Published in final edited form as:
J Am Coll Cardiol. 2012 July 31; 60(5): 388–396. doi:10.1016/j.jacc.2012.03.030.

Mortality Benefit with Prasugrel in the TRITON-TIMI 38 Coronary Artery Bypass Grafting (CABG) Cohort: Risk-Adjusted Retrospective Data Analysis

Peter K Smith, MD[*], **Lawrence T Goodnough, MD**[†], **Jerrold H Levy, MD**[‡], **Robert S Poston, MD**[§], **Mary A Short, MSN**[‖], **Govinda J Weerakkody, PhD**[‖], and **LeRoy A LeNarz, MD**[‖]

[*]Duke University Medical Center, Durham, NC

[†]Stanford University, Stanford, CA

[‡]Emory University Hospital, Atlanta, GA

[§]University of Arizona School of Medicine, Tucson, AZ

[‖]Lilly USA, LLC, Indianapolis, IN

Abstract

Objectives—The objective of this study is to characterize the bleeding, transfusion and other outcomes of patients related to the timing of prasugrel or clopidogrel withdrawal prior to coronary artery bypass grafting (CABG).

Background—There is little evidence to guide clinical decision making regarding the use of prasugrel in patients who may need urgent or emergency CABG. Experience with performing CABG in the presence of clopidogrel has raised concern about perioperative bleeding complications that are unresolved.

Methods—A subset of the TRITON TIMI 38 study, where patients with acute coronary syndrome were randomized to treatment with aspirin and either clopidogrel or prasugrel, underwent isolated CABG (N=346). A supplemental case report form was designed and administered, and the data combined with the existing TRITON-TIMI 38 database. Baseline

Corresponding Author: Peter K Smith, MD Box 3442 Duke University Medical Center Durham, NC 27710 Phone: (919) 684-2890 Fax: (919) 681-7905 smith058@mc.duke.edu.

Author Contributions P.K. Smith, L.T. Goodnough, J.H. Levy, and R.S. Poston participated in the surgery advisory board which led to requests for additional data collection. M.A. Short, G.J. Weerakkody and L.A. LeNarz developed supplemental case report forms and a statistical analysis plan with the assistance of P.K. Smith and L.T. Goodnough. G.J. Weerakkody conducted statistical analyses. P.K. Smith, M.A. Short, and G.J. Weerakkody wrote the first draft of the manuscript. All authors participated in the conception and design of the study, interpretation of data, reviewed each manuscript draft critically for intellectual content, and approved the final version. The TRITONTIMI 38 Publications Committee approved of the conduct of this analyses and reviewed the manuscript prior to submission. No payment was received for manuscript development.

Relationship with Industry Disclosure: M.A. Short, G.J. Weerakkody, and L.A. LeNarz are employees of and report equity ownership or stock options in Eli Lilly and Company. P.K. Smith, L.T. Goodnough, J.H. Levy and R.S. Poston have received honoraria as consultants for Eli Lilly and Company. P.K. Smith has also served as a consultant to Bayer Corporation, Baxter Corporation and Cubist Pharmaceuticals.

CLINICAL TRIAL ID: H7T-MC-TAAL; http://clinicaltrials.gov/ct2/show/NCT00097591;NCT0097591

imbalances were corrected for using elements of the European System for Cardiac Operative Risk Evaluation and The Society of Thoracic Surgeons predictive algorithm.

Results—A significantly higher mean 12 hr chest tube blood loss (655±580 ml vs. 503±378 ml, p=0.050) was observed with prasugrel compared to clopidogrel, without significant differences in red blood cell transfusion (2.1 units vs. 1.7 units, p=0.442) or the total donor exposure (4.4 units vs. 3.0 units, p=0.463). All-cause mortality was significantly reduced with prasugrel (2.31%) compared to 8.67% with clopidogrel (adjusted odds ratio [OR], 0.26, p=0.025).

