]	2 (0.03)	0	-	NE
Toxic skin eruption	1 (0.01)	3 (0.04)	-	NE
Skin necrosis	0	1 (0.01)	-	NE
Dermatitis exfoliative	2 (0.03)	1 (0.01)	-	NE
Skin exfoliation	8 (0.12)	8 (0.12)	1.00	0.994
Exfoliative rash	0	1 (0.01)	-	NE
Allergic Reactions				
Patients with one or more of the following	292 (4.33)	282 (4.20)	1.03	0.703
Anaphylactic reaction	2 (0.03)	4 (0.06)	-	NE
Rash[c]	216 (3.20)	192 (2.86)	1.13	0.238
Drug eruption	2 (0.03)	6 (0.09)	-	NE
Pruritis[d]	58 (0.86)	76 (1.13)	0.76	0.113
Urticaria[e]	29 (0.43)	23 (0.34)	1.26	0.412

a Clinically significant TEAEs were a set of prospectively defined adverse events that were of special interest.

b SJS was reported in 2 patients treated with prasugrel during chronic therapy (10 months and 15 months respectively). Neither discontinued study drug and both cases resolved. In each case, symptoms resolved after discontinuation of other drugs (1 patient was on metformin and pioglitazone, the other on a quinalone antibiotic) that had been recently started.

c Includes rash, and rash (generalized, pruritic, erythematous, maculo-papular, papular, macular, or vesicular).

d Pruritis included pruritis and pruritis generalized.

e Urticaria included urticaria and urticaria generalized.

Source: Q8408,Q1731.

6.5.4. Safety Conclusions

In TRITON-TIMI 38, key safety findings associated with prasugrel treatment were primarily due to mechanism-related risk of bleeding. The bleeding risk associated with prasugrel was higher than with clopidogrel for prespecified bleeding endpoints (including non-CABG related TIMI Major, TIMI Life-Threatening [including fatal], and TIMI Major or Minor bleeding).

Risk for bleeding with prasugrel was assessed by prespecified univariate and post-hoc multivariable analyses. For prasugrel, subgroups associated with a statistically significant increase in non-CABG-related TIMI Major bleeding were: ≥75years of age , body weight <60 kg, and history of prior TIA/stroke. Age ≥75 years also appeared to be a primary risk factor for spontaneous fatal hemorrhage associated with prasugrel. In patients age <75 years, no difference in the incidence of spontaneous fatal bleeding was observed between treatment groups. Fatal hemorrhages associated with the vascular access site or surgical procedures were uncommon and occurred only in prasugrel-treated patients. Careful management of the access site and discontinuation of prasugrel prior to surgery may minimize this risk.

When analyses were performed excluding those subgroups identified as independent risk factors for bleeding (body weight <60 kg, ≥75years of age , and a history of prior TIA/stroke), similar rates of non-CABG TIMI Major bleeding were observed between treatment groups through 360 days.

There was a similar incidence of common non-hemorrhagic adverse events and serious adverse events between treatment groups. There were more non-benign neoplasms observed in prasugrel-treated patients. This topic is discussed further in Section 7.1. There were fewer prasugrel-treated subjects with serious adverse events of neutropenia or abnormal hepatic function. There were no cases of TTP associated with prasugrel treatment.

6.6. Patients Who Underwent CABG

In TRITON-TIMI 38, 484 patients required CABG surgery during the study. Forty-seven of these patients never received study drug. Efficacy analyses were conducted on all randomized patients who underwent CABG (n=484). Safety analyses were conducted on the subgroup of patients treated with study drug (n=437). The analyses were conducted on events that occurred from the time of CABG surgery to the end of follow-up. Patients who experienced a primary efficacy endpoint prior to CABG were not censored for this analysis.

6.6.1. Efficacy in Patients who Underwent CABG

Table 6.24 shows the occurrence of efficacy outcomes after CABG. The incidence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke was lower in patients randomized to prasugrel compared to clopidogrel. The Kaplan-Meier curves for the time

from CABG to first occurrence of the composite endpoint separate early in favor of prasugrel although the difference does not achieve statistical significance (Figure 6.28).

Table 6.24. Patients Reaching Efficacy Outcomes after CABG.

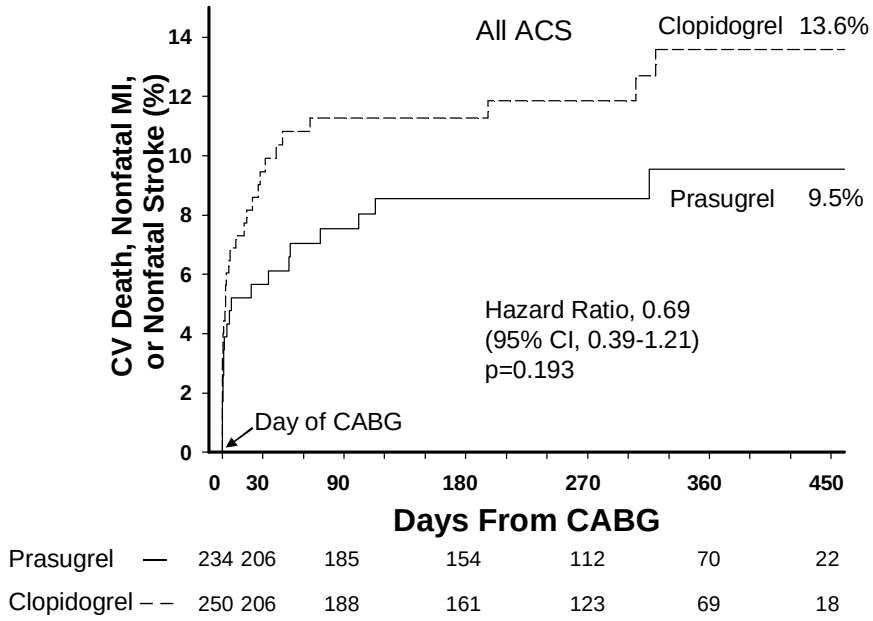
Efficacy Endpoints	Prasugrel N=234 n (%)[a] [%][b]	Clopidogrel N=250 n (%)[a] [%][b]	HR (95% CI)	p-value
CV Death, Nonfatal MI, Nonfatal Stroke	20 (8.5) [9.54]	30 (12.0) [13.59]	0.687 (0.390, 1.210)	0.193
CV Death	8 (3.4)	17 (6.8)		
Nonfatal MI	9 (3.8)	13 (5.2)		
Nonfatal Stroke	4 (1.7)	3 (1.2)		

a Observed rate

b K-M estimate at 450 days

Abbreviation: N = number of patients undergoing CABG; n = number of patients reaching endpoint.

Source: SMEFFIE2_CABG_briefingdoc_table4.doc, Data source for CV estimates K-M for 484 CABG.csv



Source: Data source for CV events KM for 484 patients.csv.

Figure 6.28. Time from CABG to first primary efficacy endpoint for all CABG patients from efficacy population (N=484).

6.6.2. Safety in Patients who Underwent CABG

Table 6.25 shows the percentage of patients reaching safety outcomes from time of CABG through study end. The incidence of CABG-related TIMI Major bleeding was higher in patients treated with prasugrel compared to patients treated with clopidogrel.

Table 6.25. Patients Reaching Safety Outcomes After CABG

Safety Endpoint	Prasugrel N=213 n (%)	Clopidogrel N=224 n (%)	p-value
CABG-related TIMI Major Bleeding	24 (11.27)	8 (3.57)	0.002

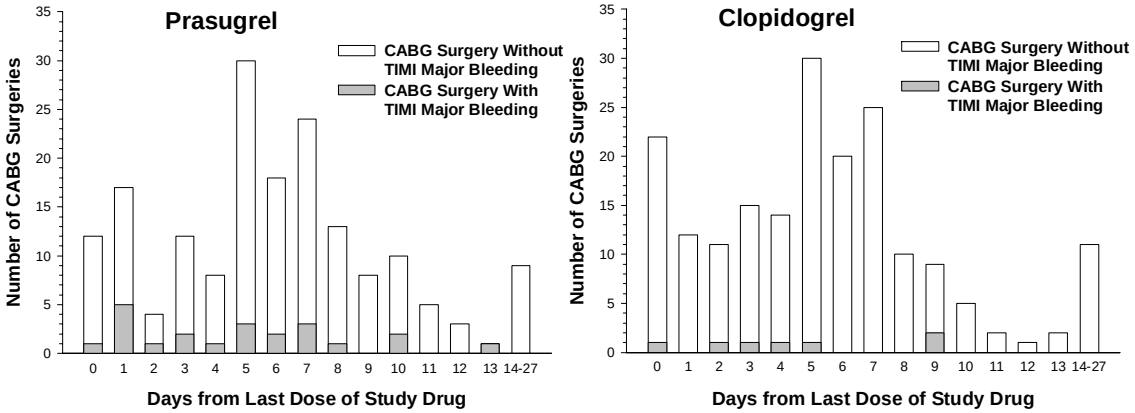
Abbreviations: N = number of treated patients undergoing CABG; n = number of treated patients undergoing CABG with CABG-related bleeding events.
Source: Q1616.

Two of the CABG-related TIMI Major bleeds in prasugrel-treated patients and none in clopidogrel-treated patients were adjudicated as fatal. One of these patients underwent CABG and planned transmyocardial revascularization with YAG laser 7 days after discontinuing study drug. Platelet function testing the day prior to surgery was normal. CABG was unsuccessful due to diffuse disease. Surgery was complicated by bleeding, ventricular fibrillation, and cardiac arrest with death occurring in the operating room.

The other patient underwent primary PCI for the index event of STEMI, and received both study drug and open label clopidogrel on the day of randomization. Shortly following PCI, the patient developed cardiogenic shock and underwent repeat catheterization with placement of an intra-aortic balloon pump (IABP). Repeat PCI was unsuccessful, and the patient underwent emergency CABG. Surgery was complicated by bleeding which was controlled intraoperatively. In the immediate post-operative period, the patient required emergency re-exploration for cardiogenic shock which revealed a dilated, poorly functioning heart with no evidence of bleeding.

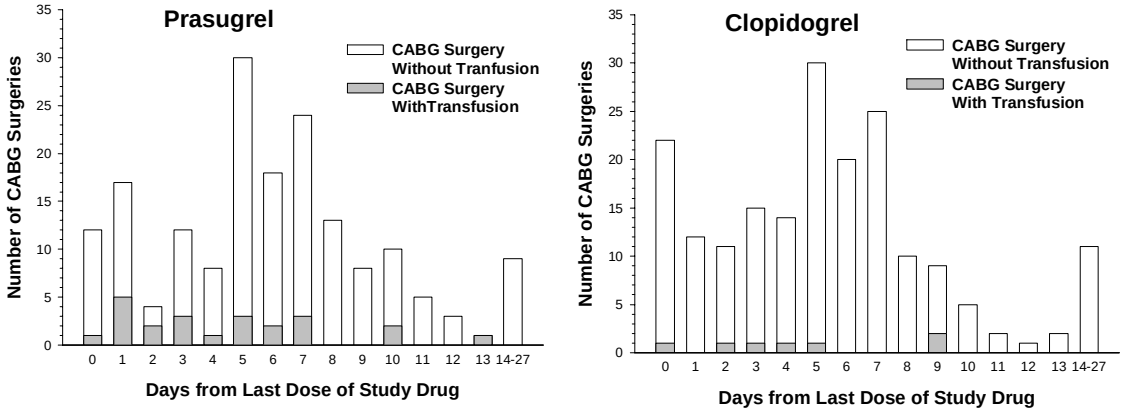
6.6.3. Timing of Study Drug Discontinuation Prior to CABG

The increased risk of bleeding associated with prasugrel in patients is limited to CABG surgery performed within 7 days of the last dose of prasugrel (Figure 6.29). For patients who discontinued study drug within 7 days of surgery, 18 prasugrel-treated patients and 5 clopidogrel-treated patients experienced a CABG-related TIMI Major bleed. During this time period there was also an increase in the need for any PRBC or whole blood transfusion, and transfusion of $\geq$4 units of PRBC or whole blood in patients treated with prasugrel (Figure 6.30 and Figure 6.31). When the interval between the most recent dose of prasugrel and CABG surgery is more than 7 days, the risk of TIMI Major bleeding and transfusion was low, and similar in each treatment group.



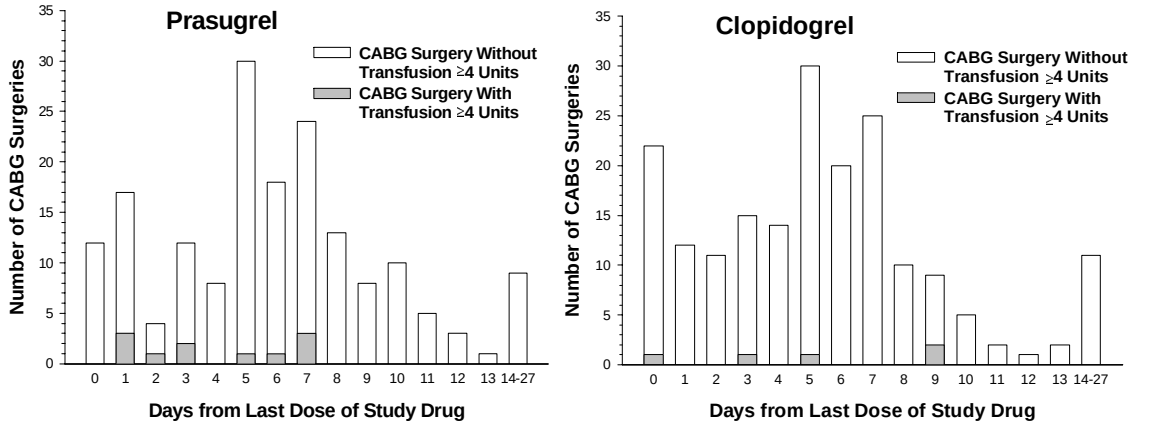
Source: FQAESIE2_CABG_briefingdoc_transf_and_bld_sheet.csv.
N = 437 All treated CABG patients. A patient (not included in the graphs below) who was assigned to prasugrel experienced a CABG-related TIMI Major bleeding event 28 days after the last dose of study drug. However, the patient was treated with open-label clopidogrel after discontinuation of study drug until 4 days prior to CABG.

Figure 6.29. CABG-related TIMI Major bleeding.



Source: FQAESIE2_CABG_briefingdoc_transf_and_bld_sheet.csv.

Figure 6.30. Transfusions of any PRBC or whole blood associated with CABG surgery.



Source: FQAESIE2_CABG_briefingdoc_transf_and_bld_sheet.csv.

Figure 6.31 Transfusions ≥4 units of PRBC or whole blood associated with CABG surgery.

The increased risk of CABG-related bleeding with prasugrel treatment was not associated with an increased risk of mortality. Fewer prasugrel-treated patients died after CABG compared to clopidogrel-treated patients (Table 6.26). For patients who underwent CABG within 7 days of the last dose of study drug, there were fewer deaths in prasugrel treated compared to clopidogrel-treated patients.

Table 6.26. CABG All-Cause Mortality CEC Adjudicated – All Treated Patients who Underwent CABG

	Prasugrel % (n/N)	Clopidogrel % (n/N)
Death in patients after CABG	3.3 (7/213)	7.6 (17/224)
Death within 30 days of CABG	1.9 (4/213)	5.8 (13/224)
Death more than 30 days after CABG	1.4 (3/213)	1.8 (4/224)
Death in patients who had CABG within 7 days of last dose of study drug	3.7 (5/134)	9.0 (14/156)

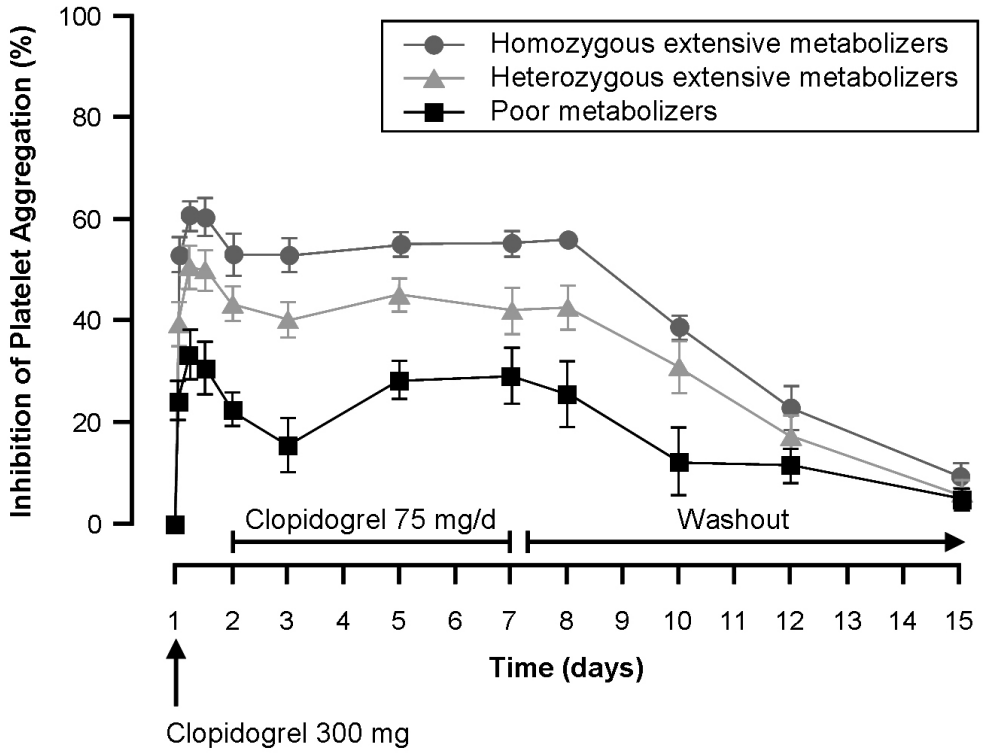
Source: /SPREE/RMP/Clinical/Primary Care/CS747/Acute Coronary Syndrome/H7T-MC-TAAL/Output/US Affiliate/project13/CABG_adhoc_mortality.rtf.

6.6.4. Conclusions Regarding Prasugrel Treatment in Patients who Undergo CABG

The composite endpoint of CV death, nonfatal MI, or nonfatal stroke following CABG surgery was lower for prasugrel-treated patients compared to clopidogrel-treated patients. In patients undergoing CABG within 7 days of the last dose, prasugrel was associated with an increased risk of bleeding. Bleeding risk was low and similar in each treatment group for patients who discontinued study drug more than 7 days prior to surgery. The higher incidence of CABG-related bleeding in prasugrel-treated patients was not

associated with an increase in all-cause death. Compared to clopidogrel, fewer patients treated with prasugrel died after CABG.

The increased risk of bleeding within 7 days of the last dose of prasugrel is not unexpected. Prasugrel treatment results in higher levels of platelet inhibition compared to clopidogrel and the time to recovery of platelet function depends on the extent of inhibition prior to discontinuation of therapy. For example, recovery of platelet function is more rapid in patient who are poor metabolizers of clopidogrel compared to intermediate metabolizers (heterozygous extensive metabolizers) and extensive metabolizers (homozygous extensive metabolizers based on CYP2C19 genotype (Figure 6.32) (Kim et al. 2008).



Source: Adapted from Kim et al. 2008.
Data are expressed as mean values ± s.e.m.

Figure 6.32. Inhibition of platelet aggregation (5 µmol/l ADP) by CYP2C19 genotype.

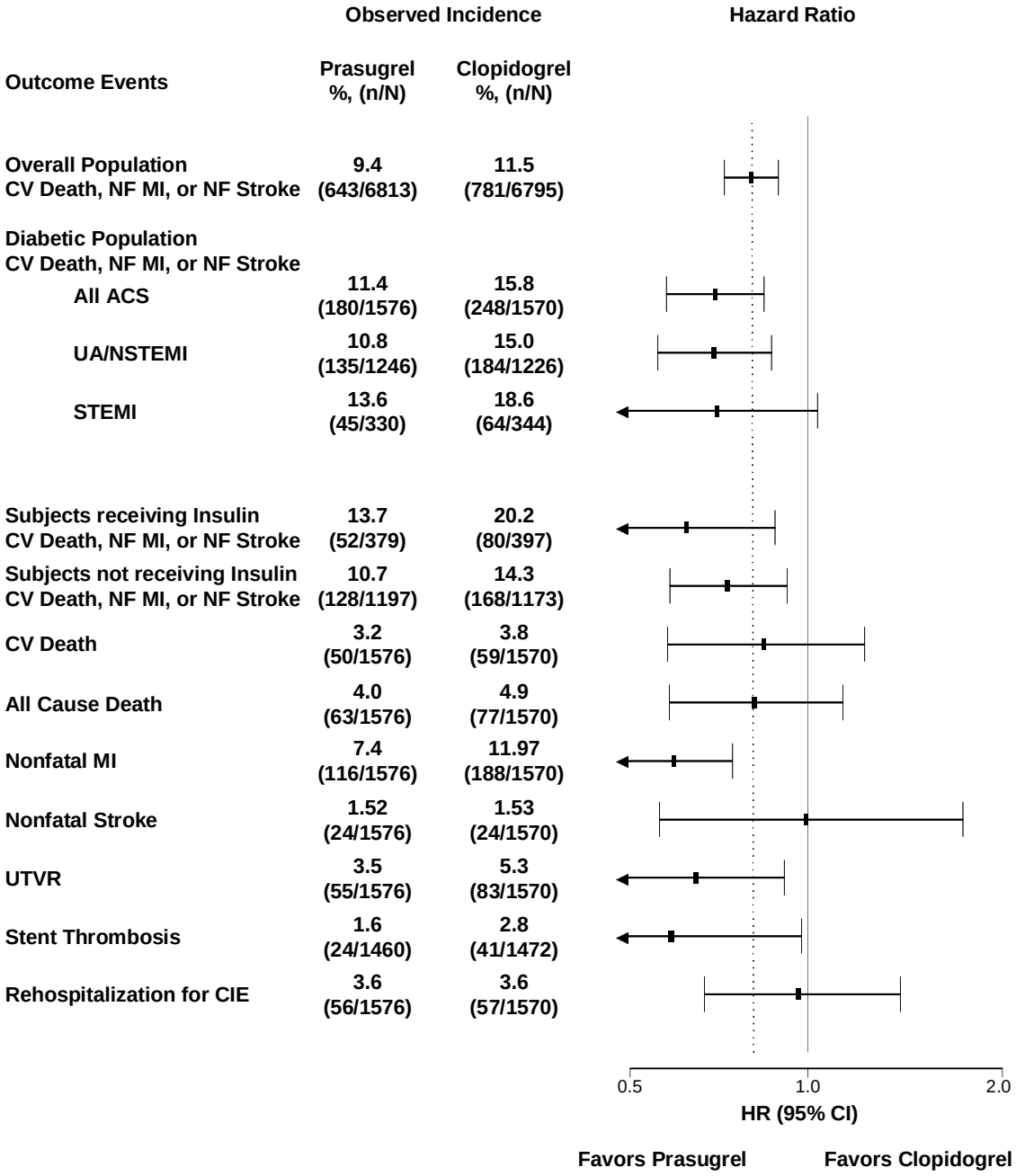
6.7. Subgroups of Special Interest in TRITON-TIMI 38

6.7.1. Patients with Diabetes Mellitus

Patients with diabetes represented 23% of the TRITON-TIMI 38 study. Safety and efficacy of prasugrel in diabetics is provided below.

6.7.1.1. Efficacy

The incidence of the primary endpoint with prasugrel compared to clopidogrel was significantly reduced in patients with diabetes. The relative benefit of prasugrel compared to clopidogrel in the reduction of ischemic endpoints was consistent in patients receiving insulin and those not receiving insulin. Treatment also favored prasugrel for the components of the primary and secondary endpoints including a reduction in the incidence of stent thrombosis (Figure 6.33).

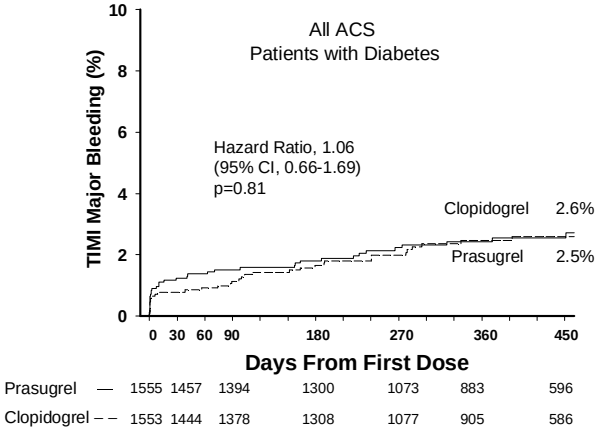


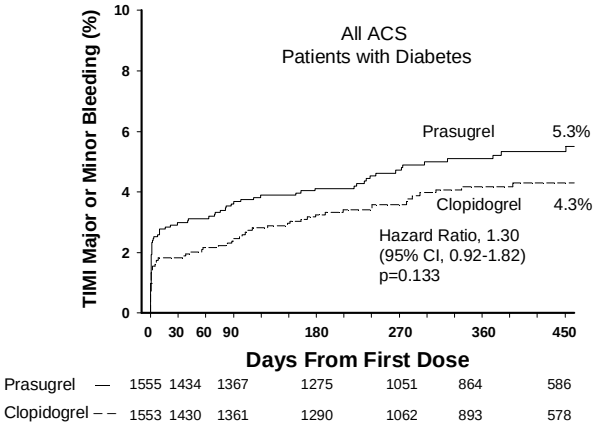
Source: Q176, Q7360, Q7365, Q8196.

Figure 6.33. **Observed incidence and hazard ratios for primary composite endpoint (CV death, Nonfatal MI, or Nonfatal Stroke) and components of the primary and secondary endpoints for All ACS patients with diabetes.**

6.7.1.2. Safety

Among treated patients with diabetes, there was no difference in non-CABG related TIMI Major bleeding between treatment groups. A higher incidence of non-CABG related TIMI Major or Minor bleeding events was observed in prasugrel-treated patients compared to clopidogrel-treated patients (Figure 6.34).



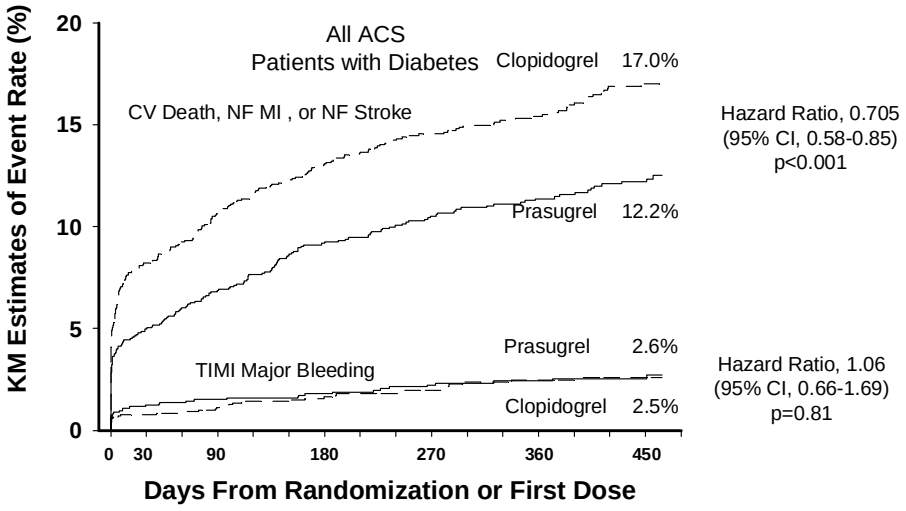


Source: Q7450 Source: Q7455.