Conclusion—Despite an increase in observed bleeding, platelet transfusion and surgical re-exploration for bleeding, prasugrel was associated with a lower rate of death following CABG compared to clopidogrel.

Keywords

Acute coronary syndrome; prasugrel; coronary artery bypass grafting; mortality; clopidogrel

INTRODUCTION

Coronary artery bypass grafting (CABG) is one of the most frequently performed cardiac surgical procedures and impacts the management of one quarter of a million patients each year. The benefit of antiplatelet therapy early in the process of acute coronary syndrome (ACS) is well documented, but is less certain when CABG may be the preferred treatment option [1-3]. Studies have reported a substantial increased risk of CABG-related major bleeding as a result of concurrent antiplatelet (thienopyridine) therapy [4-8]. Others have reported that the relationship between timing of thienopyridine withdrawal preoperatively and CABG is only modest and quite variable [9-12]. Further complicating the issue is that, despite the potential for surgical bleeding problems, several studies suggest that there may be an ischemic and/or mortality benefit with some degree of platelet inhibition in patients undergoing CABG [3-8]. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38, prasugrel was associated with an increased risk of CABG-related bleeding compared to clopidogrel (13.4% vs. 3.2%; p<0.001) when adjudicated by the TIMI criteria [6]. However, a trend toward reduction in CABG mortality in those patients randomized to the prasugrel treatment was noted as a potential offsetting benefit among the patients undergoing CABG [13]. The trial design was not adequate to correct for baseline imbalances in patients who were not randomly assigned to undergo CABG, and the bleeding outcome data were insufficient to accurately characterize surgical bleeding, the known risk factors associated with bleeding and the complications related to bleeding. Accordingly, the current study utilizes the analysis of additional data which was acquired to expand the prior database and to allow characterization of perioperative bleeding (i.e., to allow further analysis of type, extent, other bleeding risk factors and management of bleeding) as potentially related to the timing of thienopyridine withdrawal prior to CABG. Supplementary data was also acquired to facilitate generation of risk adjustment models for CABG (European System for Cardiac Operative Risk Evaluation [EURO] Score [14] and The Society of Thoracic Surgeons Score [STS] [15]). These models were then used to estimate preoperative mortality risk for patients who underwent CABG subsequent to enrollment and treatment with either prasugrel or clopidogrel in the TRITON-TIMI 38 study. The goal of this analysis is to provide additional information to facilitate the assessment of risk benefit with respect to the preoperative administration of thienopyridines.

METHODS

The study design and principal results from the pivotal phase 3 TRITON-TIMI 38 trial have been published [6, 16]. Briefly, 13,608 subjects with ACS to be managed with PCI were randomized to receive a loading dose (60 mg prasugrel or 300 mg clopidogrel) followed by a daily maintenance dose (10 mg prasugrel or 75 mg clopidogrel) for up to 15 months in combination with aspirin [6]. The primary efficacy endpoint was the time of first occurrence of any element of the composite of cardiovascular (CV) death, nonfatal MI, or nonfatal stroke. Safety was assessed by TIMI bleeding criteria [16] and based on fall in hemoglobin, or intracranial hemorrhage versus actual measurement of chest tube output.

A supplemental case report form was developed to collect additional data from patients in TRITON-TIMI 38 who underwent CABG at any time point during the study. The data collection was designed to characterize the relationship of the withdrawal of thienopyridine prior to CABG to cumulative chest tube drainage and transfusions and to collect additional clinical risk factors for bleeding and adverse outcomes. An analysis plan was prospectively developed to include recognized risk adjustment methods for CABG (EURO score and STS scoring) mortality. Supplementary retrospective data collection was conducted by chart review and limited to the information captured during the subject's study participation. This was performed with the acknowledgement or approval of the ethics committee, regulatory board, or as required by local regulations. The data were independently analyzed by a statistician from Duke University Medical Center. The corresponding author had full access to the data in the study.