Figure 6.34. Kaplan-Meier estimates of the incidence of non-CABG-related TIMI major (top) and TIMI Major or Minor (bottom) bleeding events while at risk – All ACS patients with diabetes.

6.7.1.3. Balance of Efficacy and Safety in Patients with Diabetes Mellitus

Figure 6.35 illustrates the balance between efficacy and safety in patients with diabetes treated with prasugrel. The treatment benefit was consistent with that observed in the overall population. There appeared to be a similar risk for non-CABG related TIMI Major bleeding between treatment groups in patients with diabetes.



Source: Q7450, Q8151

Figure 6.35. K-M estimates of the incidence of the primary composite endpoint and of non-CABG related TIMI Major bleeding for All ACS patients with diabetes.

6.7.1.4. Conclusions Regarding Prasugrel Treatment in Patients with Diabetes Mellitus

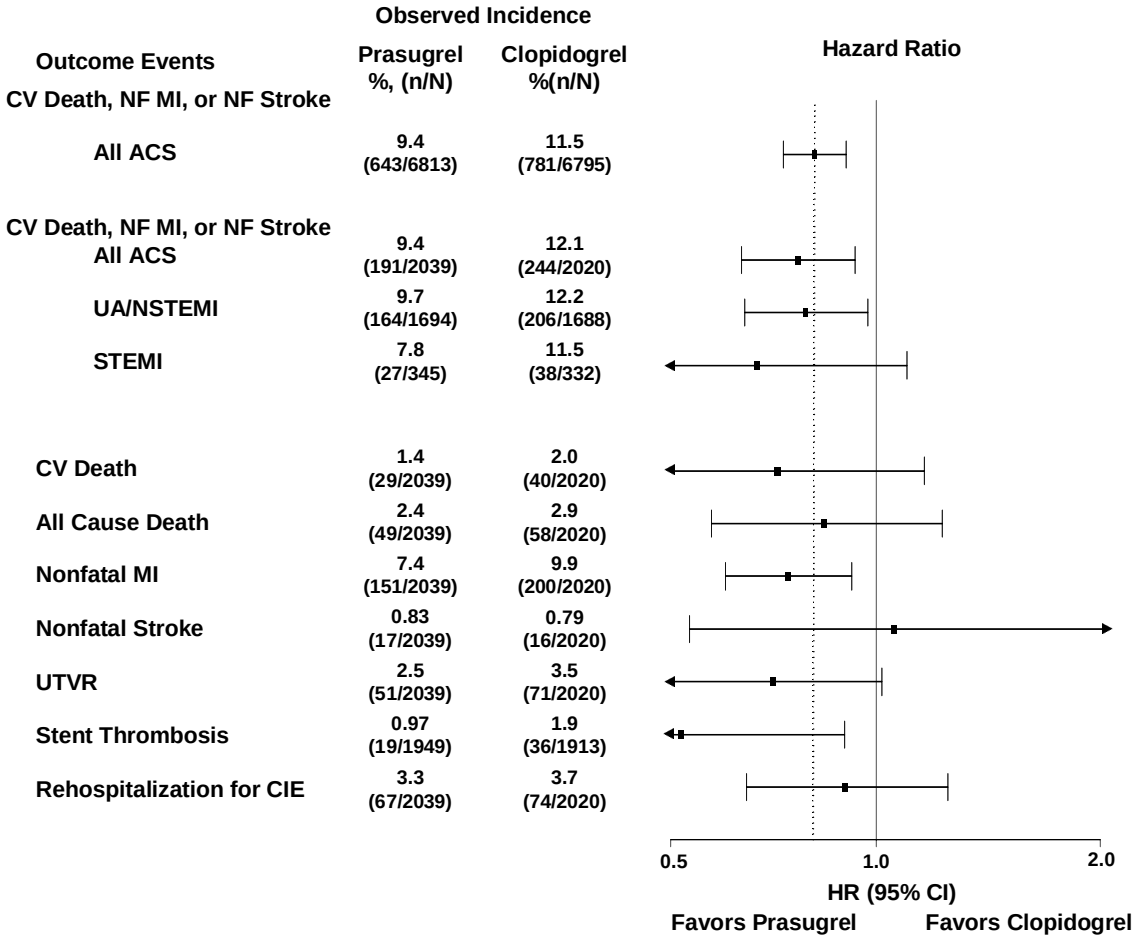
In patients with diabetes, prasugrel treatment compared to clopidogrel treatment was associated with a reduction in ischemic events without an observed increase in TIMI Major bleeding.

6.7.2. Patients Enrolled in the United States

Patients enrolled in the United States represented 30% of the TRITON–TIMI 38 study. Safety and efficacy of prasugrel in the US population is provided below.

6.7.2.1. Efficacy

Figure 6.36 shows the percentage of patients in the United States who reached the primary and secondary endpoints. The incidence of the primary composite endpoint was statistically significantly lower in patients randomized to prasugrel compared to clopidogrel in the UA/NSTEMI and All ACS populations. Treatment also favored prasugrel for the components of the primary endpoint and for most components of the secondary endpoints including a reduction in the incidence of MI and stent thrombosis.

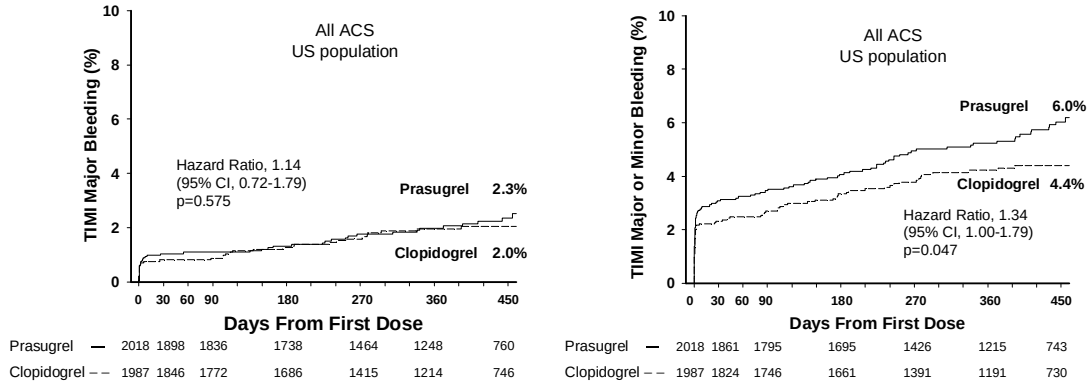


Source: Q176, Q7120, Q7140.

Figure 6.36. Observed incidence and hazard ratios for primary composite endpoint (CV death, Nonfatal MI, or Nonfatal Stroke) and components of the primary and secondary endpoints for All ACS patients enrolled in the United States.

6.7.2.2. Safety

Figure 6.37 shows the percentage of patients in the United States who experienced non-CABG-related TIMI Major and TIMI Major or Minor bleeding events. The incidence of non-CABG TIMI Major bleeding was similar in each treatment group. The number of fatal hemorrhages was similar in each treatment group (3 prasugrel versus 2 clopidogrel). There was a statistically significant higher incidence of non-CABG TIMI Major or Minor bleeding events in the prasugrel treatment arm.

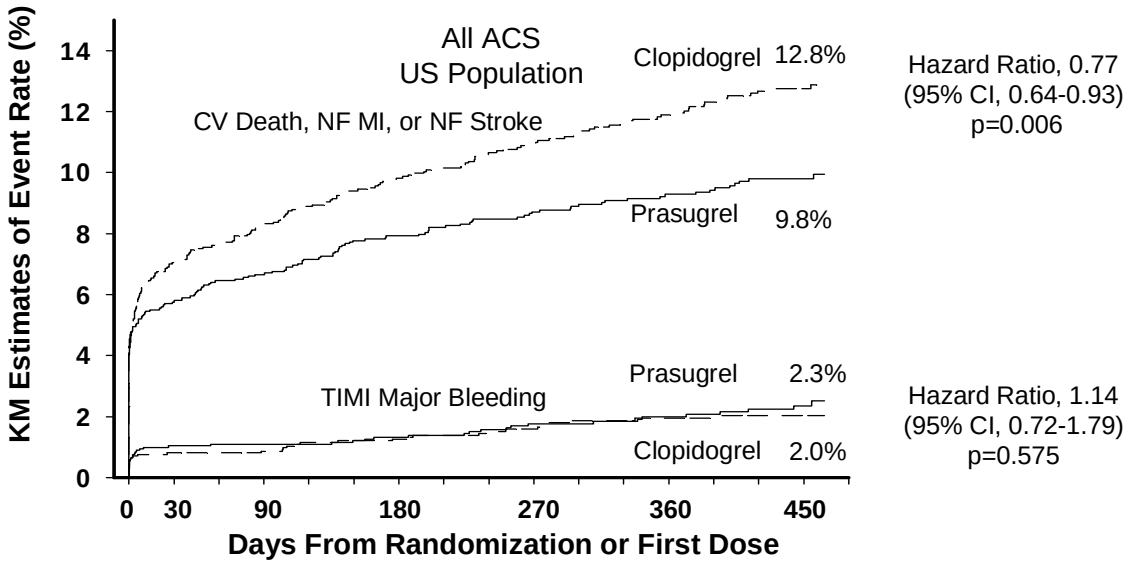


Source: Q7185. Source: Q7200.

Figure 6.37. Kaplan-Meier estimates of the incidence of TIMI major (left) and TIMI major or minor (right) bleeding events in United States patients - all treated All ACS patients.

6.7.2.3. Balance of Safety and Efficacy in the US Population

Figure 6.38 illustrates the balance between efficacy and safety in patients enrolled in the United States treated with prasugrel. The treatment benefit in the US was consistent with that observed in the overall population, while there appeared to be no increased risk for non-CABG related TIMI Major bleeding in patients treated with prasugrel.



Source: Q7135, Q7185.

Figure 6.38. K-M estimates of the incidence of the primary composite endpoint and of non-CABG related TIMI Major bleeding for All ACS patients enrolled in the United States.

6.7.2.4. Conclusions Regarding Prasugrel Treatment in the US Population

In the United States population, prasugrel treatment was associated with a reduction in the incidence of the primary and secondary efficacy endpoints compared to clopidogrel. This reduction was consistent with the effect observed in the entire study population. Risk of non-CABG related TIMI Major bleeding was similar in prasugrel- and clopidogrel-treated patients, while a statistically significant increase in non-CABG related TIMI Major or Minor bleeding was observed in the prasugrel treatment group.

6.7.3. Patients ≥75 Years of Age

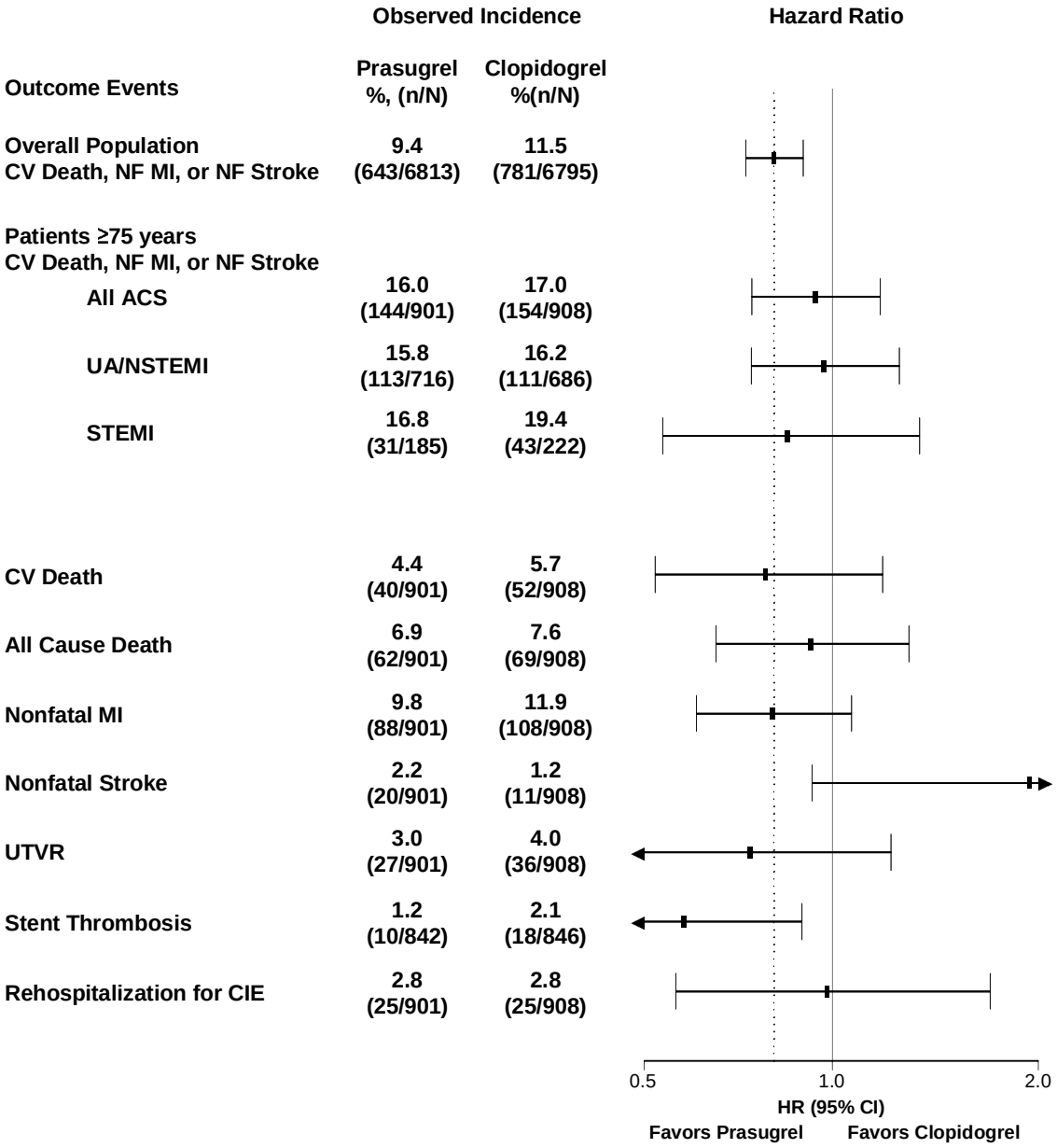
Patients ≥75 years of age represented 13.3% of the study population and were of particular interest for the following reasons:

- Regulatory guidance emphasizes the importance of including patients ≥75 years of age in clinical testing programs for new molecular entities that are likely to have significant use in the elderly (http://www.fda.gov/cder/guidance/iche7.pdf).
- Patients ≥75 years of age are at higher risk of bleeding with antiplatelet, antithrombin, and fibrinolytic therapies (Alexander et al. 2005, Sinnaeve et al. 2006). In CURE, the major bleeding event rate for patients treated with aspirin alone was higher for patients ≥75 years (3.6%) compared patients <65 years (2.1%; PLAVIX USPI 2008).
- Patients ≥75 years of age had increased bleeding when treated with dual antiplatelet therapy. In CURE, the major bleeding event rate for patients treated with clopidogrel plus aspirin was higher for patients ≥75 years (5.9%) compared patients <65 years (2.5%; PLAVIX USPI 2008).

6.7.3.1. Efficacy in Patients ≥75 Years of Age

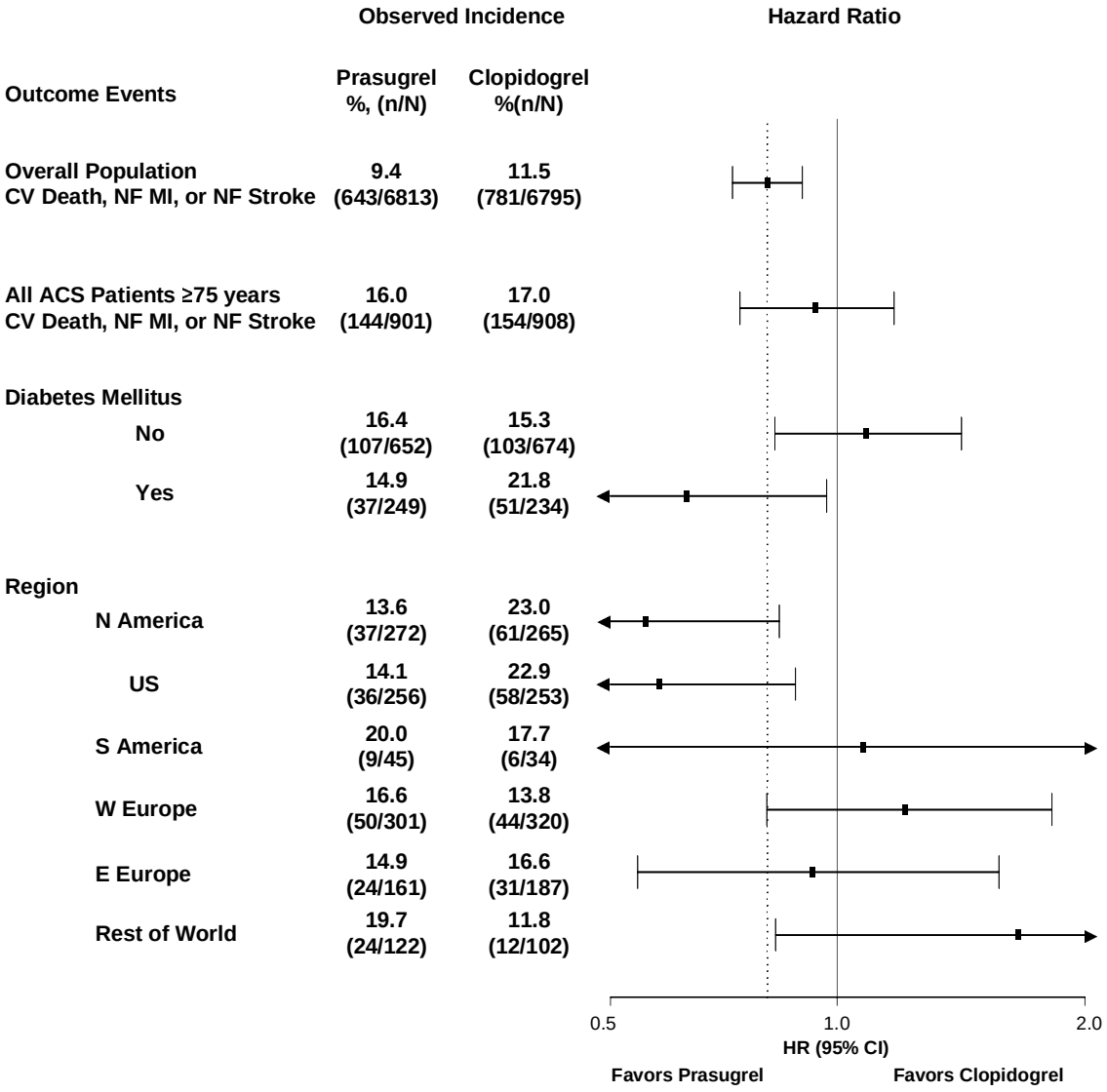
Figure 6.39 shows the percentage of patients ≥75 years of age who reached the primary and secondary efficacy endpoints. There was a similar incidence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke between treatment groups (Figure 6.39a). Prasugrel reduced the risk of the composite endpoint (CV death, nonfatal MI, nonfatal stroke) compared to clopidogrel among patients ≥75 years of age with DM or enrolled the US (Figure 6.39b). There was a lower rate of nonfatal MI in patients ≥75 years of age randomized to prasugrel compared to clopidogrel. CV death and all-cause death were similar in each treatment group.

There was a higher incidence of stroke in patients ≥75 years of age randomized to prasugrel compared to clopidogrel.



Source: Q176, Q3670.

Figure 6.39a . **Observed incidence and hazard ratios for primary composite endpoint (CV death, Nonfatal MI, or Nonfatal Stroke) and components of the primary and secondary endpoints for All ACS patients ≥75 years of age.**

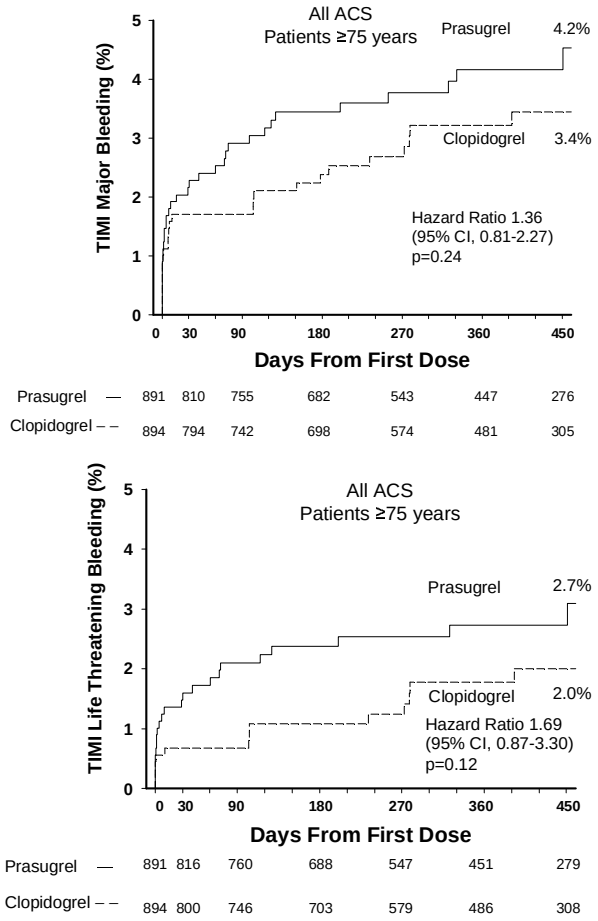


Source: Q176, Q3670, Q3740, Q3730.

Figure 6.39b. Observed incidence and hazard ratios for primary composite endpoint (CV death, Nonfatal MI, or Nonfatal Stroke) for All ACS patients ≥75 years of age.

6.7.3.2. Safety in Patients ≥75 Years of Age

Figure 6.40 shows the percentage of patients ≥75 years of age who experienced non-CABG related TIMI Major bleeding events or non-CABG related TIMI Life-Threatening bleeding events. Bleeding rates were higher in patients treated with prasugrel than in patients treated with clopidogrel.



Source: Q8144. Source: Q8331.

Figure 6.40. Kaplan-Meier estimates of the incidence of TIMI major (top) and life-threatening (bottom) bleeding events in patients ≥75 years of age - All ACS patients.

The absolute increase in the risk of both non-CABG related Major and non-CABG related Life-Threatening bleeding in patients treated with prasugrel compared to clopidogrel for those patients ≥75 years was greater than that observed for those <75 years (Table 6.27). This increased risk indicates a much smaller number needed to harm (to incur one additional bleeding event). For life-threatening bleeding, the number needed to harm associated with prasugrel treatment in patients <75 years of age is approximately 300, while the number for patients ≥75 years is approximately 100. Additionally, among patients ≥75 years of age, there were more spontaneous fatal hemorrhages in those treated with prasugrel compared to those treated with clopidogrel (9 prasugrel, 0 clopidogrel).

Table 6.27. Percentage of Patients with Non-CABG-Related TIMI Major or Life-Threatening Bleeding by Age Categories (TRITON-TIMI 38)

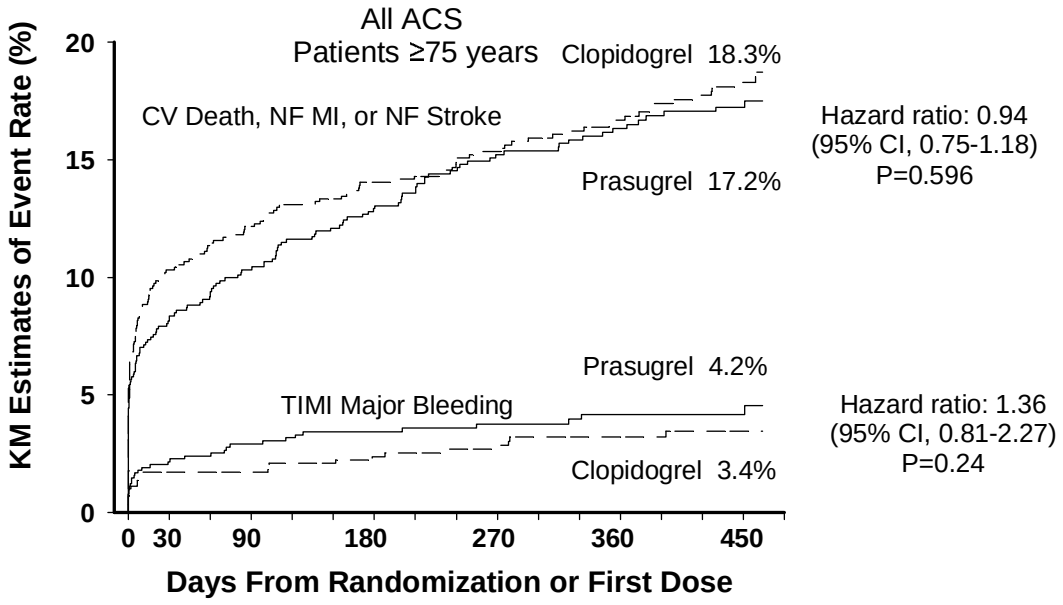
	Non-CABG-Related TIMI Major Bleeding			Non-CABG-Related TIMI Major Life-Threatening		
	Prasugrel	Clopidogrel	Absolute Difference	Prasugrel	Clopidogrel	Absolute Difference
Age <75 years	1.91% (112/5850)	1.46% (85/5822)	.45%	1.06% (62/5850)	0.72% (42/5822)	.34%
Age ≥75 years	3.82% (34/891)	2.91% (26/894)	.91%	2.58% (23/891)	1.57% (14/894)	1.01%

Percentages are based on observed rates

Source: Q1146, Q3810, Q3805

6.7.3.3. Balance of Efficacy and Safety in Patients ≥75 Years of Age

Figure 6.41 illustrates the balance between efficacy and safety in patients ≥75 years of age treated with prasugrel. Through 180 days there appears to be a treatment benefit with prasugrel, which then diminishes through 450 days.



Source: Q8144, Q3900.

Figure 6.41. K-M estimates of the incidence of the primary composite endpoint and of non-CABG related TIMI Major bleeding for All ACS patients ≥75 years of age.

6.7.3.4. Conclusions Regarding Prasugrel Treatment in Patients ≥75 Years of Age

In the population ≥75 years of age, prasugrel treatment was associated with a reduction in the incidence of the primary and secondary efficacy endpoints for some subpopulations.

Outcomes of patients enrolled in the United States or with a history of diabetes appeared to favor treatment with prasugrel. However, there was an increased risk of non-CABG related TIMI Life-Threatening and fatal bleeding, particularly spontaneous fatal hemorrhages. Increased exposure to prasugrel's active metabolite may be a factor in the increased risk for bleeding in patients ≥75 years of age. Dose adjustment to decrease exposure may reduce the risk in this population.

6.7.4. Patients Weighing <60 kg

Low body weight has been associated with increased risk of adverse outcomes with the use of antiplatelet or antithrombotic agents (Alexander et al. 2005).

In clinical pharmacology studies, body weight was the most significant patient characteristic influencing exposure to prasugrel's active metabolite (Section 5.2). A similar finding was observed in the TRITON-TIMI 38 population pharmacokinetic substudy (Table 6.28). As weight decreases, exposure to the active metabolite increases such that patients weighing <60 kg are receiving approximately 1.5 times the exposure of the reference population (≥85 kg) taking the 10-mg MD. That is, patients <60 kg are receiving the equivalent of a 15-mg MD. Therefore, patients <60 kg, who represented 4.9% of the study population, were analyzed as a subgroup of interest in TRITON-TIMI 38.

Table 6.28. Increasing Exposure to Prasugrel AM with Decreasing Body Weight during 10-mg Prasugrel MD (TRITON-TIMI 38)

	Weight		Geometric Mean	
Group	Category	N	AUC (ng•h/mL)	Ratio (90% CI)
Ref[a]	≥85 kg	507	75.8	
Test	<85 kg	646	89.9	1.185 (1.135, 1.239)
Test	<80 kg	478	92.4	1.218 (1.163, 1.276)
Test	<75 kg	337	94.1	1.241 (1.180, 1.306)
Test	<70 kg	204	100.0	1.318 (1.243, 1.399)
Test	<65 kg	118	103.9	1.370 (1.273, 1.475)
Test	<60 kg	47	107.4	1.417 (1.272, 1.578)
Test	<55 kg	21	115.8	1.528 (1.305, 1.788)
Test	<50 kg	7	134.1	1.768 (1.352, 2.313)

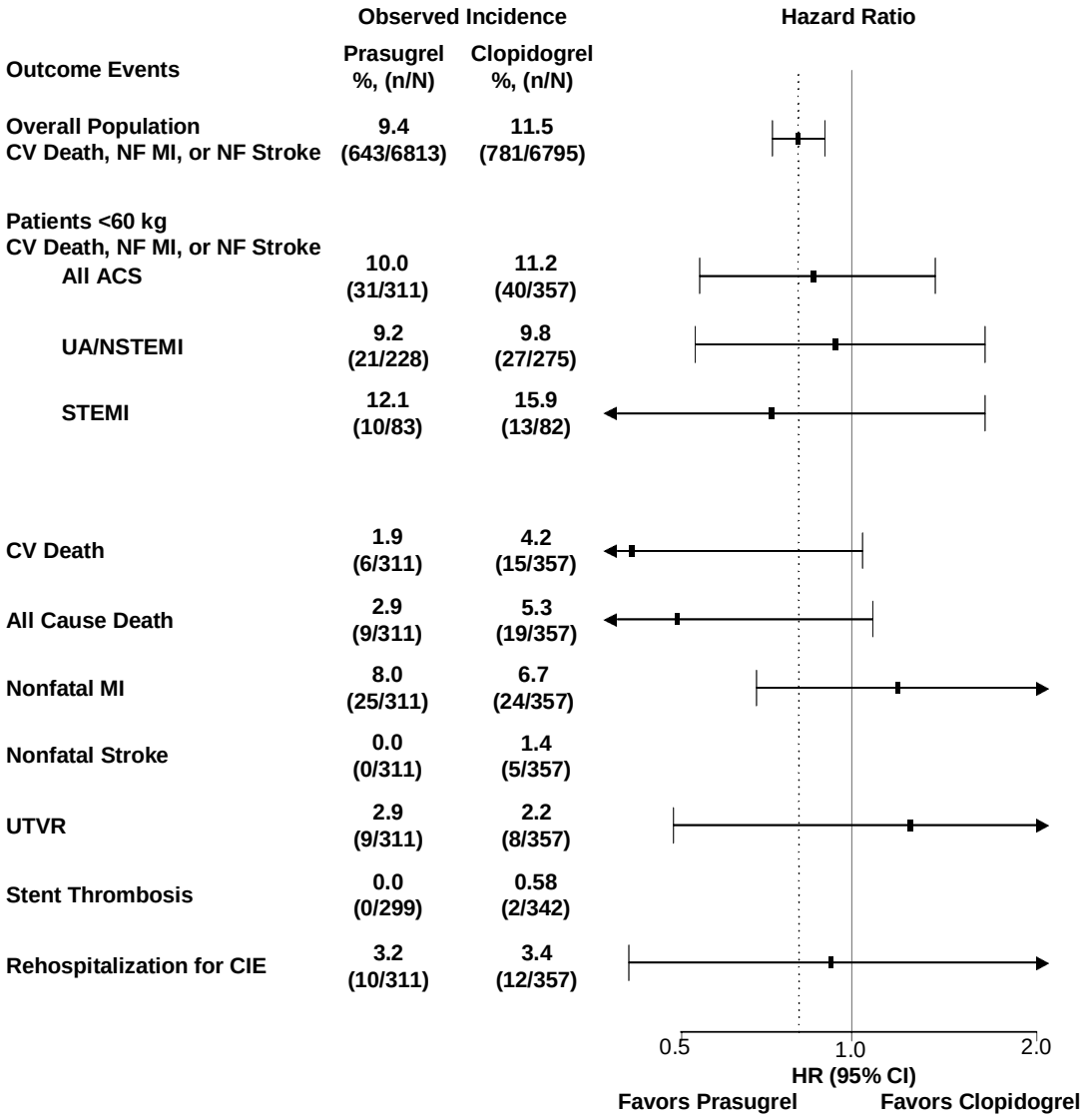
a Reference population: ≥ 85 kg approximates the median body weight across all patients in TRITON-TIMI 38.

Model: Log(AUC) = Weight Category (reference + test) + error.

Source: Table 2.7.2.35

6.7.4.1. Efficacy in Patients <60 kg

Figure 6.42 shows the percentage of patients <60 kg who reached the primary and secondary endpoints. No strokes or stent thromboses occurred in patients treated with prasugrel.

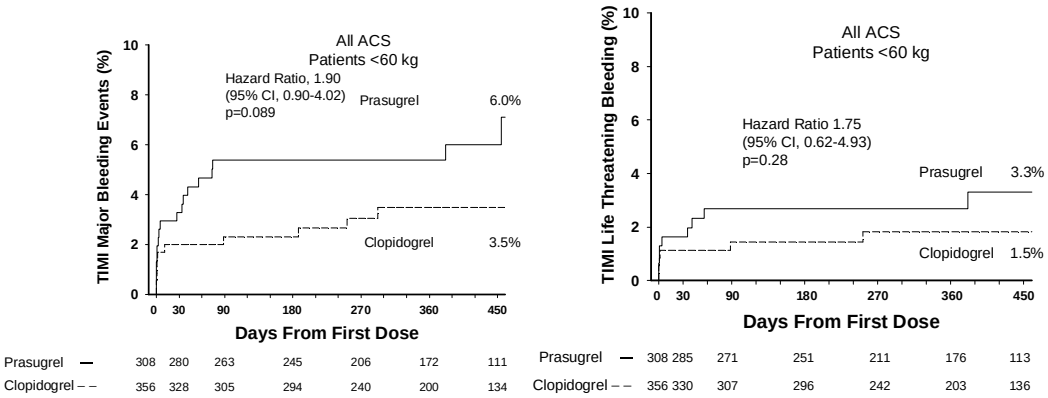


Source: Q176, Q7055.

Figure 6.42. **Observed incidence and hazard ratios for primary composite endpoint (CV death, Nonfatal MI, or Nonfatal Stroke) and components of the primary and secondary endpoints for All ACS patients <60 kg.**

6.7.4.2. Safety in Patients <60 kg

Figure 6.43 shows the incidence of patients <60 kg who experienced non-CABG related TIMI Major bleeding events or non-CABG related TIMI Life-threatening bleeding events. The incidence of bleeding was higher among patients treated with prasugrel compared with clopidogrel.



Source: Q8333 Source:Q8370

Figure 6.43. Kaplan-Meier estimates of the incidence of TIMI major (left) and Life-Threatening (right) bleeding events in patients <60 kg - All ACS patients.

The absolute increase in the risk of both TIMI Major and Life-Threatening bleeding was greater than that observed in the ≥60 kg population (Table 6.29), indicating a much smaller number needed to harm (to incur one additional bleeding event). For TIMI Major bleeding, the number needed to harm associated with prasugrel treatment in patients ≥60 kg is approximately 267, while the number for patients <60 kg is approximately 36. For TIMI Life-Threatening bleeding, the number needed to harm associated with prasugrel treatment in patients ≥60 kg is approximately 284, while the number for patients <60 kg is approximately 81.

Table 6.29. Percentage of Patients with Non-CABG-Related TIMI Major or Life-Threatening Bleeding by Weight and Age Categories (TRITON-TIMI 38)

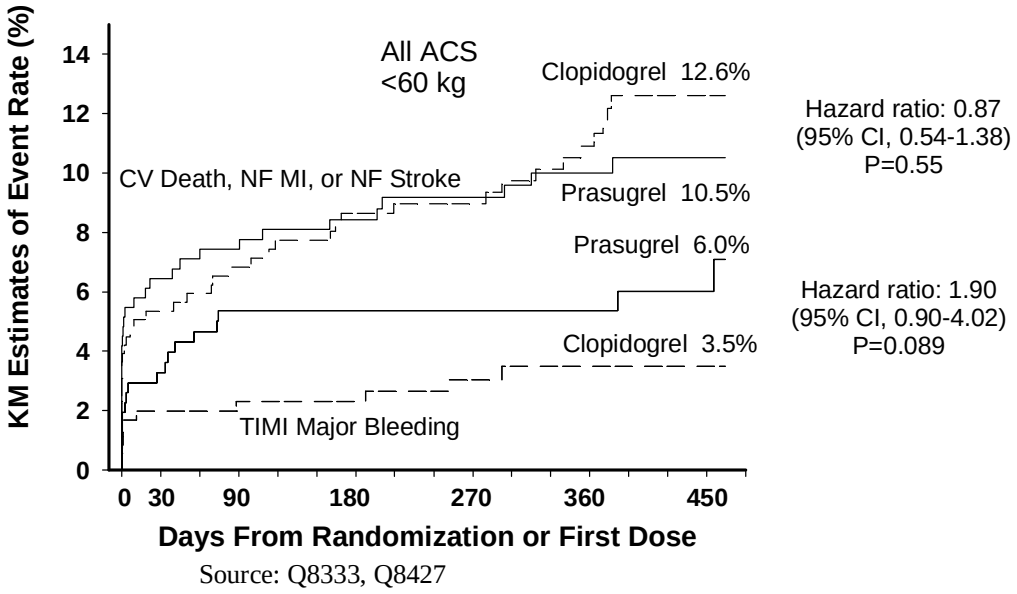
	Major			Life-Threatening		
	Prasugrel	Clopidogrel	Absolute Difference	Prasugrel	Clopidogrel	Absolute Difference
Weight ≥ 60 kg	1.95% (124/6373)	1.57% (99/6299)	.38%	1.13% (72/6373)	0.78% (49/6299)	.35%
Weight <60 kg	5.84% (18/308)	3.09% (11/356)	2.75 %	2.92% (9/308)	1.69% (6/356)	1.23%

Percentages are based on observed rates

Source: Q3820, Q3815

6.7.4.3. Balance of Efficacy and Safety in Patients <60 kg

Figure 6.44 illustrates the balance between efficacy and safety in patients <60 kg treated with prasugrel.



Source: Q8333, Q8427

Figure 6.44. Kaplan-Meier balance of safety and efficacy - weight.

6.7.4.4. Conclusions Regarding Prasugrel Treatment in Patients <60 kg

Among patients <60 kg, those treated with prasugrel experienced a benefit in the primary endpoint compared to those treated with clopidogrel, consistent with the results observed in the overall population. However, patients treated with prasugrel had a higher rate of TIMI Major bleeding and TIMI Life-Threatening bleeding.

Increased exposure to prasugrel's active metabolite may be a factor in the increased risk for bleeding in patients <60 kg. Dose adjustment to decrease exposure may reduce the risk in this population.

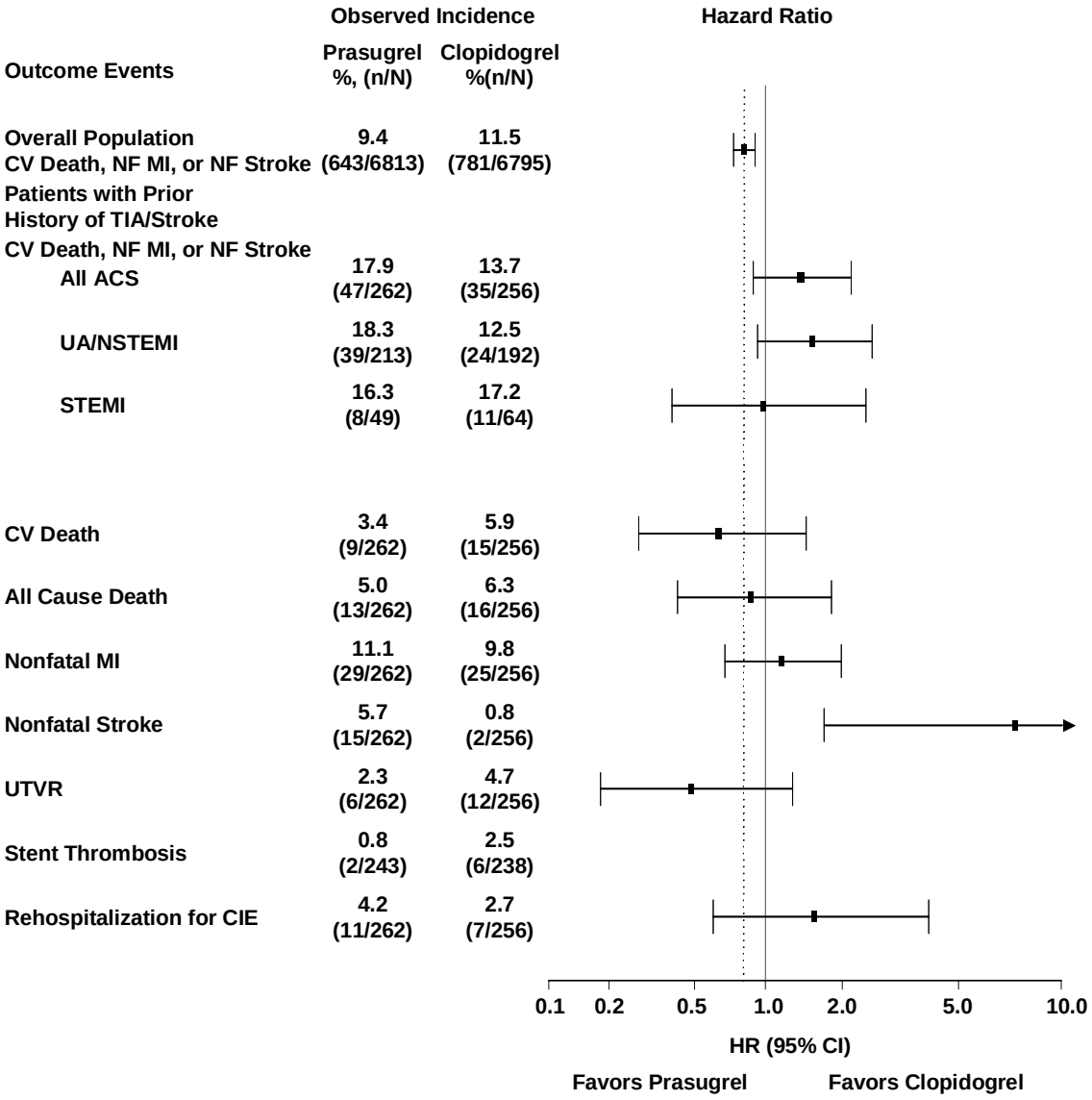
6.7.5. Patients with Prior TIA/Stroke

Results of previous studies showed that patients with a history of TIA or stroke have an increased risk of bleeding complications with dual antiplatelet therapy (aspirin and clopidogrel; Diener et al 2004; Soman et al. 2006). In TRITON-TIMI 38, the subgroup of patients with prior TIA/stroke was a prespecified subgroup for safety analyses but not for efficacy analyses. These patients, who represented 3.8% of the study population, were also analyzed as a subgroup of interest.

6.7.5.1. Efficacy in Patients with Prior TIA/Stroke

Figure 6.45 shows the percentage of patients with prior TIA/stroke who reached the primary and secondary endpoints. There was a statistically significant treatment-by-history of TIA/stroke interaction, indicating a lack of treatment benefit for prasugrel

compared to clopidogrel with regard to the primary endpoint (p=0.015). This lack of benefit was primarily due to a statistically significant increase in nonfatal and fatal stroke. There was no significant difference between treatment groups in the incidence of nonfatal MI.



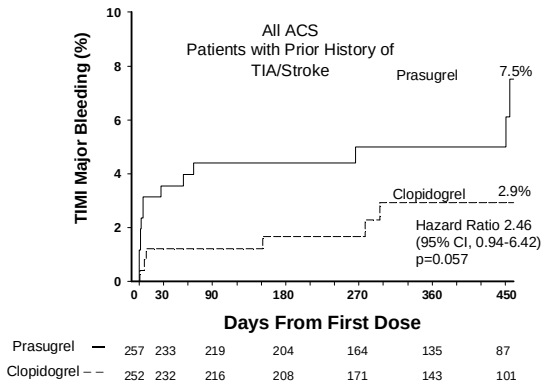
Source: Q176, Q3970.

Figure 6.45. Observed incidence and hazard ratios for primary composite endpoint (CV death, Nonfatal MI, or Nonfatal Stroke) and components of the primary and secondary endpoints for All ACS patients with prior TIA/stroke.

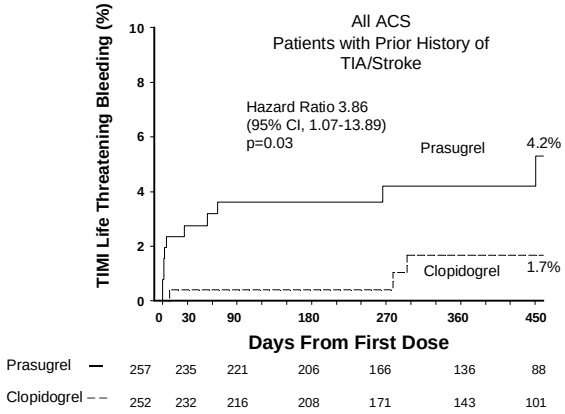
6.7.5.2. Safety in Patients with Prior TIA/Stroke

Figure 6.46 shows the percentage of patients with prior TIA/stroke who experienced non-CABG-related TIMI Major bleeding events or non-CABG-related TIMI Life-threatening

bleeding events. Among patients with prior TIA or stroke, those treated with prasugrel had a higher incidence of bleeding compared to patients treated with clopidogrel. Six patients treated with prasugrel had symptomatic ICH, compared to none with clopidogrel.



Source: Q8371.



Source: Q8372.

Figure 6.46. Kaplan-Meier estimates of the incidence of TIMI major bleeding events in patients with prior TIA/stroke - all treated All ACS patients.

6.7.5.3. Conclusion Regarding Prasugrel Treatment in Patients with Prior TIA/Stroke

In patients with prior TIA/stroke, treatment with prasugrel was associated with an increased risk of non-CABG related TIMI bleeding and no reduction of the primary composite endpoint compared with clopidogrel. These results indicate the potential for harm from prasugrel in this population and therefore, the Sponsor is proposing a contraindication for this group.

These findings are consistent with those of previous studies indicating potential harm associated with dual antiplatelet therapy in patients with prior TIA/stroke. This finding is reflected in the PLAVIX USPI (2008) which states, "In patients with recent TIA or stroke who are at high risk of recurrent ischemic events, the combination of aspirin and PLAVIX® has not been shown to be more effective than PLAVIX alone, but the combination has been shown to increase major bleeding".

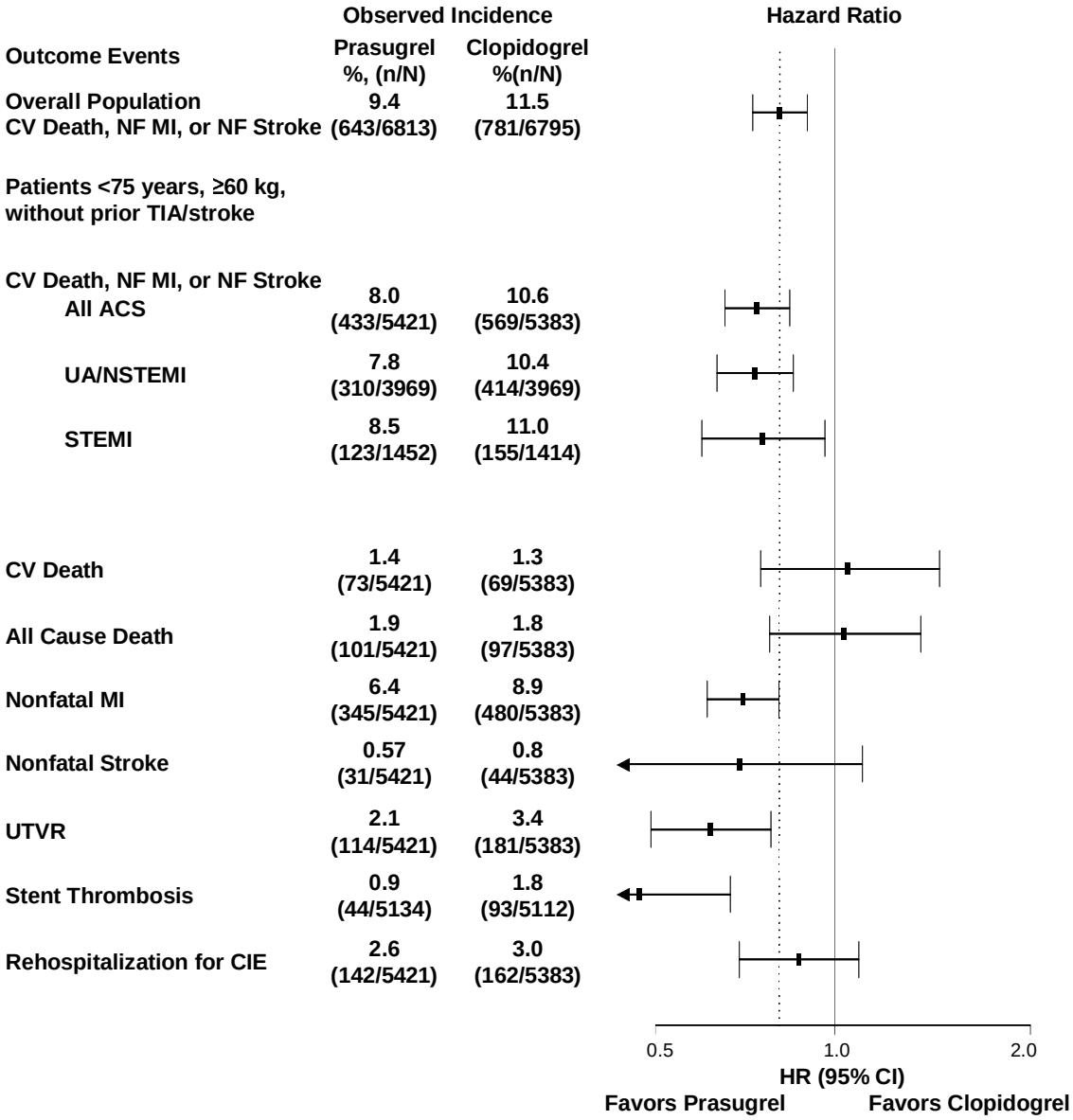
6.7.6. Patients <75 years of Age, ≥60 kg, and without prior TIA/stroke

As discussed in Section 6.5.1.1, prior TIA/stroke, age ≥75 years, and weight <60 kg were independent risk factors for non-CABG related TIMI Major bleeding with prasugrel treatment. Patients without these risk factors represent approximately 80% of the TRITON-TIMI 38 study population.

Among these patients, prasugrel was well-tolerated compared to clopidogrel as evidenced by a similar rate of discontinuation from study drug (15.79% prasugrel, 15.72% clopidogrel). A higher percentage of patients treated with prasugrel discontinued for a hemorrhagic adverse event (1.78% prasugrel, 1.05% clopidogrel). However, discontinuation of study drug due to a hemorrhagic adverse event was an infrequent cause of study drug discontinuation in both treatment groups. More than 90% of patients who discontinued study drug did so for a non-hemorrhagic adverse event or for reasons other than an adverse event.

6.7.6.1. Efficacy in Patients <75 years, ≥60 kg and without prior TIA/stroke

Figure 6.47 shows the percentage of patients aged <75 years of age, ≥60kg and without prior TIA/stroke who reached the primary and secondary endpoints. The efficacy benefit of prasugrel versus clopidogrel seen in the All ACS population was maintained in this subpopulation.

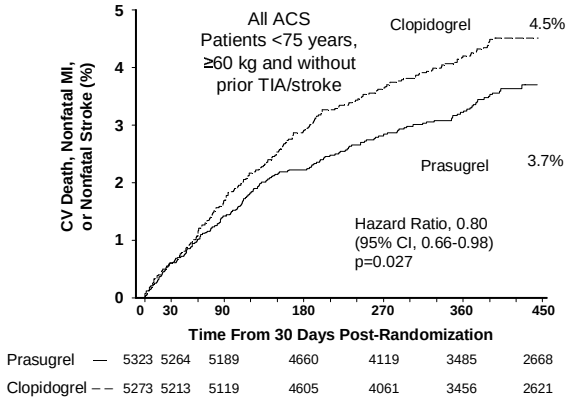


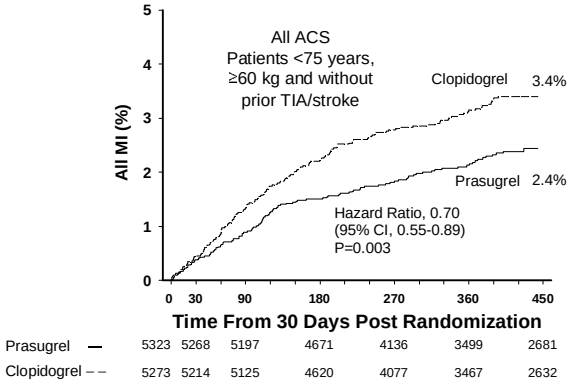
Source: Q7285, Q7280, Q176.

Figure 6.47. Observed incidence and hazard ratios for primary composite endpoint (CV death, Nonfatal MI, or Nonfatal Stroke) and components of the primary and secondary endpoints for All ACS patients in patients <75 years of age, ≥60 kg, and without prior TIA/stroke.