Population

The initial study population included the 485 subjects who underwent CABG with or without concomitant cardiac procedures during their participation in the TRITON-TIMI 38 study from November 2004 to January of 2007. In 36 patients a supplementary case report form could not be obtained. Two of the 36 (one randomized to prasugrel but did not receive study drug, one randomized to clopidogrel and received drug prior to the procedure) failed to survive surgery, and were included while the remaining 34 (prasugrel=11 and clopidogrel=23) with missing supplemental data were excluded (leaving N=451). Three additional patients were excluded due to an inability to determine the type of operative procedure performed (leaving 448). Thus, the EURO score and STS risk-adjusted predicted mortality was considered calculable for 446 of these 448 patients. The cohort of 448 included all deaths and all but 2 patients who were classified in the TRITON-TIMI 38 trial as having had TIMI major/minor bleeds (1 prasugrel and 1 clopidogrel patient).

The cohort of 448 patients was heterogeneous, and included patients with major concomitant cardiac procedures in addition to CABG (N=26), open label use of antiplatelet therapy prior to the procedure (N=20) and patients who did not receive study medication (N=56). Therefore, the key population of interest was further refined to include only the cohort of patients who underwent isolated CABG and received study drug prior to procedure (N=346).

Safety and Mortality Analysis

Selection bias may be introduced due to the non-randomized nature of the decision to perform CABG and the timing of study drug withdrawal; this could confound the comparison between prasugrel and clopidogrel. Thus, predicted probability of periprocedural mortality was used to adjust for potential imbalances and to validate comparisons. The predicted probability of mortality was calculated using EURO Score [14] or STS Score [15] methods. For the purpose of calculating EURO and STS score based on risk factors, any missing values were considered as absence of that risk factor as

recommended by the STS National Cardiac Database Committee. The primary safety endpoint was cumulative chest tube output in the first 12 postoperative hours following CABG. Key secondary safety endpoints included incidence of surgical re-exploration for bleeding, mortality within 30 days following CABG, occurrence of CV death, nonfatal MI, or nonfatal stroke within 30 days following CABG and total donor exposure. No adjustment was made for the possible selection bias in comparison of bleeding risk between prasugrel and clopidogrel due to the absence of a widely accepted measure for predicted risk of CABG-related bleeding.

Statistical Methods

Major surgical characteristics and mortality were analyzed for isolated CABG and for major cardiac procedures in addition to the CABG procedure (CABG+). Statistical analyses and summaries are presented for isolated CABG procedures. Surgical characteristics, medical history, pre-operative and post-operative (collected in hospital until discharge or on readmission within 30 days of CABG) state, hemodynamic and catheterization information, concomitant medication use during the periprocedural period, and the predicted probability of mortality at the time of CABG were summarized for each study drug. Statistical comparisons of these characteristics between prasugrel and clopidogrel are guided by the data type: comparison of distributions of nominal data using the Cochran-Mantel-Haenszel general association test, comparison of medians using the Cochran-Mantel-Haenszel row mean score test for ordinal data, comparison of medians via Kruskal-Wallis test, and comparison of means using two-sample t-test or ANOVA as appropriate, for interval scale data.

Average cumulative chest tube blood loss at 12 hours following CABG was compared using the Kruskal-Wallis test. Kaplan-Meier methodology was used for estimating the time profiles of cumulative hazard. A Cox-proportional hazards model was used for estimating the unadjusted hazard ratio, prasugrel versus clopidogrel. Comparison between time profiles were conducted using the log-rank test. Comparison of the risk of all-cause death, CV death, all cause death through 30 days from CABG, and in-hospital death between prasugrel and clopidogrel was performed using logistic regression analysis and the predicted probability of periprocedural mortality was included as a covariate. Separate analyses were performed using the STS predicted mortality score and the Euroscore as covariates and produced similar results. All analyses were done with SAS software (version 9.1, SAS Institute, Cary, North Carolina).