Figure 6.48 shows the Kaplan-Meier estimates of the incidence of the primary endpoint more than 30 days after randomization and the Kaplan-Meier estimates of the incidence of MI more than 30 days after randomization. The continued divergence in favor of prasugrel indicates that in patients <75 years of age, ≥60 kg, and without prior

TIA/stroke, treatment with prasugrel continues to reduce ischemic events including MI during chronic treatment.





Source: Q8258. Source: Q8261.

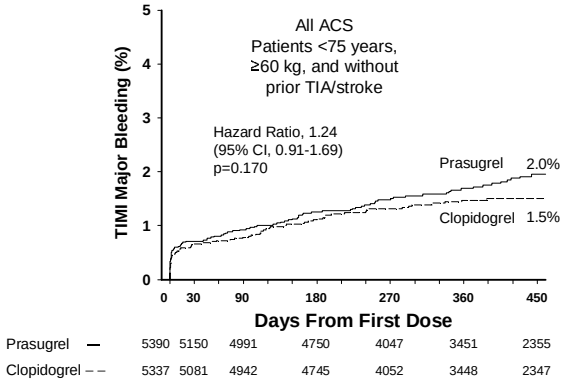
Figure 6.48. Kaplan-Meier estimates of the incidence of the primary efficacy endpoint (top) and the incidence of MI (bottom) from 30 days after randomization- patients <75 years of age, ≥60kg, and without prior TIA/stroke.

6.7.6.2. Safety in Patients <75 Years of Age, ≥60 kg, and without prior TIA/stroke

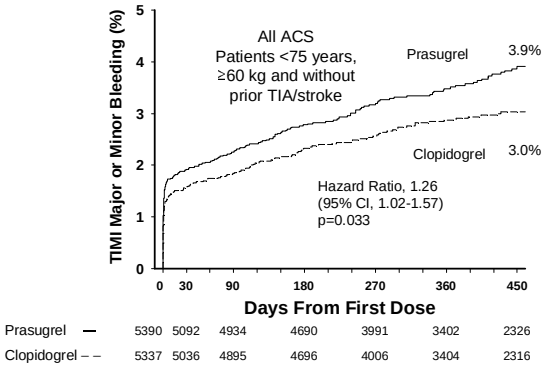
Figure 6.49 shows the incidence of non-CABG related TIMI Major, and TIMI Major or Minor bleeding for patients who are <75 years of age, ≥60 kg and without prior TIA/stroke. The incidence of non-CABG related TIMI Major bleeding was similar in each treatment group through approximately 360 days. Thereafter, the bleeding rates in the prasugrel arm remained constant while no further events were observed in patients treated with clopidogrel.

There were 9 non-CABG related fatal hemorrhages in patients treated with prasugrel and 4 in patients treated with clopidogrel. Of the fatal hemorrhages in patients treated with prasugrel, 3 were spontaneous (all ICH) and 6 were provoked (1 traumatic ICH, 3 access site-related, and 2 after gastric surgery). Of the fatal hemorrhages in patients treated with

clopidogrel, all were spontaneous (3 ICH, 1 GI). Therefore, the number of spontaneous fatal hemorrhages was similar in each treatment group (3 prasugrel versus 4 clopidogrel).



Source: Q8146.

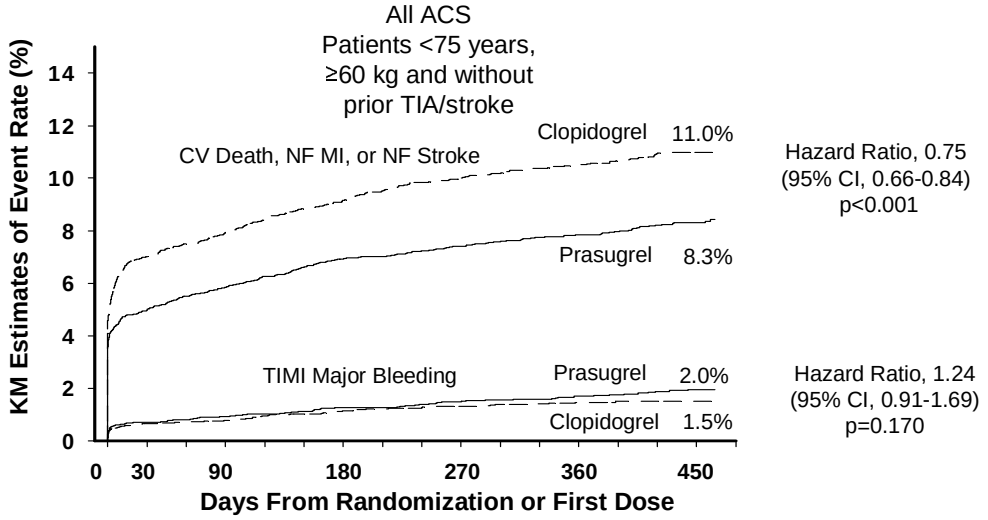


Source: Q8396

Figure 6.49. Kaplan-Meier estimates of the incidence of TIMI Major (left) TIMI Major or Minor (right) events in patients <75 years of age, ≥60 kg and without prior TIA/stroke.

6.7.6.3. Balance of Efficacy and Safety in Patients <75 years of Age, ≥60 kg, and without Prior TIA/stroke

Figure 6.50 illustrates the balance between efficacy and safety in patients <75 years of age, ≥60 kg, and without prior TIA/stroke treated with prasugrel.



Source: 8146, 8145.

Figure 6.50. K-M estimates of the incidence of the primary composite endpoint and of non-CABG related TIMI Major bleeding for All ACS patients in the optimal cohort.

6.7.6.4. Conclusions Regarding Prasugrel Treatment in Patients <75 years of Age, ≥60 kg, and without prior TIA/stroke

Consistent with findings in the overall ACS population, in patients <75 years of age, ≥60 kg, and without prior TIA/stroke, prasugrel demonstrated superior efficacy to clopidogrel as measured by the primary composite endpoint. An increasing treatment benefit was evident more than 30 days after randomization and was sustained through the end of the study.

The incidence of TIMI Major bleeding was similar in each treatment group. The number of spontaneous fatal hemorrhages was similar in each treatment group.

7. Special Topics

Introduction

The purpose of this section of the Advisory Committee briefing document is to provide a consolidated discussion of items discussed with the FDA during the review of the prasugrel application, in addition to the efficacy and safety data described in earlier sections of this document. The special topics included in this section are:

- Data related to neoplasms
- Stent thrombosis adjudication process
- Pharmacogenetics
- Interactions with drugs that elevate gastric pH
- Tablet performance

7.1. Neoplasms

7.1.1. Regulatory History

In TRITON-TIMI 38, a higher number of prasugrel-treated patients (175/6741, 2.60%) compared to clopidogrel-treated patients (138/6716, 2.05%) experienced an adverse event coded to the "Neoplasms Benign, Malignant, and Unspecified (including Cysts and Polyps)" system organ class (HR=1.26; p=0.043). After excluding non-neoplasms and benign neoplasms, there was a higher incidence of non-benign GI neoplasms in the prasugrel treatment group. The Sponsor concluded that, although a possible causative effect or play of chance could not be excluded, the imbalance most likely resulted from the higher incidence of bleeding in the prasugrel group bringing more events to medical attention (i.e., a detection or ascertainment bias).

During review of the application, the FDA expressed concern that prasugrel may promote tumor growth and requested follow-up information on these patients. Additional data were obtained on 311 of the 313 patients. Follow-up information included tumor type, tumor location, malignancy status (benign, non-benign, or unknown), events prompting evaluation leading to diagnosis (e.g., evaluation of GI bleeding), presence of metastasis, and vital status after database lock. A number of the 311 patients were determined to not have had a neoplasm based on follow-up information from the investigator. The Sponsor and the FDA met to review the data and agree on which events constituted new non-benign neoplasms diagnosed after the start of study drug (n=174). This document utilizes the patient classifications agreed upon during that meeting.

The FDA also requested additional toxicology studies, although their conclusion, based on review of the initial toxicology data included in the application, was that the weight of evidence suggests prasugrel is neither a "complete carcinogen" nor a "tumor promoter."

7.1.2. Summary of Nonclinical Carcinogenicity Studies

Prasugrel was not genotoxic in two in vitro tests (Ames bacterial gene mutation test, clastogenicity assay in Chinese hamster fibroblasts) and in one in vivo test (micronucleus test by intraperitoneal route in mice). No compound-related tumors were observed in a 2-year rat study with prasugrel at oral doses up to 100 mg/kg/day (>100 times the recommended therapeutic exposures in humans (based on plasma exposures to the major circulating human metabolite). There was an increased incidence of tumors (hepatocellular adenomas) in mice exposed for 2 years to high doses (>250 times the human metabolite exposure). These tumors are common in mice and are most likely related to chronic enzyme induction and are not considered relevant to human risk.

Based on the FDA's review of the toxicology studies included in the application, they concluded that the weight-of-evidence suggests that prasugrel is neither a "complete carcinogen" nor a "tumor promoter." Specifically, the FDA provided the following comments to the Sponsor:

"Two-year chronic bioassays in two rodent species are the current "gold standard" for assessing carcinogenicity of new drugs as well as other products. Results from these studies have been shown to identify virtually all known human carcinogens. Prasugrel was adequately tested in chronic bioassays using both rats and mice. When tested up to 70 times the clinical exposure, prasugrel was negative in a 2-year rat carcinogenicity study. Statistically significant increases in hepatocellular adenomas were seen in a mouse 2-year carcinogenicity study at a dose 250-fold the clinical exposure. These tumors are common in mice and are most likely related to chronic enzyme induction and are not considered relevant to human risk. Other data also add to the weight of evidence that prasugrel is not carcinogenic.

1) Prasugrel was tested and found to be without activity in an ICH (International Conference on Harmonization)-compliant battery of genetic toxicology tests including a bacterial mutation assay, chromosomal aberration assay in cultured mammalian cells, and in vivo chromosomal damage assay in mice.

2) The normally high frequencies of spontaneous tumors at the end of two years in rodents were similar in treated and control groups suggesting that prasugrel did not cause tumor promotion or progression.

3) In silico structure activity assessment suggests that prasugrel is not carcinogenic."

The results of several additional toxicology studies recently requested by FDA provide additional strong support that prasugrel is not a tumor promoter. Specifically, cell culture studies with three human tumor cell lines (lung, colon, and prostate) demonstrated that

exposure of serum-starved cells to prasugrel metabolites (active and primary human circulating) does not cause increases in cell proliferation relative to starved cells that were stimulated to proliferate by the addition of 10% fetal calf serum. Preliminary results (at the time of submitting this document) from studies of nude mice, implanted with lung, colon, and prostate human tumor cells, demonstrated no evidence that prasugrel causes an increase in tumor growth relative to vehicle control groups.

7.1.3. Summary of Clinical Data Including Follow-up Information

To assess any potential for prasugrel to promote tumor growth, the Sponsor conducted analyses on the:

- Incidence of new non-benign neoplasms diagnosed after start of study drug (i.e., benign neoplasms were excluded from the analyses).
- Outcomes for patients with non-benign neoplasm, excluding non-melanotic skin, known to be pre-existing at the time of randomization.

7.1.3.1. Non-benign Neoplasms Diagnosed After Start of Study Drug

Table 7.1 shows the overall incidence of non-benign neoplasms diagnosed after first dose of study drug. A numerically higher incidence of neoplasms was observed in prasugrel-treated patients.

Table 7.1. Number and Percentage of Patients with a New Diagnosis of Non-Benign Neoplasm

	Prasugrel N, n, (%)	Clopidogrel N, n, (%)	Hazard Ratio (95% CI)	p-value
First New Diagnosis	6741, 94, (1.39)	6716, 80, (1.19)	1.172 (0.870, 1.579)	0.295
First New Diagnosis Excluding Colorectal Neoplasm	6741, 75, (1.11)	6716, 70, (1.04)	1.069 (0.772, 1.481)	0.687

Source: l3543_kmcanl14_spfda_hemteae.rtf

Table 7.2 summarizes the body location of all new non-benign neoplasms and whether the neoplasm was diagnosed during evaluation of bleeding or anemia. Evaluation of bleeding or anemia appeared to prompt the diagnosis of the majority of GI neoplasms (esophagus, stomach, colorectal) and GU (kidney, urethral, and bladder). For 39 of the 50 GI neoplasms (78%), and for 15 of the 22 GU neoplasms (68%), the diagnosis was made during evaluation of bleeding or anemia. These data indicate that the evaluation of bleeding prompts the diagnosis of certain types of neoplasms. Therefore, an ascertainment bias exists for patients with bleeding complications compared with patients without bleeding complications, regardless of treatment group. In both treatment groups,

the incidence of GI neoplasms was increased 20-fold in patients with a GI bleed over those without a GI bleed (prasugrel: 5.5% versus 0.3%; clopidogrel 4.95% versus 0.22%).

The higher incidence of non-benign neoplasms observed in prasugrel patients resulted from a higher incidence of colorectal neoplasms (HR= 1.069; Table 7.1). As noted above, the majority of colorectal neoplasms in both treatment groups were diagnosed during the evaluation of bleeding or anemia (Table 7.2). This finding is similar to that reported in the clinical study report and in the primary publication of the TRITON-TIMI 38 study in the New England Journal of Medicine (Wiviott et al. 2007). The number of neoplasms not diagnosed during evaluation of bleeding or anemia was similar in each treatment group (52 prasugrel and 46 clopidogrel; p=0.55). The number of non-colorectal neoplasms diagnosed during evaluation of bleeding or anemia was the same in the 2 treatment groups (26 versus 26).

Table 7.2. Summary of Bleed/Anemia Triggered Diagnosis of New Non-Benign Neoplasms By Body Location

	Not Triggered		Bleed/Anemia Triggered		All	
	Pras	Clop	Pras	Clop	Pras	Clop
Neoplasm Location						
BONE	1	0	0	0	1	0
BRAIN	0	1	0	0	0	1
ORAL CAVITY AND PHARYNX	0	2	1	0	1	2
BREAST	3	1	0	0	3	1
LUNG AND BRONCHUS	12	7	4	5	16	12
OTHER RESPIRATORY/THORACIC	0	0	1	0	1	0
ESOPHAGUS	3	1	1	2	4	3
STOMACH	1	1	6	6	7	7
GALLBLADDER/BILIARY	2	0	0	0	2	0
PANCREAS	2	3	0	0	2	3
LIVER	0	1	0	0	0	1
COLORECTAL	3	2	16	8	19	10
PROSTATE	5	7	3	2	8	9
KIDNEY AND URETHRAL	2	1	4	2	6	3
BLADDER	3	1	2	7	5	8
GYNECOLOGIC	1	0	1	1	2	1
MALIGNANT MELANOMA	3	2	0	0	3	2
OTHER SKIN	5	13	1	0	6	13
ENDOCRINE	1	0	0	0	1	0
LEUKEMIA	1	1	0	0	1	1
LYMPHOMA	2	1	0	0	2	1
OTHER HEMATOLOGIC/BLOOD	0	0	0	1	0	1
METASTASIS WITHOUT PRIMARY KNOWN	1	0	1	0	2	0
OTHER UNKNOWN PRIMARY	0	1	0	0	0	1
UNKNOWN	1	0	1	0	2	0
All	52	46	42	34	94	80

Source: l4457_fqcanl16_loca_bldan_spfda.rtf

7.1.3.2. Non-benign Neoplasms Excluding Nonmelanotic Skin Cancers

The above analyses include all new non-benign neoplasm, including nonmelanotic skin cancers (NMSC), as the prospectively defined statistical analysis plan did not separate out these cancers from the overall analysis of neoplasms. The FDA conducted a post hoc analysis with the exclusion of nonmelanotic skin cancers. The rationale provided to the Sponsor by the FDA for excluding these cancers was that they were less clinically important and there was a lack of preclinical signal in skin neoplasms with prasugrel.

In response, the Sponsor consulted experts in the field of oncology and tumor promotion to obtain guidance on whether such analyses should exclude nonmelanotic skin cancers. Based on feedback from the consultants, the Sponsor believes that analyses to detect any signal of tumor promotion should include nonmelanotic skin cancers for the following reasons:

- The relevant question is whether there is evidence for tumor promotion across a wide variety of tumors, even those readily treatable.
- The only scientific rationale to exclude a tissue from analysis is that the tissue has no exposure to the drug. Both prasugrel and clopidogrel are found in skin tissue.
- Systemic exposure to some carcinogens result in skin cancers (e.g., arsenical poisoning; Leung 2001; Gawkrodger 2004). The ability of any drug to induce skin cancer is a significant toxicity.
- Skin tumors are sensitive to known tumor promoters (Slaga 1983; Yuspa 1994).
- Skin is an active mitotic organ.
- Skin tumors are likely to have a lower probability of providing false negatives.
- A number of known carcinogens are capable of producing tumors in multiple organ systems including skin (Guo et al. 2001; Navarro Silvera and Rohan 2007).
- Recent assessment of the role of drugs in cancer promotion included melanotic and nonmelanotic skin cancers (ezetimibe/Vytorin – Peto et al. 2008).
- Exclusion of any specific type of cancer would be post hoc and subject to bias.

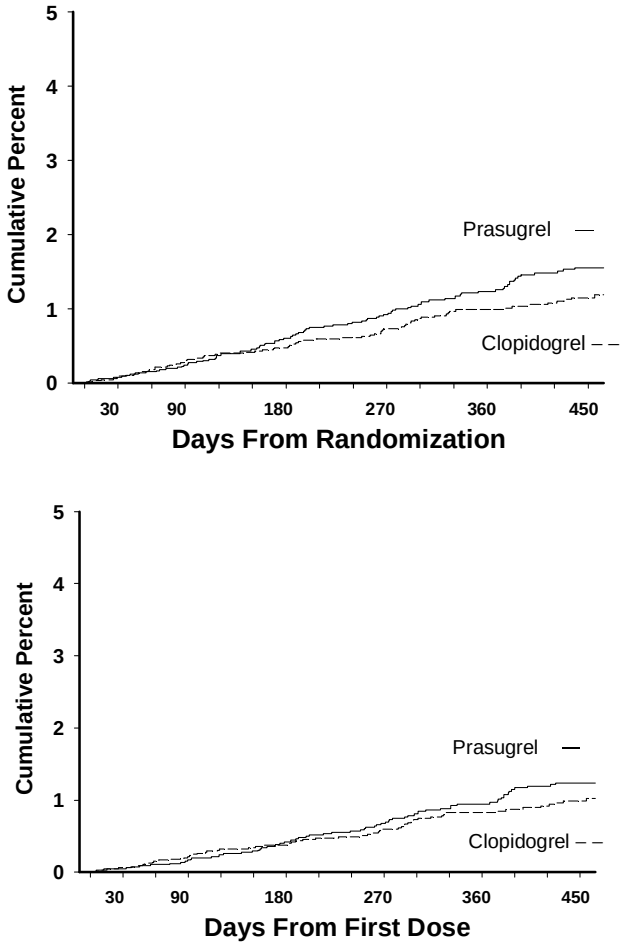
The Sponsor believes that any drug-induced cancer represents a significant toxicity. However, the Sponsor did reanalyze the data excluding nonmelanotic skin cancers. There were more nonmelanotic skin cancers in patients treated with clopidogrel compared to prasugrel (6 prasugrel versus 13 clopidogrel). Table 7.3 shows the incidence of new non-benign neoplasms and the incidence after excluding colorectal neoplasms. A higher incidence of neoplasms was observed in prasugrel-treated patients (88 prasugrel versus 67 clopidogrel, p=0.094). This difference is reduced when colorectal neoplasms are excluded (69 prasugrel versus 57 clopidogrel, p=0.289).

Figure 7.1 displays the time from first dose of study drug to diagnosis of first new non-benign neoplasm excluding nonmelanotic skin and the time from first dose of study drug to diagnosis of first new non-benign neoplasm for both treatment groups excluding colorectal and nonmelanotic skin cancers.

Table 7.3. Number and Percentage of Patients with a New Non-Benign Neoplasm Excluding Nonmelanotic Skin Cancers

	Prasugrel N, n, (%)	Clopidogrel N, n, (%)	Hazard Ratio (95% CI)	p-value
First New Diagnosis Excluding Nonmelanotic Skin Cancers	6741, 88, (1.31)	6716, 67, (1.00)	1.311 (0.954, 1.802)	0.094
First New Diagnosis Excluding Nonmelanotic Skin and Colorectal Neoplasm	6741, 69, (1.02)	6716, 57, (0.85)	1.208 (0.851, 1.716)	0.289

Source: l3543_kmcanl14_spfda_hemteae.rtf.



Source: l3543_kmcanl14_spfda_hemteae.rtf.

Figure 7.1. **Kaplan-Meier estimates of the incidence of new diagnosis of non-benign neoplasm excluding nonmelanotic skin cancers (top) and excluding both nonmelanotic skin and colorectal neoplasms (bottom).**

The above analyses excluding nonmelanotic skin cancers are also consistent with the overall analysis. When nonmelanotic skin cancers are excluded from the analysis, there is a higher incidence of new non-benign neoplasms in patients treated with prasugrel. However, when colorectal neoplasm are excluded from the analysis, there is no difference between treatment groups in the incidence of new non-benign neoplasms.

7.1.3.3. Outcomes in patients with New Non-benign Neoplasms

In TRITON-TIMI 38, the incidence of CEC adjudicated malignancy-related death in all randomized patients at study end was low and comparable between treatment groups (Table 7.4).

Table 7.4. All Malignancy Deaths at Study End - CEC Adjudicated All Treated Patients

	Prasugrel N=6741	Clopidogrel N=6716	Total N=13457	p-Value
Malignancy Related Deaths	21[a]	17	38	0.63

a In discussion with the FDA, a patient previously reported as a malignancy death was determined to not have malignancy. This patients is included in this table but is excluded from subsequent analyses of malignancy.
Source: l0544_fqmalj12_neoplasm_death.rtf.

Table 7.5 shows the incidence of all-cause death and malignancy death at study end and after study end for patients diagnosed with a new non-benign neoplasm. The randomized comparison between treatment groups in TRITON-TIMI 38 extends up to study end. The incidence of all-cause death, and malignancy death at database lock was similar in each treatment group.

In patients with new non-benign neoplasms, the number of malignancy related deaths after study end was higher in patients treated with prasugrel. This difference is predominantly due to higher GI malignancy death in patients treated with prasugrel. .

Table 7.5. Death in Patients Reporting a New Non-Benign Neoplasm.

	Deaths At Study End		Deaths After Study End[a]	
	Prasugrel N=94 % (n)	Clopidogrel N=80 % (n)	Prasugrel N=74[b] % (n)	Clopidogrel N=67 % (n)
All-Cause Death	20% (19)	16% (13)	22% (16)	16% (11)
Malignancy Death	17% (16)	16% (13)	19% (14)	15% (10)
GI Malignancy Death	7.4% (7)	8.8% (7)	6.8% (5)	1.5% (1)

[a] deaths from study end to the end of extended follow-up
[b] one patient was alive at study end but no additional information was available during extended follow-up
Source: l1580, l0544

7.1.3.4. Pre-existing Non-benign Neoplasms

The Sponsor also assessed outcomes through database lock for all patients with pre-existing non-benign neoplasms as reported in the original submission. Table 7.6 shows no difference between all-cause death, malignancy deaths, or metastasis, all objective measures of a possible tumor stimulatory effect, between prasugrel and clopidogrel within this cohort.

Table 7.6. Outcomes at Study End for Patients with Pre-existing Non-Benign Neoplasm

	Excluding NMSC	
	Prasugrel N = 137 n (%)	Clopidogrel N = 132 n (%)
All-Cause Deaths	10 (7.30)	10 (7.58)
Malignancy Deaths	4 (2.92)	3 (2.27)
Treatment-emergent Metastasis	6 (4.38)	5 (3.79)
Use of Anti-Neoplastic Agents	7 (5.11)	8 (6.06)

Source: l1580_fqcanl18_death_conmed.rtf

7.1.4. Biologic Plausibility for Antiplatelet Agents as Tumor Promoters

Platelet activation and aggregation are known to be associated with malignancy (Evangelista et al. 2007):

- High platelet counts are predictive of poor survival in a number of cancers including lung, renal, gastric, colorectal, and breast (Juraz et al. 2004).
- Tumor cells aggregate platelets, in a process known as tumor cell-induced platelet aggregation (TCIPA), which in turn increases survival of cancer cells via a number of different pathways (Juraz et al. 2004). TCIPA involves cancer-cell-mediated stimulation of platelet granules, leading to the release of potent proaggregatory agents such as ADP (Juraz et al. 2004).
- Activation of the P2Y12 receptor has been shown to promote growth and de-differentiation of rat C6 glioma cells via reduction in cAMP concentration and stimulation of the ERK1/2 and PI3-K/Akt signaling cascades (Krzeminski 2007).

These considerations might lead one to expect that if thienopyridines had any effect on neoplasia at all, it would be an inhibitory one.

7.1.5. Conclusions regarding Neoplasms

The Sponsor believes that there is no identified biological hypothesis to support the pro-carcinogenicity or tumor promotion of prasugrel. Pre-clinical data suggest that inhibition of platelet activation and aggregation would be more likely to inhibit tumor growth rather than promote growth. An extensive battery of toxicology studies confirms that prasugrel is neither a “complete carcinogen” nor a “tumor promoter.” Additionally, the higher incidence of non-benign neoplasms observed in prasugrel treated patients resulted primarily from a higher incidence of colorectal neoplasms, the majority of which were

diagnosed during the evaluation of bleeding or anemia. These data suggest a plausible explanation that the increased incidence of neoplasms observed in prasugrel treated patients results from ascertainment bias.

In TRITON-TIMI 38, hundreds of prespecified analyses were conducted to assess the safety of prasugrel relative to clopidogrel therapy. On the basis of chance alone, the Sponsor anticipated that significant associations ($p<0.01$) of prasugrel with adverse outcomes (other than bleeding) might be observed. The initial observation of a higher number of prasugrel-treated patients with adverse events coded to the "Neoplasms Benign, Malignant, and Unspecified (including Cysts and Polyps)" system organ class was marginally significant ($p=0.043$) without correction for multiple comparisons. A plethora of post-hoc exploratory analyses were conducted, including the incidence of new non-benign neoplasms and new non-benign neoplasms excluding nonmelanotic skin cancers. These analyses found no statistically significant differences between treatment groups, even without correction for multiple comparisons ($p=0.295$ and $p=0.094$, respectively). The various neoplasm-related observations could all just be the result of chance.

TRITON-TIMI 38 was not designed to ask or answer questions concerning drug-induced tumor promotion. Although the Sponsor believes that the currently available data do not provide credible evidence that prasugrel promotes the growth of pre-existing, undiagnosed tumors, a direct causative effect cannot be excluded. Therefore, the Sponsor is planning to collect information on the incidence of neoplasms in the TRILOGY-ACS Study. This study has an external oncology working group to provide expert oversight on the data collection and analysis of neoplasm events.

7.2. Stent Thrombosis

7.2.1. Background and Regulatory History

In September 2006, concerns of late stent thrombosis with drug eluting stents were raised at the European Congress of Cardiology. The TRITON-TIMI 38 study was concurrently collecting information on a very large number of patients with ACS and coronary stents, including investigator assessment of stent thrombosis. Therefore, the TRITON operations committee developed a plan to include CEC adjudication of stent thrombosis in TRITON-TIMI 38 and to assess whether the intensity of antiplatelet therapy would impact this endpoint.

In consultation with interventional cardiologists, the Academic Research Consortium (ARC) definite plus probable stent thrombosis definition was chosen as the key endpoint. The CEC charter was amended to include stent thrombosis as a prespecified secondary endpoint. The charter called for adjudication on a clinical basis using information from discharge summaries, autopsy reports, and cardiac catheterization reports. In late 2006, the FDA agreed with the proposed data collection for stent thrombosis adjudication, including the use of angiographic reports rather than the review of angiograms. The FDA

indicated that if any review of actual angiograms was considered worthwhile, specific angiograms would be requested. The planned analyses for stent thrombosis were incorporated into the statistical analysis plan, which was submitted to the FDA prior to database lock.

During regulatory review, the FDA inquired on the potential implication of not including review of angiograms as part of the adjudication process. To demonstrate the robustness of the analyses, the sponsor provided a number of sensitivity analyses including those contained in Table 7.7.

Table 7.7. Additional Analyses of Stent Thrombosis

	Prasugrel	Clopidogrel	RR	p-value[a]
Primary Analysis				
CEC adjudicated (Definite + Probable)	68	142	0.48	<0.001
Sensitivity Analyses				
CEC adjudicated (Definite)	52	122	0.42	<0.001
Site Reported	139	204	0.68	<0.001
Concordant (CEC and Site Reported)	44	100	0.44	<0.001

a Fisher's exact test.

Source: Regulatory Response – letter from TIMI to Dr Macias, 22 August 2008.

Late in the review of the application, the FDA requested that, for 12 cases adjudicated as definite stent thrombosis by the TRITON CEC, angiographic films be obtained and reviewed by a core laboratory with subsequent adjudication by an independent group. The FDA also asked that 18 control cases (events adjudicated as not stent thrombosis and matched by age, sex, and lesion) be reviewed in the same manner. The Sponsor selected the PERFUSE core lab to review the angiograms and the Harvard Clinical Research Institute (HCRI) to adjudicate the events. The PERFUSE core lab reviewed the angiograms without access to any TRITON CEC findings or the individual cardiac catheterization reports. The HCRI adjudicated the events with access to all source documents, the PERFUSE core lab reading of the angiogram, and TRITON CEC findings other than those regarding stent thrombosis.

7.2.2. Results

There was concordance between the TRITON CEC and HCRI in 26 of 30 cases (Table 7.8). For the 12 cases identified by the FDA (positively adjudicated by TRITON-TIMI 38 CEC), 8 cases were adjudicated by HCRI as definite or probable stent thrombosis and 4 cases were adjudicated as no stent thrombosis. For the 18 control cases (negatively adjudicated by TRITON-TIMI 38 CEC), all cases were adjudicated as no stent thrombosis.

Table 7.8. HCRI Adjudication

	Results of HCRI Adjudication		
	Definite	Probable	No Stent Thrombosis
Adjudicated as Stent Thrombosis by TRITON CEC	7	1	4
Controls, adjudicated as not a stent thrombosis by TRITON CEC	0	0	18

Source: Table 1 and Table 3 of Regulatory Response 5 December 2008

Table 7.9 shows the 4 cases adjudicated as stent thrombosis by the TRITON-TIMI 38 CEC but not as stent thrombosis by the HCRI. The Sponsor reviewed each of these cases to understand why the TRITON CEC adjudicated them as definite stent thrombosis. In each case, it was clearly understandable why the TRITON CEC adjudicated these cases as definite stent thrombosis.

Table 7.9. Discordant Cases

Case	Investigator-Reported Stent Thrombosis	Clinical History consistent with Stent Thrombosis and Thrombus present by clinical report	Ischemic Symptoms at Rest	MI Involving Target Vessel Territory
1	Yes	Yes	Yes	Yes
2	No	Yes	Yes	Yes
3	Yes	Yes	Yes	No
4	No	Yes (distal to stent)	Yes	No

Source: Table 6 of Regulatory Response 5 December 2008

7.2.3. Conclusions

Prasugrel treatment was associated with a robust reduction in what can be termed "clinically adjudicated stent thrombosis" across clinical characteristics and stent types. The CEC reviewed clinical information and source documentation provided by sites, including catheterization reports. Since the entire process was done with all participants blinded to treatment assignment, including clinical investigators and clinical events committee members, systematic bias is unlikely.

The concordance of the TRITON-TIMI 38 CEC and the HCRI adjudication in this small sample of selected cases was reasonably high (26 of 30 patients). Of the 18 matched controls which had been adjudicated by the TRITON-TIMI 38 CEC as no stent thrombosis, all were reassessed as no stent thrombosis by HCRI. Of the 12 cases originally adjudicated as stent thrombosis, 8 cases were readjudicated by HCRI as

definite or probable stent thrombosis and 4 cases were readjudicated as no stent thrombosis. In each of the 4 discordant cases, it was clearly understandable on review of the source documents why the TRITON-TIMI 38 CEC adjudicated these cases as definite stent thrombosis.

Differences in adjudication results as observed between the TRITON-TIMI 38 CEC and the HCRI are to be expected when technical aspects of the adjudication processes differ. The HCRI results suggest that these adjudicators gave a higher weighting to the results of the PERFUSE core lab interpretation of the angiogram than to the investigator's cardiac catheterization report or clinical findings. The review by the TRITON-TIMI 38 CEC did not include the angiogram, and was therefore focused on the investigator reports, which may have contained observations during fluoroscopy but not captured on angiography, and clinical data including previously adjudicated myocardial infarction in the territory of the placed stent.

7.3. Pharmacogenetics

7.3.1. Background

Both prasugrel and clopidogrel are prodrugs that require biotransformation to active metabolites by cytochrome P450 (CYP) enzymes. Prasugrel is rapidly hydrolyzed to a thiolactone in the intestine and then oxidized to its active metabolite in a single CYP-dependent step. Conversely, esterases shunt the majority of clopidogrel to an inactive pathway with the remaining prodrug requiring two separate CYP-dependent oxidative steps for conversion to the active metabolite (Figure 5.1) (Kurihara et al. 2005; Rehmel et al. 2006; Farid et al 2007a). The CYP genes are polymorphic with certain forms conferring altered or loss-of-function enzymatic function (Table 7.10) (Ingelman-Sundberg et al. 2007). Consequently, CYP genetic variation may impact conversion to active metabolite, and subsequent clinical response to thienopyridines differentially.

7.3.2. CYP Genetic Variation and Exposure to Thienopyridine Active Metabolite and Platelet Response

7.3.2.1. Healthy Subjects Pharmacokinetics and Pharmacodynamics

Table 7.10 provides the observed genotypes and predicted phenotype classifications for the 346 healthy subjects participating in the clinical pharmacology studies.

Table 7.10. Genotyping Results by Gene and Predicted Metabolic Phenotype

Gene	Dichotomous classification[b]	Predicted Phenotype[b]	Observed Genotypes[a]	Number of Subjects (%)			
				Clinical Pharmacology Studies		TRITON-TIMI 38	
				Clopidogrel	Prasugrel	Clopidogrel	Prasugrel
CYP2C19	Non-carrier	UM	*17/*17, *1A/*17	44 (30)	37 (16)	n/a[e]	n/a[c]
		EM	*1A/*1A	53 (36)	93 (41)	1064 (73)	1048 (72)
	Carrier	IM	*1A/*2A, *1A/*3, *1A/*4, *1A/*8	43 (29)	78 (35)	357 (24)	372 (26)
		PM	*2A/*2A, *2A/*3, *2A/*4 *2A/*5A, *2A/*8	8 (5)	18 (8)	38 (3)	35 (2)
	n/a	Unknown[c]	*1A/*9, *1A/*10, *2A/*17, *6/*17	NI[c]	NI[c]	NI[c]	NI[c]
CYP2C9	Non-carrier	EM	*1A/*1A, *1A/*2A, *1A/*11A, *1A/*12	143 (89)	213 (90)	1226 (84)	1213 (84)
	Carrier	IM	*1A/*3A, *2A/*2A, *2A/*3A, *2A/*11A, *2A/*12, *3A/*11A, *3A/*12, *6/*11A	17 (11)	23 (10)	221 (15)	226 (16)
		PM	*3A/*3A	0 (0)	0 (0)	9 (1)	8 (1)
	n/a	Unknown[c]	*1A/*5, *1A/*8, *1A/*9, *9/*9	NI[c]	NI[c]	NI[c]	NI[c]
CYP2B6	Non-carrier	EM	*1A/*1A, *1A/*1C, *1C/*1C	101 (65)	155 (67)	777 (68)	798 (71)
	Carrier	IM	*1A/*6, *1A/*9, *1C/*6 *1C/*9, *1C/*13, *6/*9	55 (35)	75 (33)	306 (27)	271 (24)
		PM	*9/*9	0 (0)	0 (0)	64 (6)	58 (5)
CYP3A5	Non-carrier	EM	*1A/*1A	9 (6)	11 (5)	7 (1)	6 (0)
		IM[d]	*1A/*3A, *1A/*6, *2A/*3A	31 (19)	53 (23)	144 (11)	151 (12)
	Carrier	PM	*3A/*3A, *3A/*3F, *3A/*6	121 (75)	170 (73)	1130 (88)	1095 (87)
CYP3A4	Non-carrier	EM	*1A/*1A, *1A/*18	162 (100)	238 (100)	1392 (100)	1377 (100)
	Carrier	IM	None				
		PM	None				
CYP1A2	Non-carrier	EM	*1A/*1A, *1A/*1D, *1A/*1E, *1D/*1D, *1D/*1E, *1D/*1L, *1E/*1L, *1L/*1L	133 (86)	199 (87)	1099 (95)	1093 (94)
	Carrier	IM	*1A/*1C, *1C/*1D, *1C/*1E	21 (14)	30 (13)	59 (5)	74 (6)
		PM	*1C/*1C	0 (0)	0 (0)	0 (0)	1 (0)
	n/a	Unknown[c]	*1A/*7	NI[c]	NI[c]	NI[c]	NI[c]

Table 7.10. Genotyping Results by Gene and Predicted Metabolic Phenotype (concluded)

[a] Genotyping was performed using the Affymetrix Targeted Human DMET 1.0 Assay (98% of genotypes) (Daly et al. 2007; Dumaual et al. 2007) and bi-directional sequencing or exon-specific polymerase chain reaction amplification followed by restriction fragment length polymorphism gel electrophoresis (2% of genotypes).

[b] Alleles were classified *a priori* by their known effect on enzymatic function (Adapted from Ingleman-Sundberg et al. 2007; Karolinska Institute www.cypalleles.ki.se 2007; Data on file.). Subjects were dichotomized based on whether or not they possessed at least one significantly reduced-function allele, carriers and non-carriers. The extended categorical classification, including ultra-rapid (UM), extensive (EM), intermediate (IM), or poor metabolizer (PM) genotypes.

[c] The predicted metabolic phenotypes of these observed genotype combinations are unknown. They were therefore excluded from analyses.

[d] For CYP3A5, intermediate metabolizer genotypes confer near-normal activity and were therefore a priori combined with the extensive metabolizer genotypes.

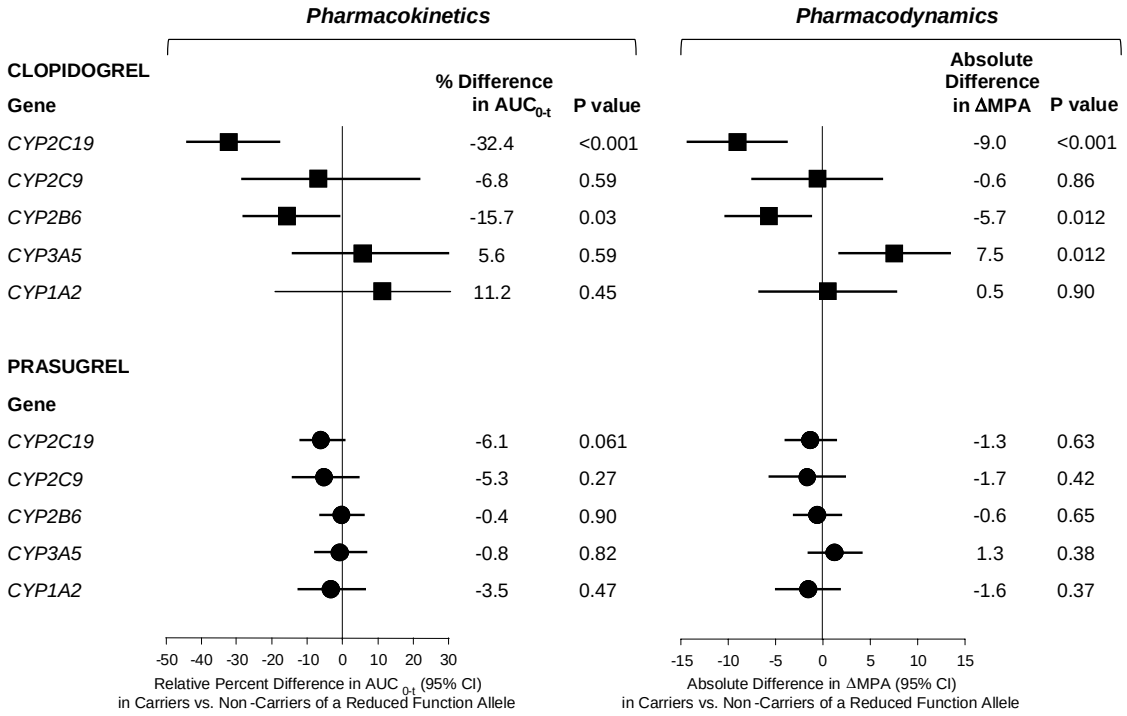
[e] CYP2C19*17 not measured for TRITON.

Source Mega et al 2008a

Using likelihood ratio tests based on linear mixed-effects models, with the primary outcomes being exposure to active drug metabolite [$\log(AUC_{0-t})$] and platelet inhibition (ΔMPA), no significant effect was found for any CYP in response to prasugrel treatment (Figure 7.2). In subjects treated with clopidogrel, carriers of at least 1 CYP2C19 reduced-function allele (34% of the study population) had a 32.4% lower exposure to clopidogrel active metabolite than did non-carriers ($p<0.001$). In unison with the effects on pharmacokinetic parameters, clopidogrel carriers also had a diminished pharmacodynamic effect, with reduction of platelet aggregation that was 9 absolute percentage points less than in non-carriers ($p<0.001$).

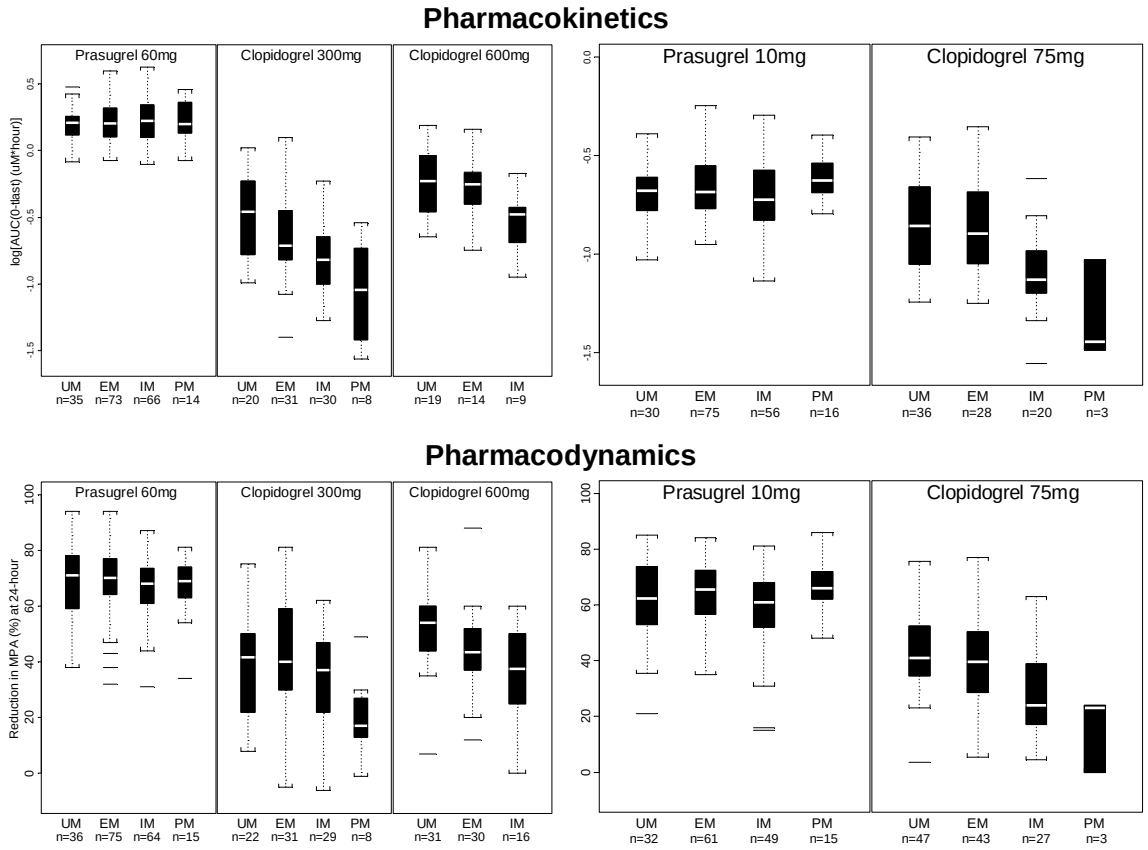
Furthermore, when the extended CYP2C19 genotypic classification was used (ultra-rapid, extensive, intermediate, and poor metabolizer genotypes), there was a gradient of effect to clopidogrel: subjects with the ultra-rapid metabolizer genotypes exhibited the highest exposure and greatest inhibition of platelet aggregation and subjects with the poor metabolizer genotypes had the lowest exposure and least platelet inhibition with both loading and maintenance doses (Figure 7.3). The pharmacokinetic and pharmacodynamic effects of a CYP2C19 reduced-function allele were consistent for clopidogrel after a loading dose (both 300 mg and 600 mg clopidogrel) and during maintenance dosing (75 mg clopidogrel), in contrast to prasugrel where no significant effect was observed (Figure 7.3).

In addition, carriers of a reduced-function CYP2B6 allele also tended to have lower plasma exposure to clopidogrel active metabolite (-15.7%, $p=0.03$) and had significantly less reduction of platelet aggregation (5.7 absolute percentage points less, $p=0.01$) to clopidogrel. No associations with CYP3A4 alleles were tested because no subjects carried the reduced function alleles assayed. Carrier status for a reduced-function allele for the other 3 CYP genes (CYP2C9, CYP3A5, CYP1A2) was not associated with a consistent attenuation of the pharmacokinetic and pharmacodynamic response to clopidogrel, nor was carrier status for any of the CYP genes associated with a significant attenuation in response to prasugrel (Figure 7.2).



Model-based estimates of the effects associated with carriage of at least one reduced-function allele in five genes encoding CYP enzymes on the pharmacokinetic, area under the plasma concentration-time curve of the active metabolite from time of dose to last measurable concentration (AUC_{0-t}) and pharmacodynamic response, light transmission aggregometry in response to 20 μM ADP expressed as absolute reduction in maximal platelet aggregation from baseline (ΔMPA), to prasugrel and clopidogrel. Results for subjects receiving loading or maintenance doses of drug have been combined. The threshold for statistical significance was 2 sided $p<0.01$. The horizontal lines represent 95% confidence intervals.
Source: Close et al. 2008; Mega et al 2008a.

Figure 7.2. Genetic effects on pharmacokinetic and pharmacodynamic responses to Prasugrel and Clopidogrel.



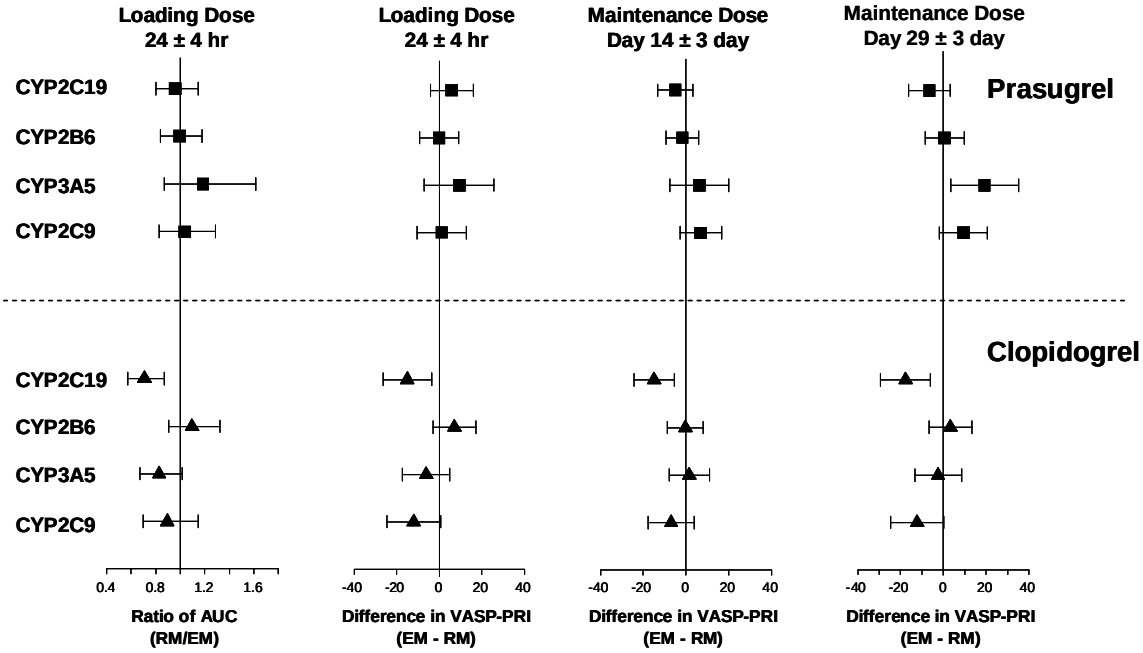
EM denotes extensive metabolizer, IM intermediate metabolizer, PM poor metabolizer, and UM ultra-rapid metabolizer. AUC_{0-t} is area under the plasma concentration-time curve of the active metabolite from time of dose to last measurable concentration.
Source: Close et al. 2008; Mega et al. 2008a.

Figure 7.3. Relationship between CYP2C19 Predicted Phenotype and pharmacokinetic (top) and pharmacodynamic (bottom) parameters following loading and maintenance doses of prasugrel and clopidogrel among a combined set of 346 healthy subjects.

7.3.2.2. Stable Coronary Artery Disease Patient Pharmacokinetics and Pharmacodynamics

Remarkably similar results were observed in patients with stable coronary artery disease receiving a 60-mg/10-mg dose of prasugrel (n=51) or a 600-mg/75-mg dose of clopidogrel (n=47). No significant effect on exposure or platelet response as measured using the VASP assay (Biocytex Platelet VASP kit, Marseille, FR) (Angiolillo et al. 2007), the Verify*Now*™ P2Y12 assay (VN-P2Y12, Accumetrics, San Diego, CA, USA), and light transmission aggregometry in response to 20 µM ADP expressed as absolute reduction in maximal platelet aggregation from baseline (ΔMPA), was observed for

carriers of CYP2C19 reduced function alleles for prasugrel (Figure 7.4). Conversely, and similar to the observation in healthy subjects, reduced exposure to active metabolite and decreased attenuation of platelet response was observed for clopidogrel carriers of CYP2C19 reduced function alleles.



For CYP2C9, CYP2B6, and CYP3A5, there was no statistically significant genetic effect on the active metabolite exposure or PD response for either drugs. $AUC_{0-\infty}$ is area under the plasma concentration-time curve of the active metabolite from time of dose to last measurable concentration. VASP-PRI is vasodilator- stimulated phosphoprotein platelet reactivity index.
Source: Varenhorst et al. 2008.

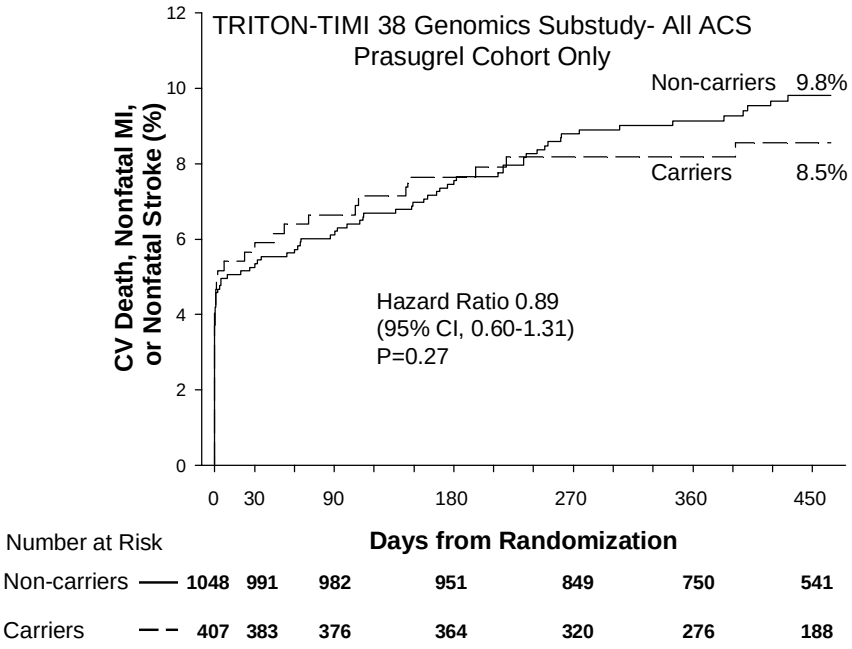
Figure 7.4. Pharmacokinetic and Pharmacodynamic Responses for Other Analyzed Cytochrome P450 Genes.

7.3.2.3. Clinical Outcomes in Patients with Acute Coronary Syndrome in the TRITON-TIMI 38 Genetic Substudy

Pharmacogenetic analyses were performed on 2943 patients enrolled in a phramacogenetic substudy of TRITON-TIMI 38 (Table 7.10). In this genetic substudy, the rate of the primary efficacy endpoint (CV death, nonfatal MI, or nonfatal stroke) in the prasugrel arm (9.4%) was similar to the rate in the overall trial (9.9%); in contrast, the rate in the clopidogrel arm (9.3%) was lower than the rate observed in the overall trial (12.1%). The inconsistency between the observed rates for the pharmacogenetic substudy and those of the overall trial limits interpretation of between drug comparisons.