RESULTS

Patients

A patient flow diagram (including deaths for each group) for the retrospective analysis is illustrated in Figure 1. Patients with procedures in addition to CABG (for example, concomitant valve repair or replacement, aortic surgery, ventricular septal defect repair etc) were designated as CABG+ (N=26) leaving the majority of patients in the isolated CABG group (N=422). The CABG+ group required longer cardiopulmonary bypass time [mean, (SD) 83 (38) minutes for isolated CABG compared to 140 (46) minutes for CABG+] and had increased mortality (5.5% for isolated CABG compared to 30.8% for CABG+). Due to the heterogeneity of the CABG+ group and limited ability to risk-adjust for the complex procedures, the main analyses focused on the isolated CABG group and were limited to those who received study drug prior to CABG without exposure to open label clopidogrel prior to CABG.

There was no difference in time from randomization to isolated CABG procedure between treatment groups (Figure 2). Demographics and medical history for the isolated CABG group are summarized in Table 1. Preoperative and procedural characteristics are summarized in Table 2. Eight-five percent of the procedures were elective, consistent with the majority of them being performed more than 90 days following the enrolling unstable angina event. There was a significantly higher percentage of chronic pulmonary disease and on-pump procedures in the clopidogrel cohort. There was no evidence of interaction between the decision to perform off-pump CABG and the presence of chronic obstructive pulmonary disease (COPD), and no association of mortality with the choice of on-pump compared to off-pump CABG performance. There was a statistically significantly higher mean and median activated clotting time post-protamine observed in the off-pump prasugrel group. Concomitant medication use within 5 days and 1 day of the CABG procedure included aspirin, unfractionated heparin, low molecular weight heparin, direct thrombin inhibitors, and glycoprotein IIb-IIIa inhibitors, with no significant differences between the prasugrel and clopidogrel cohorts. At 5 days prior to the procedure, the most commonly used concomitant medication was aspirin (prasugrel, 61%; clopidogrel 66%), as was the case at 1 day prior to CABG (prasugrel, 37%; clopidogrel, 41%).

In the isolated CABG cohort, 106 patients in the prasugrel group and 126 patients in the clopidogrel group waited 1 to 7 days off study drug prior to CABG (Days from last dose to CABG for both groups are displayed in Table 2). Within this group, 4 patients in the clopidogrel group experienced non-fatal MIs, 3 on 1 day and 1 on 2 days after the last dose of study drug. One of the MIs at 1 day after the last dose of study drug was related to a definite or probable stent thrombosis. There were no ischemic events observed in the prasugrel group who discontinued drug up to 7 days awaiting surgery.

Bleeding and Transfusions

Figure 3 illustrates individual patient chest tube blood loss at 12 hours. The data were highly variable, but there was a significantly higher overall mean chest tube blood loss at 12 hours in the prasugrel compared with clopidogrel group (655±580 [25th 300, 50th 455, 75th 800] ml vs. 503±378 [25th 250, 50th 395, 75th 640] ml, p=0.050). There was no significant relationship between the duration of study drug withdrawal and this difference between study drugs. The incidence of platelet transfusion was significantly higher in the prasugrel group compared with clopidogrel (17.96% vs. 9.82%, p=0.033) as was the mean number of platelet units transfused (0.78 units vs. 0.39 units, p=0.047). However, there was no significant difference in packed red blood cell transfusion (2.1 units vs. 1.7 units, p=0.442) or the total donor exposure (packed red blood cell + whole blood + platelets + cryoprecipitate + fresh frozen plasma) between the prasugrel and clopidogrel groups (4.4 units vs. 3.0 units, p=0.463). There was a trend toward a higher incidence of surgical re-exploration for bleeding in the prasugrel group (n=11, surgical source of bleeding identified in 8 patients) compared with the clopidogrel group (n=4, surgical source of bleeding identified in 3 patients).

Postoperative Status

There was no difference in hospital length of stay between cohorts. Table 3 reports details of the postoperative period and hospital readmission post CABG.

Mortality

The mean EURO score was 3.32±2.9 and 3.62±3.2, and the mean predicted probability of mortality by EURO score was 0.04±0.06 and 0.05±0.09, in the prasugrel and clopidogrel cohorts respectively. The mean predicted probability of mortality by STS score was 0.01±0.03 and 0.02±0.04 in the prasugrel and clopidogrel cohorts. Figure 4 depicts the fold

elevation in predicted risk score as assessed by EURO score for each patient by day from last dose of study drug to isolated CABG procedure. Mortality was similar (3/16 prasugrel, 3/14 clopidogrel) when CABG was performed on the same day as last dose of study drug. These patients were at a higher predicted risk of death per EURO score (Figure 4). When study drug was discontinued for 1 or more days, the mortality was lower with prasugrel (1/156 prasugrel vs. 12/158 clopidogrel). There were no deaths (0/72) in prasugrel patients having CABG with 1 to 5 days of drug withdrawal and 6 deaths in clopidogrel patients having CABG (6/85) under the same conditions (see Figure 4).

All-cause mortality was 2.31% in the prasugrel cohort compared to 8.67% in the clopidogrel cohort (adjusted odds ratio [OR] and 95% confidence interval [CI] of 0.26 [0.08-0.85], p=0.025). The mortality rate at 30 days adjusted for imbalances at baseline, when analyzed by logistic regression per EURO scoring, remained statistically significant (adjusted OR and 95% CI: 0.17 [0.04-0.79], p=0.024). Similar results were observed when mortality was adjusted for STS mortality risk score. CV death within 30 days following CABG was 0.58% for the prasugrel cohort compared to 5.78% for the clopidogrel cohort (OR, 0.11, 95% CI [0.01-0.84], p=0.034). Overall CV death was 1.73% for the prasugrel cohort compared to 6.94% for the clopidogrel cohort (OR, 0.25; 95% CI [0.07-0.98], p=0.047). A Kaplan-Meier curve of the cumulative incidence of all-cause death for the prasugrel and clopidogrel isolated CABG groups is illustrated in Figure 5. There was a statistically significantly lower risk of mortality in the prasugrel group compared with the clopidogrel group before and after adjustment to baseline differences with predicted EURO score mortality risk. In-hospital mortality for prasugrel and clopidogrel was 3/173 and 8/173 respectively. The mortality benefit observed in the prasugrel cohort appeared to be similar whether or not dual antiplatelet therapy treatment was resumed following the CABG procedure (Table 3).

DISCUSSION

Current American College of Cardiology/American Heart Association guidelines recommend the early use of adenosine diphosphate receptor $P2Y_{12}$ inhibitors in patients with ACS in whom percutaneous coronary intervention (PCI) is anticipated [17, 18]. The guidelines also recommend delaying elective CABG for 5 or more days after the last dose of clopidogrel and 7 days after the last dose of prasugrel, if possible [18]. However, these guidelines are based on consensus opinions and there are concerns that a delay of CABG to reduce bleeding risk may come at the expense of increased risk of myocardial injury/infarction (MI), and/or stent thrombosis while awaiting surgery [19]. Concern about CABG-related bleeding and difficulty in accurately identifying which patients will require CABG potentially limits early initiation of platelet inhibition along with the potential benefits of thienopyridines in non-ST-segment elevation myocardial infarction ACS [20]. This retrospective analysis of the patients undergoing CABG in the TRITON-TIMI 38 trial is the first characterization of outcomes in patients receiving prasugrel followed by a CABG procedure, and provides information about the relationship between residual antiplatelet drug activity, perioperative bleeding, and mortality. Overall, this study supports the perception that an increase in residual antiplatelet drug effect increases bleeding and transfusion; however, an increase in residual antiplatelet effect was also shown to be associated with a reduction of mortality hazard in patients treated with prasugrel, compared to clopidogrel. Multivariate analyses and standard mortality risk adjustment methodology indicates that this difference is not related to any other potential confounders.