Concordant with and extending the pharmacokinetic and pharmacodynamic findings, prasugrel-treated patients with at least 1 CYP2C19 reduced-function allele did not

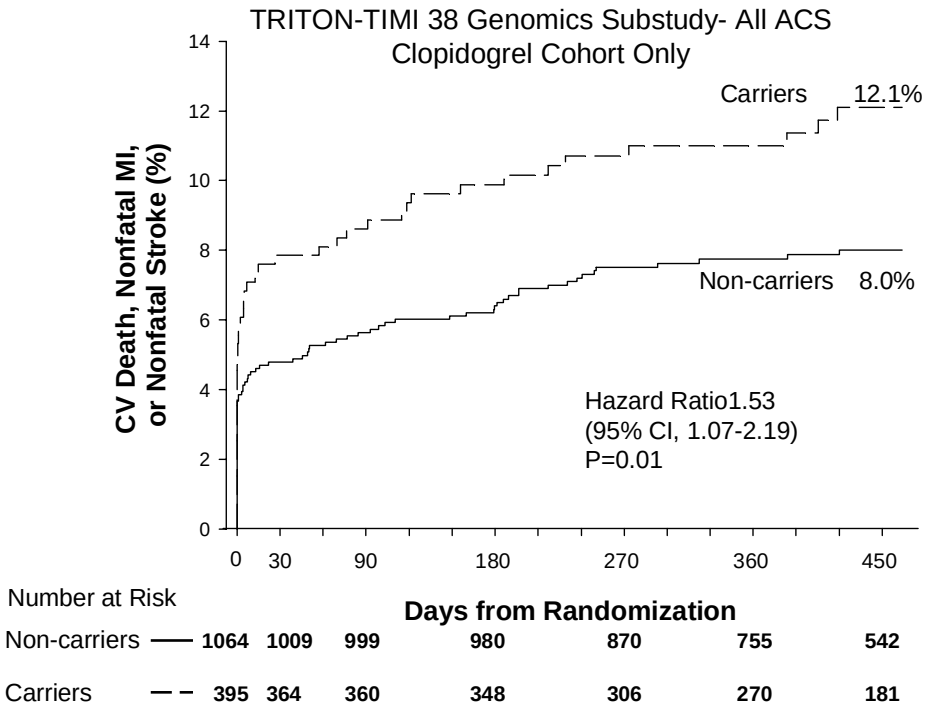
experience significant differences in the rate of CV death, nonfatal MI, or nonfatal stroke at 15 months, when compared to non-carriers (Kaplan-Meier estimates 8.5% versus 9.8%; Cox Proportionate HR=0.89, 95% CI 0.60 to 1.31, p=0.27, Figure 7.5) or definite or probable stent thrombosis as defined by the Academic Research Consortium (0.5 versus 1.0%; HR=0.58, 95% CI: 0.13 to 2.69, p=0.76).



Source: Mega et al. 2008b.

Figure 7.5. CYP2C19 reduced function allele carrier status and clinical outcomes in 1455 patients treated with Prasugrel.

Clopidogrel-treated patients with at least 1 CYP2C19 reduced-function allele (N=395, 27.1% of the treatment arm) were at significantly higher risk of the primary efficacy endpoint of CV death, nonfatal MI, or nonfatal stroke at 15 months when compared to non-carriers (Kaplan-Meier estimates 12.1 versus 8.0%; Cox Proportionate HR=1.53, 95% CI: 1.07 to 2.19, p=0.001 [Gehan-Wilcoxan]; Figure 7.6). A directionally consistent hazard was observed among clopidogrel-treated patients carrying a CYP2C19 reduced-function allele for each of the components of the primary efficacy endpoint, including CV death (2.0 versus 0.4%; HR=4.79, 95% CI: 1.40 to 16.37), nonfatal MI (10.1% versus 7.5%; HR=1.38, 95% CI: 0.94 to 2.02), and nonfatal stroke (0.88% versus 0.24%; HR=3.93, 95% CI: 0.66 to 23.51). Clopidogrel-treated carriers of a CYP2C19 reduced-function allele also had a 3-fold higher risk of stent thrombosis (2.6 versus 0.8%; HR=3.09, 95% CI: 1.19 to 8.00, p=0.02).



Source: Mega et al. 2008a.

Figure 7.6. CYP2C19 reduced function allele carrier status and clinical outcomes in 1459 patients treated with Clopidogrel.

No significant associations between any of the other CYP genotypes and the primary efficacy outcome were observed, nor did the rates of non-CABG related TIMI Major or Minor bleeding differ significantly across any CYP genotype for either drug.

7.3.3. Conclusions Regarding Pharmacogenetics

These results provide strong evidence that CYP genetic variation has no relevant effect on prasugrel active metabolite exposure, on platelet inhibition, or protection from recurrent ischemic events for prasugrel. Within the same studies, CYP genotype variations reduced exposure to the clopidogrel active metabolie, reduced the level of platelet inhibition, and were associated with worse clinical outcomes. These latter findings reduce the likelihood that the absence of an effect on prasugrel is a false negative.

7.4. Interactions with Drugs that Elevate Gastric pH

7.4.1. Background and Regulatory History

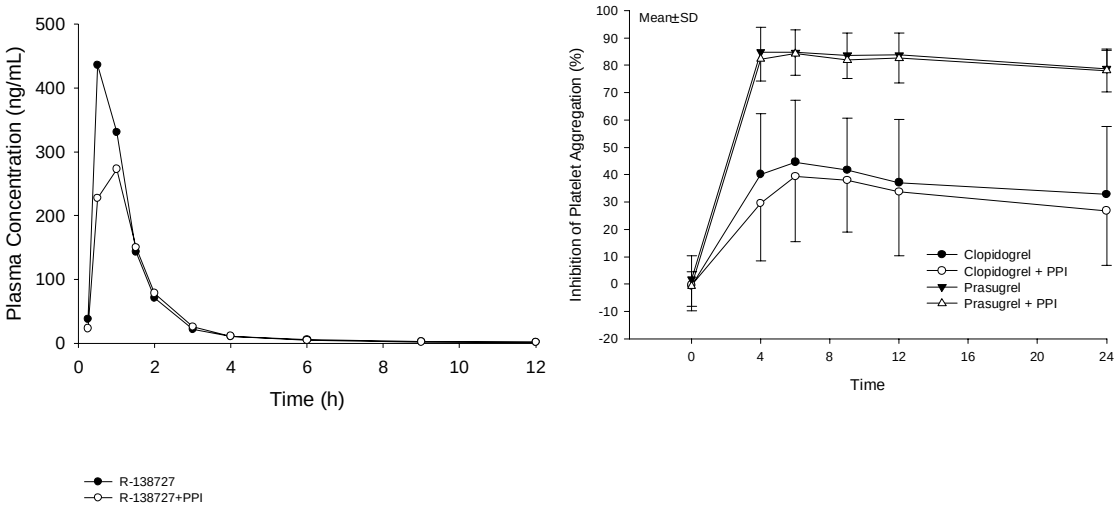
In vitro data show that prasugrel's dissolution is faster at acidic than neutral pH. Therefore, treatment with drugs that increase gastric pH could potentially slow the rate and/or extent of dissolution of prasugrel. Based on this potential interaction, the effect of

concomitant use of PPIs and H_2-blockers on the PK, PD, efficacy and safety of prasugrel was evaluated.

During the review of the application, FDA requested additional information regarding the clinical impact of drugs that elevate gastric pH on the safety and efficacy of prasugrel.

7.4.2. Effect of Elevated Gastric pH on the Pharmacokinetics and Pharmacodynamics of Prasugrel and Clopidogrel in Healthy Subjects

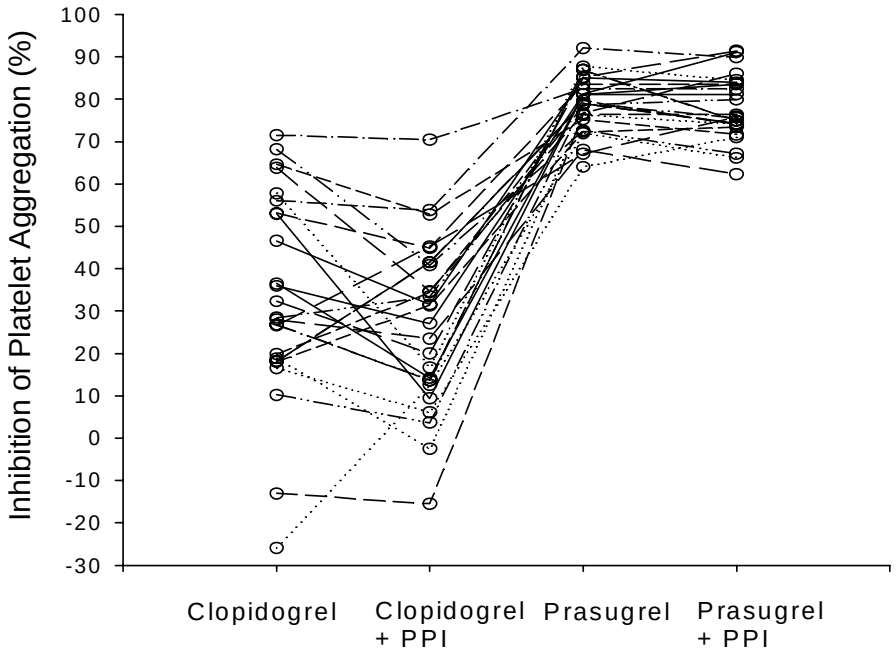
Study TAAI assessed the effect of co-administration of lansoprazole on the PK/PD of prasugrel HCl. Co-administration of lansoprazole did not decrease exposure to prasugrel's active metabolite (90% CI of geometric mean AUC within 0.8 to 1.25) following a 60-mg loading dose (Figure 7.7). C_{max} was reduced by nearly 30%, with no change in t_{max}. There was no effect on mean IPA measured 4 to 24 hours post dose (Figure 7.7). IPA was significantly higher following a prasugrel LD when compared to a clopidogrel 300-mg LD, with or without lansoprazole.



Source: Small 2008 et al 2008a

Figure 7.7. Geometric mean plasma concentrations for prasugrel's active metabolite with and without lansoprazole (left) and mean MPA to 20 µM ADP through 24 hours following a 60-mg dose of prasugrel HCl or 300 mg of clopidogrel (right) - TAAI.

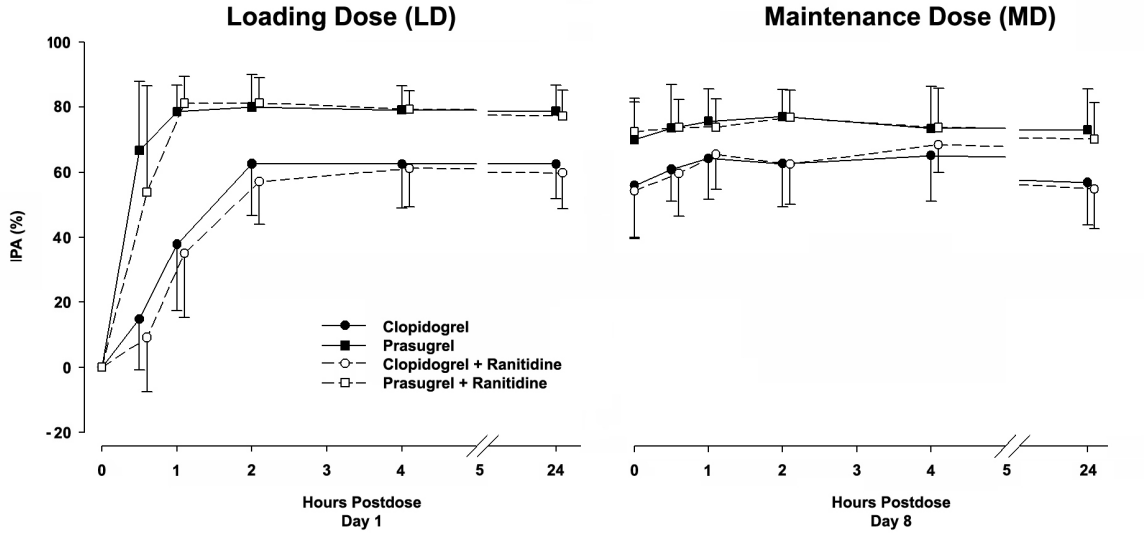
Figure 7.8 shows individual IPA response to 20 µM ADP at 24 hours after dosing. Considerable response variability was observed with clopidogrel with and without lansoprazole. Following administration of lansoprazole, there was an increase in the number of subjects with IPA less than 20% (considered the threshold for non response). In contrast, the IPA for prasugrel was unaffected by co-administration of lansoprazole.



Source: Small 2008 et al 2008a

Figure 7.8. **Relationship between IPA by clopidogrel alone, clopidogrel and lansoprazole, prasugrel alone, and prasugrel and lansoprazole in response to 20 µM ADP 24 hours after dosing. Patients were administered all treatments in a randomized crossover fashion.**

Study TABS assessed the effect of co-administration of ranitidine on the PK/PD of prasugrel.HCl (Figure 7.9). Co-administration of ranitidine did not decrease exposure to prasugrel's active metabolite (90% CI of geometric mean AUC within 0.8 to 1.25) following either a 60-mg LD or a 10-mg MD (Figure 7.7). C_{max} of prasugrel's active metabolite was reduced by 14%, although there was no change in t_{max}. No statistically significant difference in IPA was detected at any time point except for 30 minutes after the prasugrel LD.



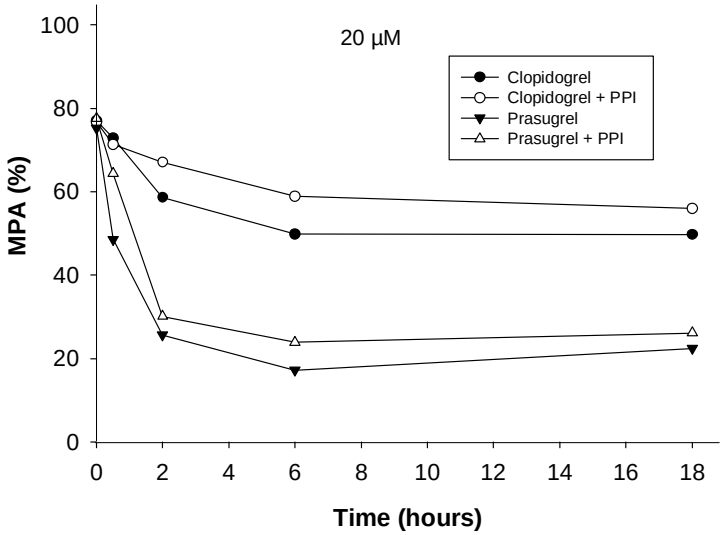
Source: Small et al 2008b

Figure 7.9. **Loading (Day 1) and maintenance dosing (Day 8) time profiles of IPA to 20 µM ADP for clopidogrel (600-mg LD/75-mg MD) and prasugrel (60-mg LD/10-mg MD), without and with ranitidine (150 mg BID).**

7.4.3. Effect of Concomitant PPI use on the Pharmacodynamics of Prasugrel and Clopidogrel in Patients Undergoing Elective PCI

The PRINCIPLE-TIMI 44 Study (described in Section 5) assessed the PD response (MPA and IPA) following a 60-mg prasugrel LD or a 600-mg clopidogrel LD in patients undergoing elective cardiac catheterization with coronary stenting. A post-hoc analysis was conducted to assess the affect of concomitant administration of a PPI on the PD response to the loading dose.

Thirty minutes following the prasugrel loading dose, MPA was significantly higher in patients on a PPI compared to those not on a PPI (p=0.002; Figure 7.10). MPA was similar at 2 and 18 hours following the loading dose. At 6 hours post dose, MPA was higher in patients on a PPI, although the level of MPA was low. Consistent with the effect on MPA, there was a higher percentage of prasugrel-treated patients on a PPI who were classified as non-responders 30 minutes post loading dose (Table 7.11).



Source: lbl002_anbioj11_by_ppi.rtf.

Figure 7.10. Mean MPA (%) responses following 60 mg Prasugrel or 600 mg Clopidogrel with and without PPI.

Thirty minutes following the clopidogrel loading dose, MPA was unchanged compared to baseline in patients who were and were not on a PPI (Figure 7.10). At 2 and 6 hours following the loading dose, MPA was higher in patients taking a PPI compared to those not taking a PPI (p=0.003 and p=0.042, respectively). From 2 hours through 18 hours, a higher percentage of patients taking a PPI were classified as nonresponders (Table 7.11).

Table 7.11. Hyporesponsiveness following administration of 60 mg prasugrel LD and 600 mg clopidogrel LD alone or with a PPI – Study TABL

	Clopidogrel 600 mg LD						Prasugrel 60 mg LD					
	PPI non-use			PPI use			PPI non-use			PPI use		
	N	# poor responder	%	N	# poor responder	%	N	# poor responder	%	N	# poor responder	%
30 min	55	48	0.873	18	16	0.889	53	19	0.358	17	11	0.647
2 hr	59	28	0.475	19	15	0.789	55	0	0.000	19	2	0.105
6 hr	58	10	0.172	19	11	0.579	54	0	0.000	18	0	0.000
18-24 hr	36	9	0.250	10	5	0.500	31	0	0.000	8	0	0.000

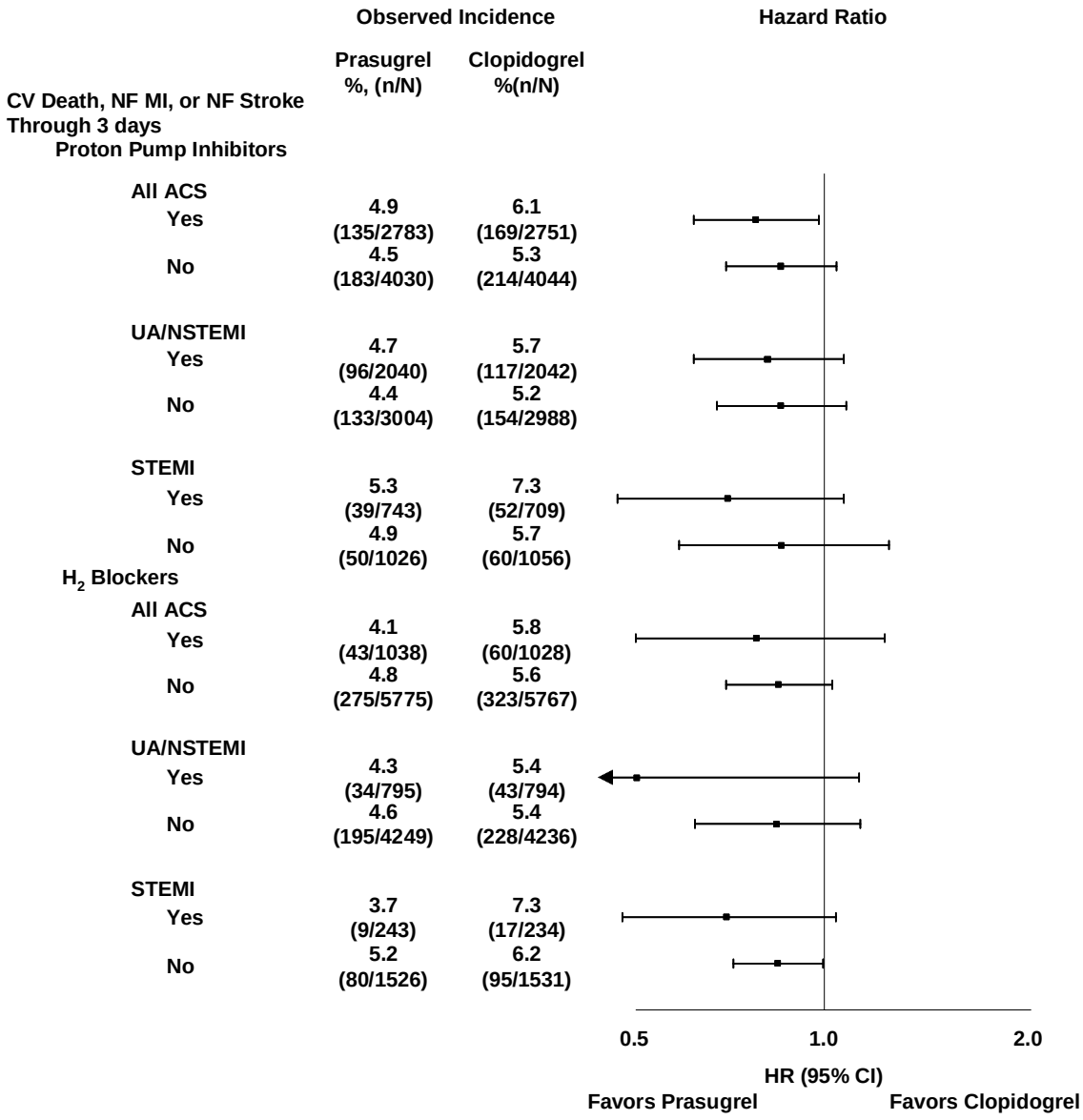
Source: lbl002_anbioj11_by_ppi.rtf.

7.4.4. Effect of PPI and H_2-Blocker use in TRITON-TIMI 38

The effect of PPI and H_2-blocker use on efficacy and safety was evaluated in TRITON-TIMI 38. In this study, prasugrel was administered without regard to use of PPI or H_2-blockers. These analyses focused on outcomes associated with the 3-day period following the loading dose as concomitant administration of a PPI or H_2-blocker with

prasugrel affects only C_{max} and t_{max} (speed of onset of platelet inhibition) and not AUC (extent of platelet inhibition). This interaction would only be relevant with the loading dose, and not the maintenance dose.

Figure 7.11 shows the relative risk, stratified by PPI or H_2-blockers use, of reaching the primary composite endpoint through 3 days following the loading dose. The observed point estimate for the hazard ratio was lower (in favor of prasugrel) in patients being treated with either a PPI or H_2-blocker compared to patients receiving neither.



Source: Q3245.

Figure 7.11. Hazard ratio and 95% confidence interval for the primary composite endpoint through 3 days stratified by concomitant use of PPI or H_2 inhibitor, all ACS patients.

Table 7.12 shows the number and percentage of patients, stratified by use of PPI and/or H_2-blocker, experiencing a TIMI Major or Minor bleeding event through 3 days following the loading dose. The bleeding risk with prasugrel treatment was always higher than with clopidogrel, suggesting a more potent antiplatelet effect with or without a PPI or H_2-blocker.

Table 7.12. Number and Percentage of Patients with non-CABG related TIMI Major or TIMI Minor Bleeding Events Through 3 Days While At Risk
Subgroup Analysis by Proton Pump Inhibitor or H_2-blocker Use

Subgroup Variable	Patient Population	Ever Used	Prasugrel N	Prasugrel n	Prasugrel %	Clopidogrel N	Clopidogrel n	Clopidogrel %	HR (95% CI)
Proton Pump Inhibitors									
	UA/NSTEMI	Yes	2028	50	2.47	2021	33	1.63	1.518 (0.978, 2.356)
		No	2973	44	1.48	2959	35	1.18	1.255 (0.805, 1.956)
	STEMI	Yes	732	20	2.73	698	29	4.15	0.653 (0.370, 1.155)
		No	1008	24	2.38	1038	16	1.54	1.550 (0.823, 2.918)
	All ACS	Yes	2760	70	2.54	2719	62	2.28	1.108 (0.787, 1.559)
		No	3981	68	1.71	3997	51	1.28	1.347 (0.937, 1.936)
H_2-blockers									
	UA/NSTEMI	Yes	791	17	2.15	785	16	2.04	1.058 (0.534, 2.093)
		No	4210	77	1.83	4195	52	1.24	1.481 (1.042, 2.106)
	STEMI	Yes	236	13	5.51	232	9	3.88	1.423 (0.608, 3.329)
		No	1504	31	2.06	1504	36	2.39	0.860 (0.532, 1.391)
	All ACS	Yes	1027	30	2.92	1017	25	2.46	1.189 (0.699, 2.021)
		No	5714	108	1.89	5699	88	1.54	1.227 (0.926, 1.626)

Source: Q3485

7.4.5. Conclusions Regarding Interactions with Drugs that Elevate Gastric pH

Concomitant administration of a PPI or H_2-blocker with prasugrel reduces C_{max} and prolongs t_{max} of the active metabolite, but does not affect the AUC. The PD effect of this interaction is evident 30 minutes following the loading dose, but is no longer evident 1 to 2 hours post-dose. This interaction would not affect the maintenance dose. The Sponsor believes that this PK/PD interaction is of minimal clinical relevance. In TRITON-TIMI 38, the reduction in the primary endpoint through 3 days after the first dose of study drug with prasugrel was consistent for patients who were on PPI or H_2-blockers, as well as for those who were not on these medications.

7.5. Tablet Performance

7.5.1. Background

In patients with ACS undergoing PCI, rapid onset of platelet inhibition following ingestion of EFFIENT may be important in preventing cardiac ischemic events during the index hospitalization. Therefore, EFFIENT is formulated as an immediate-release tablet. During maintenance dosing, patients are at a steady state level of platelet inhibition and the rate of incremental increase in platelet inhibition following each maintenance dose is of minor importance (Refer to Section 5.3).

Performance of an immediate-release tablet depends on rapid disintegration of the tablet, dissolution of the active pharmaceutical ingredient (API) and dissociation of dissolved API into neutral and charged species (for chemical compounds that are ionizable, including prasugrel). Immediate release tablets frequently contain excipients that promote tablet disintegration.

Prasugrel HCl is the API used in the manufacture of EFFIENT tablets. The tablets are formulated with excipients. During tablet manufacture and storage, a partial conversion of prasugrel hydrochloride to the base occurs. This conversion results from the HCl moiety migrating away from prasugrel hydrochloride toward the excipients, leaving behind the prasugrel base. As a result, EFFIENT tablets contain both prasugrel hydrochloride and prasugrel base, the amount of base determined by manufacturing and storage conditions.

Separation of HCl from prasugrel hydrochloride does not affect the absolute amount, stability, or potency of prasugrel within each tablet. In vitro tablet performance is unaffected. The finding that EFFIENT tablets contained both prasugrel hydrochloride and prasugrel base was detected after the start of TRITON-TIMI 38 utilizing advanced characterization techniques to gain further depth of understanding of the tablet performance. These experiments using the advanced technologies were beyond what was required by regulations governing the manufacturing and release of clinical trial material.

7.5.2. Tablet Performance and Bioavailability

Dissociation of HCl from prasugrel hydrochloride during tablet manufacture and storage does not affect the rate of tablet disintegration. However, prasugrel hydrochloride has greater solubility than prasugrel base across the pH range 1-7, although the difference between the salt and base is minimal from pH 1-3. Prasugrel base under elevated gastric pH is less soluble than prasugrel HCl, which could affect the rate of dissolution, and thus absorption. Importantly, whether prasugrel is in the base or the salt form in the tablet, once dissolved the molecule is the same, with rapid absorption and metabolism leading to formation of the active metabolite and inhibition of platelet aggregation.

An effect of varying base content on tablet performance, if any, would be most evident with the 60-mg loading dose, when the amount of drug to be dissolved is highest. The

effect on the rate of absorption due to the difference in dissolution rate would also be clinically relevant only after the loading dose (Section 5.2). Therefore, studies assessing the influence of varying base content on prasugrel pharmacokinetics and pharmacodynamics were conducted with the 60-mg loading dose. The absence of a pharmacokinetic interaction observed in studies with the loading dose indicates that no interaction would be expected with the 10-mg maintenance dose.

7.5.2.1. Under Conditions of Normal Gastric pH

At normal gastric pH (1-3), both prasugrel hydrochloride and prasugrel base dissolve rapidly and therefore, there would be no expected difference in the rate and extent of absorption between tablets of varying salt and base content. As such, prasugrel tablets with a wide range of prasugrel base content should be bioequivalent as assessed by the rate of absorption (as reflected by C_{max} and t_{max} of prasugrel's active metabolite [Pras AM]) and the extent of absorption (AUC of Pras AM).

Clinical pharmacology Study TACR was conducted in healthy subjects (n=84) not taking concomitant medications (Table 7.13). The study demonstrated that prasugrel tablets with a prasugrel base content of 5% (i.e., 95% prasugrel HCl) were bioequivalent to tablets with base contents of 58% (i.e., 42% prasugrel hydrochloride) or 70% (i.e., 30% prasugrel hydrochloride). Therefore, for patients not taking a PPI (or H_2-blocker), higher percentages of base content in EFFIENT tablets will not have a clinically relevant effect on the rate or extent of platelet inhibition following either the loading dose or maintenance dose.

Table 7.13. Statistical Comparison of Relative Bioavailability of 60-mg Prasugrel for Tablets Containing 5%, 58% or 70% Prasugrel Base – Study TACR

	Geometric LS Means			Ratio of geometric LS Means		
Parameters (Units)	60-mg prasugrel L-C	60-mg prasugrel M-C	60-mg prasugrel H-C	M-C/L-C	H-C/L-C	H-C/M-C
AUC(0-t_{last}) (ng.h/mL)	532 (505, 560)	522 (495, 550)	521 (494, 549)	0.98 (0.95, 1.01)	0.98 (0.95, 1.01)	1.00 (0.97, 1.03)
C_{max} (ng/mL)	476 (439, 516)	432 (399, 469)	422 (390, 458)	0.91 (0.84, 0.98)	0.89 (0.82, 0.96)	0.98 (0.90, 1.06)
	Medians			Median difference (approximate 90% CI [p-value]		
	60-mg prasugrel L-C	60-mg prasugrel M-C	60-mg prasugrel H-C	M-C - L-C	H-C -L-C	H-C - M-C
t_{max} (h)	0.50	0.55	0.75	0 (0,0) [0.091]	0 (0, 0.25) [0.043]	0 (0,0) [0.693]

Abbreviations: H-C = high base content; M-C = medium base content; L-C = low base content.
Source: Table APP.2.7.1.24, Table TACR.7.3

7.5.2.2. Under Conditions of Elevated Gastric pH

As the pH of the aqueous environment increases, the solubility of both prasugrel hydrochloride and prasugrel base decrease, however, the solubility of the salt exceeds that of the base. Under clinical conditions associated with elevated gastric pH (e.g., with use of a PPI or H_2-blocker), prasugrel tablets with higher base content could be associated with a lower C_{max} of the Pras AM and a delayed onset of platelet inhibition compared to tablets with a higher salt content. The AUC of Pras AM should be less affected or unaffected. As discussed in Section 5, the extent of platelet inhibition relates to AUC. Therefore, there should not be any difference in the extent of inhibition of platelet aggregation between prasugrel tablets of varying base content when co-administered with a PPI.

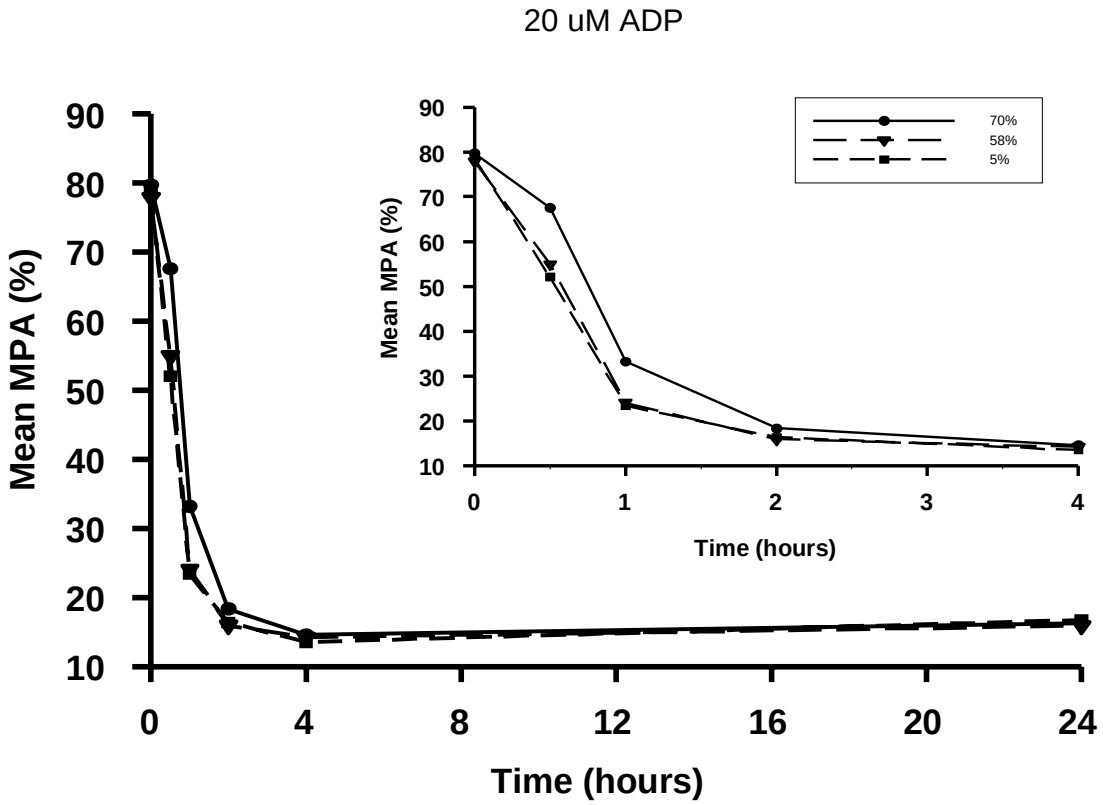
Study TACS was conducted in healthy subjects (n=42) taking the PPI lansoprazole. The study demonstrated that prasugrel tablets with prasugrel base contents of 5%, 58% or 70% were bioequivalent as assessed by AUC of Pras AM (Table 7.14). Consistent with this finding, there was no difference in the extent of platelet inhibition associated with varying salt/base content (Figure 7.12).

Table 7.14. Statistical Comparison of Relative Bioavailability of 60-mg Prasugrel for Tablets Containing 5%, 58%, or 70% Prasugrel Base with Co-administration of 30-mg Lansoprazole Daily – Study TACS

Parameters (Units)	Geometric LS Means			Ratio of geometric LS Means		
	60-mg prasugrel L-C	60-mg prasugrel M-C	60-mg prasugrel H-C	M-C/L-C	H-C/L-C	H-C/M-C
AUC(0-t_{last}) (ng.h/mL)	470 (424, 522)	467 (421, 518)	409 (368, 454)	0.99 (0.93, 1.06)	0.87 (0.82, 0.93)	0.88 (0.82, 0.93)
C_{max} (ng/mL)	331 (285, 384)	297 (257, 344)	236 (204, 274)	0.90 (0.77, 1.04)	0.71 (0.62, 0.83)	0.80 (0.69, 0.92)
	Medians			Median difference (approximate 90% CI [p-value]		
	60-mg prasugrel L-C	60-mg prasugrel M-C	60-mg prasugrel H-C	M-C - L-C	H-C -L-C	H-C - M-C
t_{max} (h)	0.75	0.75	1	0 (0, 0.25) [0.181]	0.13 (0, 0.5) [0.035]	0 (0, 0.25) [0.467]

Abbreviations: H-C = high base content; M-C = medium base content; L-C = low base content.
Source: Table APP.2.7.1.25, Table TACS.7.3

However, the observed C_{max} was 29% and 20% lower for prasugrel tablets with a base content of 70% compared to those tablets with base contents of 5% and 58%, respectively. The C_{max} was bioequivalent between the 5 and 58% base tablets based on prospectively defined equivalence regions. Consistent with this decline in C_{max}, the level of platelet inhibition was lower 30 minutes after the loading dose containing 70% base compared to the same dose of prasugrel containing either 5% base or 58% base (Figure 7.12). The differences in MPA between the 5% base and 70% base tablets and between the 58% base and 70% base tablets at 1 hour were still statistically significant, but no longer exceeded 10 percentage points, and by 2 hours, MPA were comparable among all the tablets. Therefore, for patients taking a PPI, higher percentages of base content in EFFIENT tablets may slow the rate of platelet inhibition following the loading dose but will not have a clinically relevant effect on the extent of platelet inhibition following either the loading dose or maintenance dose.



Source: Data from study TABS.

Figure 7.12. **Mean (SD) MPA to 20 μM ADP following a 60-mg dose of prasugrel containing low, intermediate, or high prasugrel base content, on a background of 30-mg lansoprazole once-daily.**

7.5.3. Effect of Tablet Performance on Efficacy and Safety in TRITON-TIMI 38

There were 13 prasugrel tablet lots used in TRITON-TIMI 38. Tablet analysis indicated that the base content of these tablets ranged from 42% to 87%. Efficacy and safety analyses focused on outcomes associated with the loading dose (i.e., outcomes through 3 days from first dose of study drug). Table 7.15 lists efficacy outcomes through 3 days after the first dose of study drug for the eight prasugrel tablet lots used in TRITON-TIMI 38. Only lots used to treat 100 or more patients were included in the analysis.

As reviewed in Section 7.4, the primary efficacy endpoint (risk of CV death/nonfatal MI/nonfatal stroke) assessed at 3 days following the LD always favored prasugrel, with and without concomitant treatment with PPI or H_2-blocker. These data do not indicate a diminished treatment effect in patients administered prasugrel with or without a PPI or H_2-blocker.

Table 7.15. Efficacy within 3 Days of Loading Dose, by Lot, in All ACS Patients

Subgroup Variable	Subgroup Value	Prasugrel			Clopidogrel			HR (95% CI)
		N	n	%	N	n	%	
Loading Dose Lot Number								
	CT515276	1277	54	4.23	1287	63	4.90	0.862 (0.599, 1.240)
	CT515306	1053	48	4.56	1071	76	7.10	0.639 (0.445, 0.917)
	CT520377	642	36	5.61	624	38	6.09	0.911 (0.577, 1.436)
	CT520423	1627	77	4.73	1611	80	4.97	0.953 (0.697, 1.303)
	CT521920	981	43	4.38	997	58	5.82	0.747 (0.503, 1.108)
	CT523864	519	27	5.20	535	42	7.85	0.654 (0.403, 1.061)
	CT524615	112	3	2.68	114	4	3.51	(,)
	CT525671	398	16	4.02	367	16	4.36	0.929 (0.464, 1.857)

Source: Q3235

7.5.4. Proposed Marketed Formulation and Labeling

Based on the understanding of factors that impact the base content, the Sponsor has implemented a manufacturing control strategy that has demonstrated that tablets are produced with a limited prasugrel base content. The proposed commercial tablets consistently meet all of the critical quality attributes such that delivery of a safe and efficacious drug to the patients is assured through the shelf life of the product.

The manufacturing control strategy will ensure that the proposed commercial tablets will maintain a level of prasugrel hydrochloride that minimizes any potential interaction when the loading dose is co-administered with a PPI or an H_2-blocker. Co-administration of a PPI with the maintenance dose is acceptable as there is no affect on the AUC of prasugrel's active metabolite or on the extent of platelet inhibition regardless of the level of base content of the EFFIENT tablet.

8. Dose Adjustment

8.1. Regulatory History

Prior to the start of TRITON-TIMI 38, the Sponsor and the FDA discussed whether a single maintenance dose would be appropriate for all patients. The FDA strongly recommended inclusion of a population pharmacokinetic substudy in TRITON-TIMI 38. The FDA also recommended manufacture of a lower strength tablet to be available at the time of approval (assuming the safety and efficacy of prasugrel were established in TRITON-TIMI 38).

The Sponsor implemented this substudy and PK samples were collected from a subset (1159) of patients to explore the relationship between patient characteristics and estimated exposure to the prasugrel active metabolite. Additional analyses explored the relationship between exposure and clinical outcomes (both safety and efficacy).

Based on FDA guidance and the results of the substudy analyses, the Sponsor's application includes the consideration of a 5-mg prasugrel MD for patients <60 kg or ≥75 years of age. These patients had high exposure to 10-mg prasugrel MD and an increased risk for bleeding during TRITON-TIMI 38.

8.2. Rationale for Dose Adjustment

Results from clinical study modelling and simulation have been used previously to support modified dosing regimens to maintain efficacy and reduce risk in special populations (CDER 1999).

In discussions with the Sponsor, the FDA stated that it was possible to make dosing adjustments for prasugrel based on exposure data alone. The FDA informed the Sponsor that when a specific dose is not studied during an efficacy trial, dose adjustment for special populations (e.g., renal or hepatic impairment, elderly, or low weight) can be based on PK data alone, provided the exposure to the lower dose in the special population is comparable to the exposure to the higher dose in the general population.

The Sponsor's rationale for recommending dose adjustment in any subgroup was based on the following:

- The subgroup of interest has higher exposure to prasugrel active metabolite compared to the general population.
- The higher exposure within the subgroup was associated with a higher risk of non-CABG related TIMI Major, or TIMI Major or Minor bleeding.
- A reduction in dose for the subgroup would maintain exposure within the range observed in the general population and would be expected to decrease the risk of bleeding.

- A reduction in dose for the subgroup would be expected to maintain efficacy.

8.3. Influence of Patient Characteristics on Exposure to the Prasugrel Active Metabolite

Population-based methods were applied to active metabolite concentration data obtained from the TRITON-TIMI 38 PK substudy. The potential influence of body weight, age, sex, body mass index, serum creatinine, tobacco use, diabetes status, prior TIA/stroke, history of atrial fibrillation, history of peripheral arterial disease (PAD), and history of peptic ulcer disease on Bayesian estimates of prasugrel active metabolite exposures were assessed.

Only the effect of body weight, age, and sex statistically significantly influenced AUC and were retained in the final statistic multivariate model based on the predefined criteria (α=0.05). There was no statistically significant influence of any other evaluated patient characteristic.

Body weight was the most statistically significant ($p<0.0001$) patient characteristic influencing exposure to the prasugrel active metabolite. Analyses stratified by body weight indicated that prasugrel's active metabolite exposure in patients weighing <60 kg was 42% higher (90% CI: 27% to 58%) than those weighing ≥85 kg (approximate median weight in TRITON).

Age was also found to statistically significantly influence exporsure to the prasugrel active metabolite ($p=0.0006$). Analyses stratified by discrete age groups indicated that prasugrel active metabolite exposure for the patients ≥75 years of age was 25% higher (90% CI: 16% to 34%) compared to patients <60 years of age, which was the approximate median age in TRITON-TIMI 38.

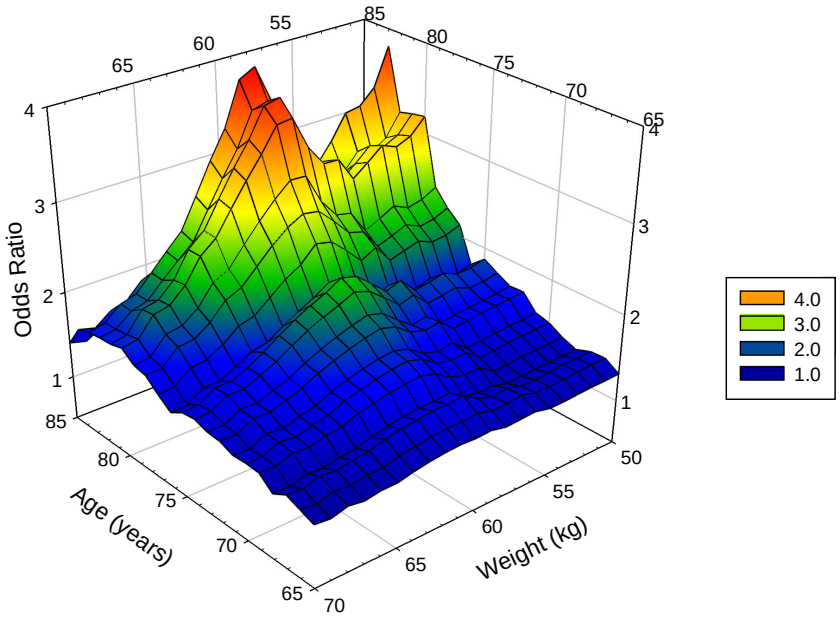
Although sex was retained in the model ($p=0.0282$), its influence on exposure after adjusting for the effects of weight and age was relatively small (with females having <8% higher exposure than males).

8.4. Risk of Bleeding in Patients <60 kg or ≥75 Years of Age

In the main TRITON-TIMI 38 study, univariate and multivariable subgroup analyses indicated that patients with low body weight and advanced age were at increased risk for non-CABG-related TIMI Major bleeding after 3 days from the first dose of prasugrel. To further characterize this risk, a classification and regression tree (CART) analysis was used to identify weight and age cutoffs which defined increased risk of bleeding. Figure 8.1a, Figure 8.1b, and Figure 8.1c show the odds ratio for the risk of non-CABG related TIMI Major bleeding, non-CABG related TIMI Life-Threatening bleeding, and non-CABG related TIMI Major or Minor bleeding, respectively, in high risk patients (weight

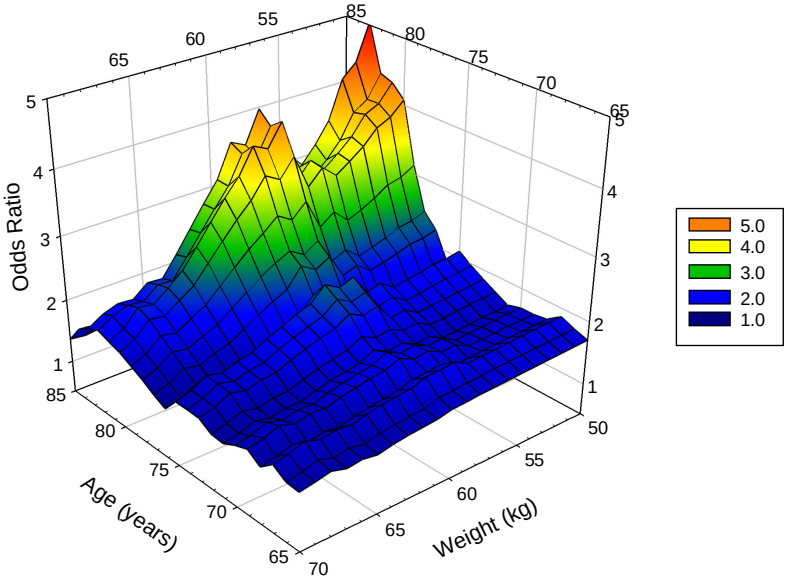
<x-value or age ≥y-value) relative to low risk patients (weight ≥x-value and age <y-value) in the prasugrel treatment group.

The CART analysis identified cut-off values of <60 kg and ≥80 years of age for increased risk of non-CABG related TIMI Major bleeding after 3 days. However, due to the regulatory classification of the very elderly as age ≥75 years, the prospective subgroup definition of age ≥75 years was utilized. The patients at highest risk are those who are at both the extremes of low weight and advanced age.



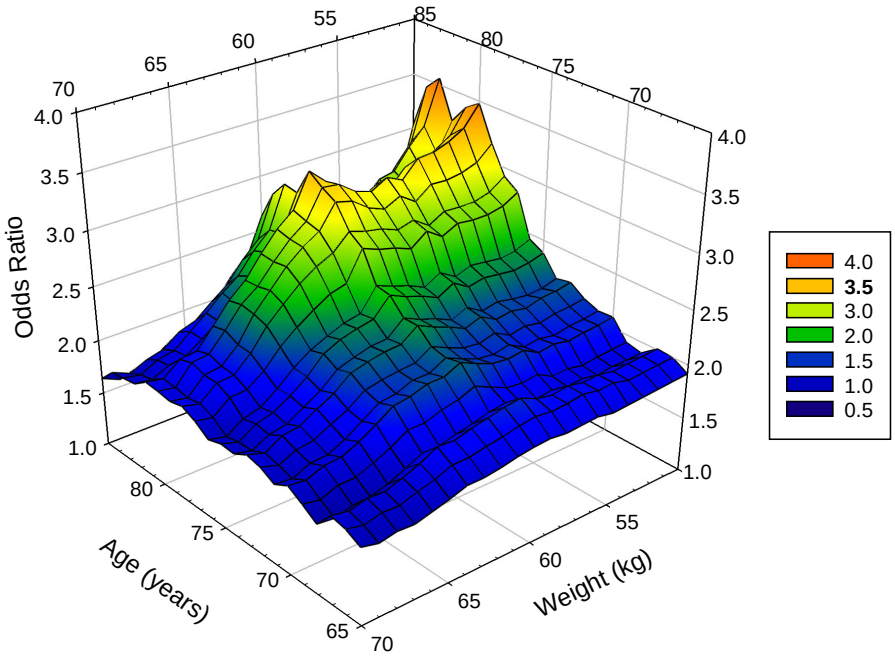
Source: l0504_ghsafl11_cutoff.rtf.

Figure 8.1a. **Odds Ratio for non-CABG-related TIMI Major bleeding with 10-mg Prasugrel MD after 3 days by decreasing weight (x-axis) and increasing age (y-axis).**



Source: l0504_ghsafl11_cutoff.rtf.

Figure 8.1b. **Odds Ratio for non-CABG-related TIMI Major Life-Threatening bleeding with 10-mg Prasugrel MD after 3 days by decreasing weight (x-axis) and increasing age (y-axis).**



Source: l0504_ghsafl11_cutoff.rtf.

Figure 8.1c. **Odds Ratio for non-CABG-related TIMI Major or Minor bleeding with 10-mg Prasugrel MD after 3 days by decreasing weight (x-axis) and increasing age (y-axis).**

8.5. Relationship between Exposure and Non-CABG Related TIMI Bleeding

The relationship between exposure to the prasugrel active metabolite and the risk of non-CABG related TIMI Major, and Major or Minor bleeding was analyzed through 3 days from the first dose of study drug and after 3 days from the first dose of study drug to assess the effect of loading dose and maintenance dose, respectively (Table 8.1). Quartiles of exposure, based on the AUC of the active metabolite, were constructed using data from all patients in the substudy. The incidence of non-CABG related TIMI Major, and Major or Minor bleeding through 3 days was also not related to exposure. After 3 days, there was a higher incidence of non-CABG related TIMI Major, and Major or Minor bleeding in the third and fourth exposure quartiles.

Table 8.1. Summary of Bleeding Events by Prasugrel Active Metabolite Exposure Quartile

	Number of Patients with Non-CABG-Related TIMI Major Bleeding				
	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	p-value[a]
Through 3 days	3 (1.03)	3 (1.03)	2 (0.69)	2 (0.69)	0.574
From 3 days	0	1 (0.34)	6 (2.08)	7 (2.42)	0.002

	Number of Patients with Non-CABG-Related TIMI Major or Minor Bleeding				
	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	p-value[a]
Through 3 days	4 (1.38)	7 (2.41)	4 (1.38)	8 (2.77)	0.391
From 3 days	1 (0.34)	3 (1.03)	10 (3.47)	8 (2.77)	0.007

[a] The two sided p-value is based on the Cochran-Armitage trend test across the 4 quartiles.

Source: Q3525 and Q3535

8.5.1. Relationship between Exposure to 10 mg Prasugrel and Bleeding in Patients <60 kg

The Sponsor performed analyses to determine if the increased risk of bleeding in patients <60 kg was related to increased exposure. The analysis was conducted by first assessing the risk of non-CABG related TIMI Major or Minor bleeding by quartiles of exposure to prasugrel's active metabolite utilizing only data from patients ≥60 kg (Table 8.2). As was observed in the overall population, increasing exposure to the active metabolite was associated with an increased risk of TIMI Major or Minor bleeding in patients ≥60 kg. Patients <60 kg were then assigned to theses quartiles. The majority of the patients <60 kg (27 of 47 patients) had levels of exposure to prasugrel's active metabolite in the fourth quartile. The only bleeding events in patients <60 kg occurred in those with exposure levels in the fourth quartile. These data indicate that patients <60 kg have higher exposure to prasugrel's active metabolite compared to the general population and that this higher exposure is associated with an increased risk of non-CABG related TIMI Major or Minor bleeding.

Table 8.2. Summary of Non-CABG-Related TIMI Major or Minor Bleeding Events After 3 Days by Quartiles of Estimated Exposure to 10 mg Prasugrel in Patients ≥60 kg

Exposure Quartile[a]	Range of AUC (ng•hr/mL)[a]	Weight					
		≥ 60 kg			< 60 kg		
		N	n	%	N	n	%
1st	23.9 < AUC ≤ 62.1	276	1	0.36	9	0	0.0
2nd	62.1 < AUC ≤ 79.2	276	2	0.72	4	0	0.0
3rd	79.2 < AUC ≤ 102.3	276	11	3.99	7	0	0.0
4th	102.3 < AUC ≤ 1991.6	276	4	1.45	27	4	14.81

[a] Exposure quartiles based on patients ≥60 kg treated with prasugrel in TRITON-TIMI 38 population PK sample.

Source: 10471_fqsafj12_auc.rtf.

8.5.2. Relationship between Exposure to 10 mg Prasugrel and Bleeding in Patients ≥75 years of Age

The Sponsor performed analyses to determine if the increased risk of bleeding in patients ≥75 years was related to increased exposure. The analysis was conducted by first assessing the risk of non-CABG related TIMI Major or Minor bleeding by quartiles of exposure to prasugrel's active metabolite utilizing only data from patients <75 years of age (Table 8.3). As was observed in the overall population, increasing exposure to the active metabolite was associated with an increased risk of TIMI Major or Minor bleeding in patients <75 years. Patients ≥75 years of age were then assigned to theses quartiles. The majority (80/110) of patients ≥75 years of age had levels of exposure in the third and fourth quartiles. Ten of the 11 bleeding events in patients ≥75 years of age occurred in patients with exposure levels in the third and fourth quartiles. In the third and fourth quartiles of exposure, patients age ≥75 years had a higher rate of bleeding, compared with patients <75 years of age, whereas in the first two exposure quartiles, the rate of bleeding was similar in the two age groups. These data indicate that patients ≥75 years of age have higher exposure to prasugrel's active metabolite compared to the general population and that this higher exposure is associated with an increased risk of non-CABG related TIMI Major or Minor bleeding.

Table 8.3. Summary of Non-CABG-Related TIMI Major or Minor Bleeding Events After 3 Days by Quartiles of Estimated 10 mg Prasugrel Exposure in Patients <75 years of Age

Exposure Quartile	Range of AUC (ng•hr/mL)[a]	Age					
		<75 years			≥75 years		
		N	n	%	N	n	%
1st	23.9 < AUC ≤ 61.7	259	1	0.39	15	0	0.0
2nd	61.7 < AUC ≤ 78.7	259	1	0.39	25	1	4.00
3rd	78.7 < AUC ≤ 102.3	258	5	1.94	35	6	17.14
4th	102.3 < AUC ≤ 1991.6	260	4	1.54	45	4	8.89

[a] Exposure quartiles based on patients <75 years treated with prasugrel in TRITON-TIMI 38 population PK sample.

Abbreviations: AUC = area under the plasma concentration-time curve; N = number of patients in exposure quartile.

Source: 10471_fqsafj12_auc.rtf.

8.6. Relationship between Exposure to Prasugrel's Active Metabolite and Efficacy Outcomes

The relationship between exposure to the prasugrel active metabolite and efficacy outcomes was analyzed through 3 days from the first dose of study drug and after 3 days from the first dose of study drug to assess the effect of loading dose and maintenance dose, respectively (Table 8.4). Quartiles of exposure, based on the AUC of the active metabolite, were constructed using data from all patients in the substudy. The incidence of the primary endpoint was not related to exposure either through 3 days or after 3 days from the first dose of study drug.

Table 8.4. Summary of Efficacy and Bleeding Events during MD by Prasugrel Active Metabolite Exposure Quartile

Number of Patients who Met Primary Efficacy Outcome of CV Death, Nonfatal MI or Nonfatal Stroke					
	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	p-value[a]
Through 3 days	10 (3.45)	7 (2.41)	9 (3.11)	15 (5.19)	0.222
From 3 days	12 (4.14)	10 (3.45)	11 (3.82)	18 (6.23)	0.218

[a] The two sided p-value is based on the Cochran-Armitage trend test across the 4 quartiles.

Source: Q3525 and Q3535.

8.7. 5-mg Prasugrel MD in Patients <60 kg or ≥75 years of Age

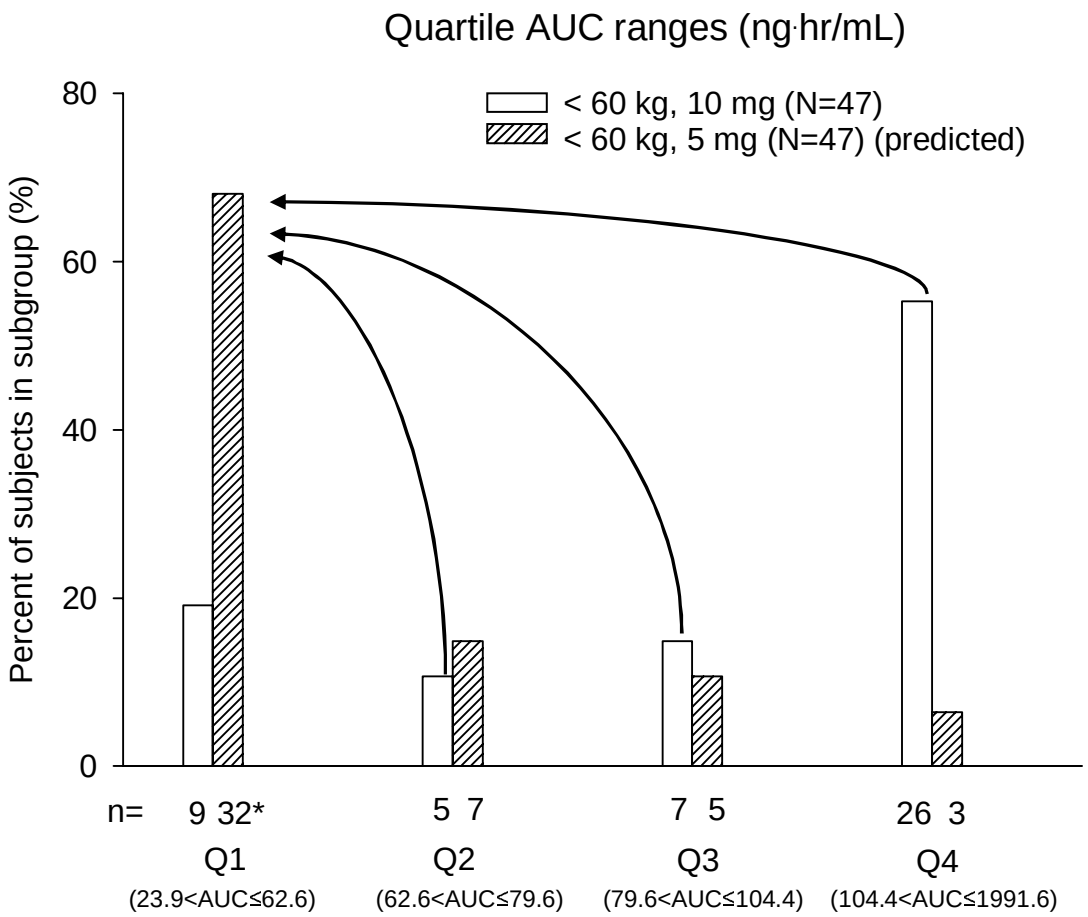
Following the previously mentioned FDA guidance that dose adjustment for special populations can be based on PK data alone provided exposure to the lower dose in the special population is comparable to exposure to the higher dose in the general population, an acceptable lower prasugrel MD in patients <60 kg, or ≥75 years of age should result in

exposure that is comparable to that of 10-mg prasugrel MD in the general population. In the general population, prasugrel active metabolite exposure in the first quartile was associated with decreased bleeding, without evidence of decreased efficacy. Therefore, a dose reduction that results in exposure levels within the first quartile in patients <60 kg or ≥75 years of age would also be expected to reduce bleeding and maintain efficacy.

Prasugrel's active metabolite exposure has been shown to be proportional to dose within the range of exposure observed during maintenance dosing (Payne et al. 2007). This relationship predicts that for any level of exposure observed with a 10-mg dose, exposure with a 5-mg dose would be 50% less. Therefore, analyses were performed to assess the predicted level of exposure to a 5-mg prasugrel MD in patients <60 kg or ≥75 years of age.

8.7.1. Predicted Exposure to 5 mg Prasugrel in Patients <60kg or ≥75 years of age

Figure 8.2 shows quartiles of exposure to the prasugrel 10-mg MD, constructed using data from all patients in the substudy, and the percentage of patients <60 kg within each quartile. Following dose reduction to 5 mg, patients <60 kg would be predicted to shift from the 4th quartile to the 1st quartile of exposure. Figure 8.3 shows the same data for patients ≥75 years of age. Following dose reduction to 5 mg, patients ≥75years of age would be predicted to shift from the 3rd and 4th quartiles to the 1st quartile of exposure. Over 95% of patients in each of these subgroups would maintain exposure above the lower limit of the first exposure quartile following 10 mg prasugrel in the general population. As noted above, this is a range that is associated with increased safety and preservation of efficacy in patients treated with prasugrel.



*two subjects are below lower end of Q1
percentages are based on number of subjects in respective subgroup

Abbreviations: N = number of patients in subgroup; Q = exposure quartile.
Exposure quartiles based on all patients in TRITON-TIMI 38 substudy.
Source: Figure APP.2.7.2.54 and Figure APP.2.7.2.55.

Figure 8.2. **Distribution of patients in weight groups by AUC quartiles – TRITON-TIMI 38.**

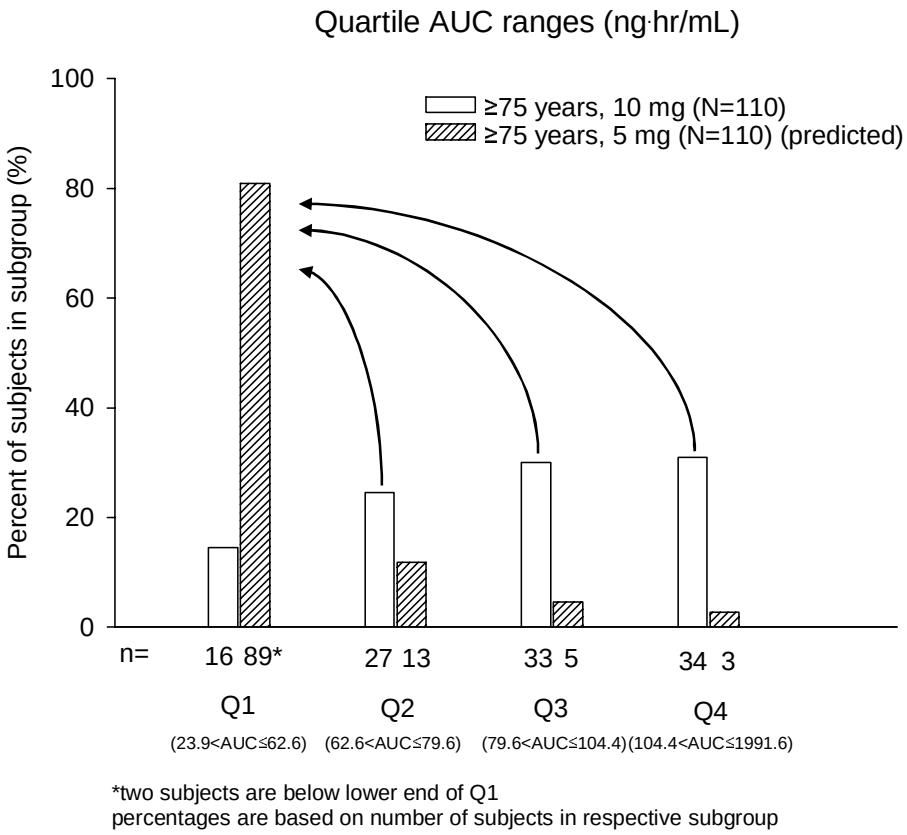


Figure 8.3. **Distribution of patients ≥60 kg in age groups by AUC quartiles – TRITON-TIMI 38.**

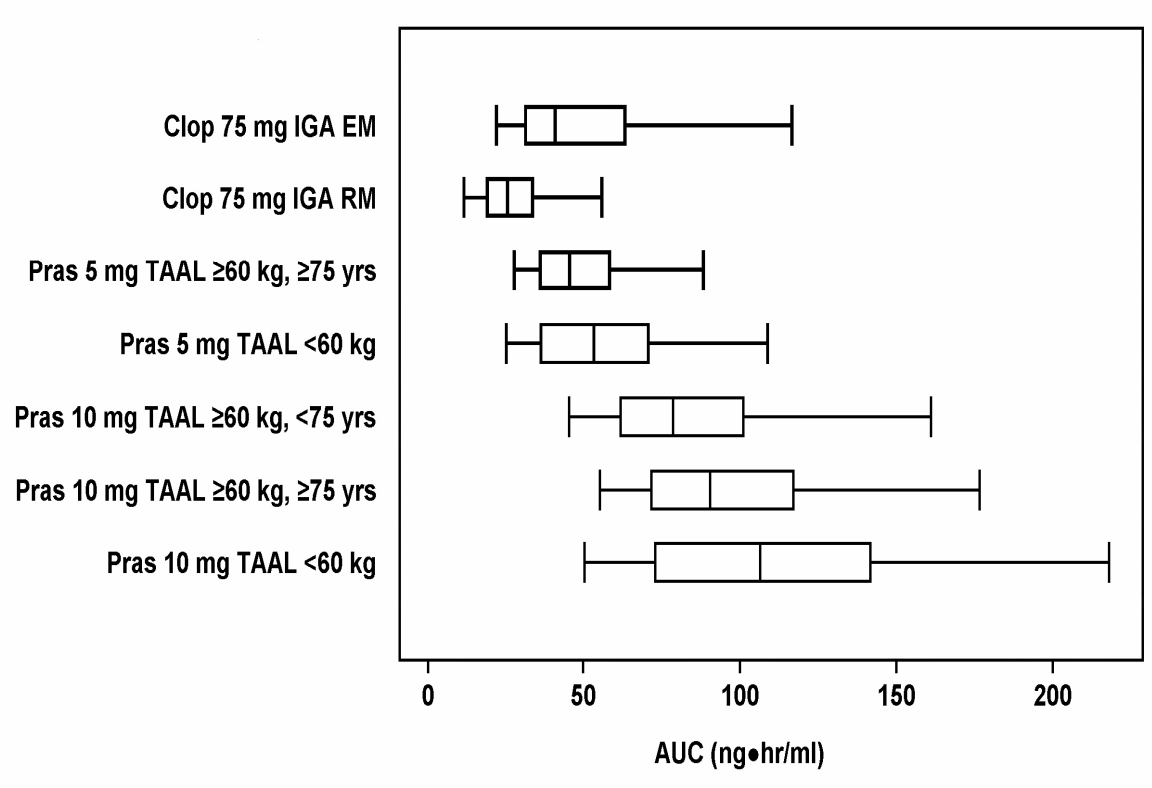
8.7.2. Comparison of 5-mg Prasugrel MD in Patients <60 kg or ≥75 Years of Age to 75 mg Clopidogrel in CYP2C19 Extensive Metabolizers

Clopidogrel is effective in reducing the risk of CV death, nonfatal MI or nonfatal stroke in patients with ACS. Common variants in the gene encoding CYP2C19 have been shown to contribute to diminished exposure to clopidogrel's active metabolite, a corresponding diminished platelet response (Section 7.3, Mega et al. 2008, Brandt et al. 2007), and increased ischemic events (Collet al. 2008, Mega et al. 2008, Simon et al. 2008). Individuals classified as CYP2C19 extensive metabolizers (EMs) have higher exposure to the clopidogrel active metabolite and better clinical efficacy outcomes than reduced metabolizers (RMs).

Therefore, maintaining a prasugrel active metabolite exposure level equal to or higher than that observed in extensive metabolizers of clopidogrel should maintain efficacy.

Direct comparison of exposures of the active metabolites of clopidogrel and prasugrel can be made because the mechanisms of action are identical, the potencies of the active metabolites at the $P2Y_{12}$ receptor are comparable, and the molecular weights differ by only 2%.

Figure 8.4 shows observed exposure to 75-mg clopidogrel in CYP2C19 EMs and CYP2C19 RMs, observed exposure to 10 mg prasugrel by different age and weight cutoffs, and predicted exposure to 5 mg prasugrel in patients <60 kg or ≥75 years of age. Exposure to 75 mg clopidogrel in most CYP2C19 EMs fell within the range of the first exposure quartile following 10-mg prasugrel in the general population (23.9 ng/mL*hr to 62.6 ng/mL*hr). After adjustment from a 10-mg prasugrel MD to a 5-mg prasugrel MD, patients <60 kg or ≥75 years of age would have exposure within the range of that seen with 75 mg clopidogrel in CYP2C19 EMs and higher than that seen with 75 mg clopidogrel in CYP2C19 RMs.

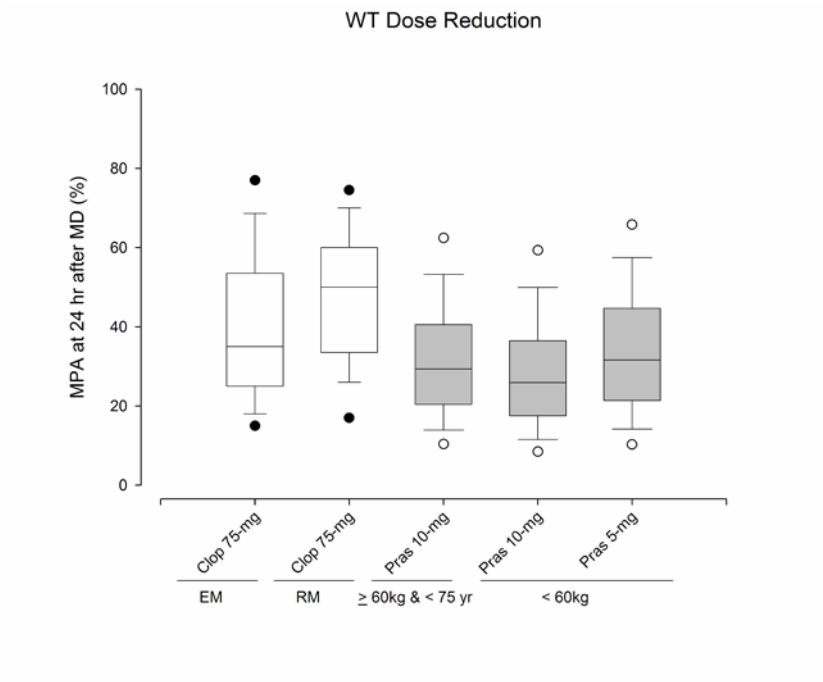


Whiskers represent 5th and 95h percentile; boxes represent 25th and 75th percentile; centre lines represent median; prasugrel data from the IGA and patients ≥60 kg and <75 years of age in TRITON-TIMI 38.
Source: \\spreeprd\genesis\SPREE\RMP\Clinical\Primary Care\CS747\Acute Coronary Syndrome\
Abbreviations: IGA = integrated genomics analysis.
Genomic\IGA\Programs\Analysis\RegResp_20080630.ssc

Figure 8.4. Comparison of exposure to 75 mg clopidogrel in EM and RM, to 10 mg prasugrel, and to 5 mg prasugrel in patients <60 kg or ≥75 years of age.

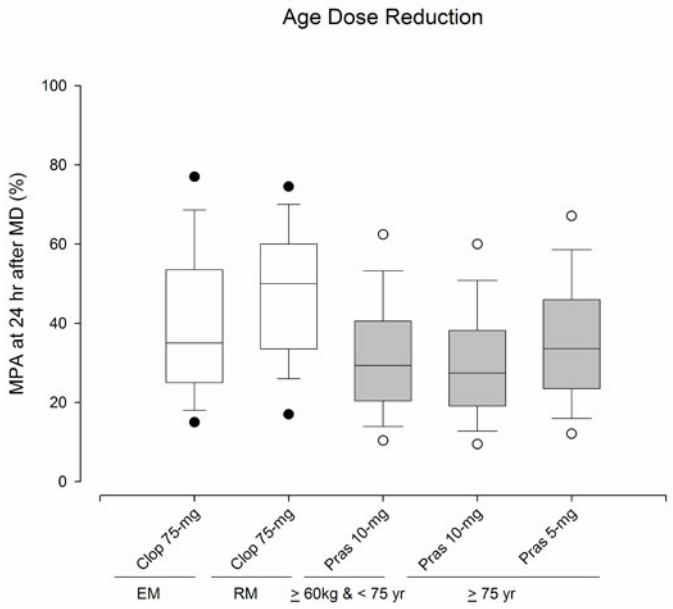
The Sponsor also performed comprehensive PK/PD modeling and simulation to predict the MPA response during 5-mg prasugrel MD in patients <60 kg or ≥75 years of age based on the previously established population PK/PD model of prasugrel and clopidogrel.

Figure 8.5 compares observed MPA following 75 mg clopidogrel in CYPC219 EMs and in CYP 2C19 RMs, predicted MPA following 10 mg prasugrel in patients ≥60 kg and <75 years, and MPA following 10 mg prasugrel and 5 mg prasugrel in patients <60 kg in the TRITON-TIMI 38 population pharmacokinetic substudy. Figure 8.6 makes the same comparisons following 5-mg prasugrel in patients ≥75 years of age. The predicted PD response to 5-mg prasugrel MD in patients <60 kg or ≥75 years of age exceeds the response to 75 mg clopidogrel in CYP2C19 RMs and is comparable to the PD response to 75 mg clopidogrel in CYP2C19 EMs.



°represents 5th and 95th percentile; whisker represents 10th and 90th percentile; box represents 25th and 75th percentile; centre bar represents median. Prasugrel data are from the Study TAAL PK substudy. Clopidogrel data are from the integrated genomic analysis dataset.

Figure 8.5. **Predicted MPA in weight subgroups during 5 mg prasugrel, 10 mg prasugrel, and 75-mg clopidogrel MD.**



°represents 5th and 95th percentile; whisker represents 10th and 90th percentile; box represents 25th and 75th percentile; centre bar represents median. Prasugrel data are from the Study TAAL PK substudy. Clopidogrel data are from the integrated genomic analysis dataset.

Figure 8.6. **Predicted MPA in age subgroups during 5-mg prasugrel, 10 mg prasugrel, and 75 mg clopidogrel MD.**

8.8. Dose Adjustment Conclusions

In TRITON-TIMI 38 increased exposure to the prasugrel active metabolite was associated with increased bleeding during maintenance dosing. Patients <60 kg or ≥75 years of age had higher exposure to the active metabolite than patients ≥60 kg or <75 years of age, respectively. Patients <60 kg or ≥75 years of age also had an increased risk of bleeding associated with prasugrel. Within each of these subgroups, the increased bleeding risk was limited to patients with the highest exposure. A reduction of the prasugrel MD from 10-mg to 5-mg for patients <60 kg or ≥75 years of age would lower exposure in these patients to predominantly the first quartile of exposure following 10 mg in the general population, where efficacy was maintained and the bleeding risk was lower. In addition, this level of exposure is similar to that seen with 75 mg clopidogrel in CYP2C19 EMS and higher than that seen with CYP2C19 RMs.

9. Effient Post-marketing Risk Management

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

At the time of submission of this briefing document, the Sponsor awaits FDA Office of Safety Evaluation feedback on proposed risk management plan.

9.1. Introduction

Effient post-marketing risk management and pharmacovigilance activities consist of 3 main components:

- Risk Specification - describes the identified and potentials risks of prasugrel.
- 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 post-marketing risk management and pharmacovigilance activities also include a REMS program which consists of a Medication Guide (MedGuide) for patients.

9.1.1. Risk Specification

Identified risks (reported events established to be Adverse Drug Reactions) with treatment of prasugrel are all related to the pharmacology of platelet inhibition and bleeding:

- Intracranial hemorrhage
- Gastrointestinal hemorrhage
- Intraocular hemorrhage
- Anemia
- Epistaxis

When bleeding events are categorized by TIMI classification, CABG-related and Non-CABG-related TIMI bleeding are identified risks associated with prasugrel treatment. The bleeding risk is increased in patients with prior TIA/Stroke, patients <60 kg, and patients ≥75 years of age.

Potential risks that may have been reported in the class, but not established to be Adverse Drug Reactions for prasugrel will be monitored and evaluated.

9.2. Pharmacovigilance and Ongoing Evaluation of Safety Information

Pharmacovigilance activities for Effient will consist of the following:

- Routine surveillance – collection and evaluation of safety data from spontaneous post-marketing reports. These may be reported either directly to the company or to the company via regulatory agencies or other companies. In addition, reports may be identified through regular reviews of the literature. Additional safety surveillance activities will seek out safety signals (from clinical study data and spontaneous reports) using qualitative (e.g., medical review) and quantitative methods (e.g., data mining). These activities will be of particular value in detection of new signals.
- Active (additional) surveillance – Post-launch active surveillance activities (through periodic data mining of the Lilly Safety System (LSS) database and FDA's Adverse Event Reporting System (AERS) and by using appropriate large administrative claims databases or hospital in-patient electronic medical records databases), which will be valuable in determining rates of reports relative to other drugs, will include the following:
    - Estimation and monitoring of the incidence of bleeding events (including mortality) in ACS patients treated with prasugrel.
    - Identification and monitoring of subpopulations at risk for bleeding events in ACS patients treated with prasugrel, which have not been previously identified.
    - Estimation and monitoring of the incidence of other targeted surveillance events in ACS patients treated with prasugrel.
    - Identification of previously unknown risks in ACS patients treated with prasugrel.

Additional studies will allow the Sponsor to continue to monitor and evaluate prasugrel safety and to determine if further actions with respect to product labeling or risk communications are necessary. These studies include:

- Study TABY (TRILOGY-ACS) – TRILOGY-ACS is a clinical outcomes study in 10,500 patients with ACS treated medically (not undergoing PCI). Randomization is stratified by age, prior clopidogrel use, and country. The study will provide data on safety and efficacy of the 5-mg maintenance dose for:
    - patients ≥75 years of age.

- patients <60 kg.

Overall comprehensive safety data from this controlled clinical trial will be collected. The study has an external oncology working group to provide expert oversight on the data collection and analysis of neoplasm events.

- Enhanced Pharmacovigilance studies in Europe:
  - In-hospital registry to monitor prasugrel use and bleeding risk during the index hospitalization compared to clopidogrel in a real life EU clinical setting.
  - Off-Label Use in Patients Post-Discharge: To monitor the off-label use post-discharge in patients treated with prasugrel. The databases will capture data pertaining to drug utilization to monitor in what patients prasugrel is used, and at what doses.

9.3. Risk Minimization

The USPI and Medication Guide are the primary vehicles through which risks associated with EFFIENT will be communicated to health care practitioners and patients.

The US package insert (USPI) clearly communicates risks. It is primarily intended for health care professionals but is available to all. Proposed labeling contains clear language regarding the following:

- **Contraindication** in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.
- **Contraindication** in patients with a history of prior transient ischemic attack (TIA) or stroke in combination with aspirin.
- **Warning and Precaution** on the increased risk of bleeding.
- **Warning and Precaution** on increased risk of bleeding in patients:
  - ≥75 years of age
  - with body weight <60 kg
  - with a propensity to bleed
  - with concomitant administration of medications that may increase the risk of bleeding, including oral anticoagulants, chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), and fibrinolytics.
- **Warning and Precaution** for patients who are to undergo elective surgery where an antiplatelet effect is not desired to discontinue prasugrel at least 7 days prior to surgery. The benefits and risks of EFFIENT should be carefully considered in patients in whom the coronary anatomy has not been defined and urgent CABG is a possibility

- **Warning and Precaution** on the risk of discontinuing therapy. Thienopyridines should be discontinued only if necessary. The optimal duration of required thienopyridine therapy is unknown. In patients who are managed with PCI and stent placement, premature discontinuation of any antiplatelet medication, including thienopyridines, could result in an increased risk of stent thrombosis, myocardial infarction, or death. Patients who require premature discontinuation of a thienopyridine (e.g., because of active bleeding) should be monitored for cardiac events. At the discretion of the patient's treating physician, once the patient is stabilized, the thienopyridine should be restarted as soon as possible.
- **Warning and Precaution** that platelet transfusion may be appropriate to reverse the pharmacological effects of EFFIENT.
- **Warning and Precaution** on the risk of TTP. TTP has been reported with the use of other thienopyridines.
- **Dosing adjustments**: the 5-mg dose is available for patients with risk factors for an increased risk of bleeding (<60 kg and for patients ≥75 years of age).

The REMS consists of a MedGuide, which will be distributed to all patients each time a prescription is filled. The MedGuide provides user-friendly safety and prescribing information to patients in order to assist them in decision-making and prevent serious adverse effects.

The goal of the MedGuide as the REMS element is to provide patients with important information regarding risks associated with use of Effient. In particular, contraindications, increased risk of bleeding in sub-populations, and bleeding risk in all patients will be highlighted.

Although the USPI and MedGuide are the foundation of knowledge dissemination, they will not exist in isolation. As appropriate, these documents will be included in promotional and educational materials. Medical symposia and educational materials will include safety information on the serious effects of Effient as appropriate.

In addition to the USPI and the MedGuide, risk to patients will be mitigated by extensive training to health care professionals. Health care professionals will have many opportunities to be educated and trained on important risk information. Within the first year of launch these educational opportunities will include, but not be limited to the following: access to promotional sales representatives;, promotional educational programs led by trained speakers; a dedicated website for healthcare professionals; access to field based medical liaisons; and access to The Lilly Answers Center (TLAC), which will provide relevant information upon inquiry including non-promotional scientific letters, accompanied by peer reviewed articles.

In addition to the MedGuide that will be distributed with the prescription, there will be a dedicated website for patients. Patients will have access to TLAC for specific questions associated with the risks of Effient. In addition, patient education materials will be available for physicians to distribute to patients.

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