This finding of increased bleeding is also consistent with other studies of antiplatelet agents where CABG was safely performed during periods of drug effect, presumably for clinical indications obviating surgical delay. Both abciximab [21] and clopidogrel [22] have been shown to have increased bleeding and transfusion outcomes compared to aspirin alone,

whereas ticagrelor had similar bleeding and transfusion rates compared to clopidogrel [23]. The observation of increased bleeding, transfusion and reexploration observed with the use of prasugrel in patients who require surgical intervention is an important finding for clinicians who are managing these patients in the perioperative setting. A better understanding of the bleeding risk will allow clinicians to be ready with respect to the potential for volume rescuscitation, platelet or other hemostatic therapy for those patients who develop life-threatening bleeding after cardiac surgery.

Like prasugrel in this study, abciximab [21] and ticagrelor [7] have been associated with improved CABG survival versus the comparator. As with these two agents, the survival differences are noted primarily in the first 30 days, suggesting that perioperative events related to surgery are effected by residual and continued antiplatelet therapy. The specific mechanism for this survival advantage was unclear for either abciximab or ticagrelor, and the event rates in the current study for other ischemic endpoints and infection endpoints were too small to add understanding given the sample size of this study. This is the first study, however, to use standard risk adjustment methods to confirm that the comparative risk is not related to other potential confounding factors.

This study has several limitations. First, it is a retrospective analysis involving patients who were randomized to receive either clopidogrel or prasugrel before an indication for CABG emerged. In this setting, there are possible unknown confounders influencing the baseline risk of CABG that differ between the study arms and may not be corrected for by the methods employed. For example, the incidence of COPD and off-pump CABG performance differed between study groups despite investigator blinding to the study drug. The presence of COPD is an incorporated risk factor in the STS and Euroscore algorithms, but the utilization of cardiopulmonary bypass could not be adjusted for with these tools. Postoperative bleeding is known to be effected by cardiopulmonary bypass and will be further explored, but mortality outcome is not similarly effected. Second, the decision to perform CABG and factors related to the timing of CABG are unknown and were therefore not characterized in this analysis. This, combined with the relatively small number of patients in various states of study drug “washout”, makes these data difficult to translate into definitive recommendations regarding optimal decision making. In addition, small subgroup size limits the statistical power associated with comparisons between prasugrel and clopidogrel, and the imputation of missing values may potentially limit the risk adjustment. Finally, the study design of the parent randomized trial, with the stated goal of PCI which was based on knowledge of the coronary anatomy before randomization, resulted in a CABG population enriched with one- and two-vessel coronary artery disease. Thus, the results are less generalizable to the typical population of patients referred for bypass surgery where 3-vessel disease predominates, or in patients who undergo complex or multiple operative procedures. Despite these limitations, this study provides important additional information to surgeons and cardiologists as they determine the appropriate antiplatelet agent to enhance outcomes after PCI, and the impact on overall patient outcome if CABG is eventually selected as the desired revascularization strategy.

In summary, the analysis focused on patients receiving isolated CABG (CABG with no additional procedures), the majority of patients in the trial. The prasugrel cohort had a statistically significantly higher chest tube blood loss as well as a significantly higher use of platelets. This analysis suggests that there may be an increased need for surgical re-exploration in prasugrel treated patients, which is consistent with the significant differences noted in the bleeding and transfusion parameters. The mortality observed in patients with high chest tube blood loss and increased transfusion requirements was associated with a high predicted risk of mortality prior to CABG [24]. Patients who had lower predicted mortality risk, did not have a subsequently increased mortality associated with higher chest tube blood

loss or increased transfusion requirements. For all patients, the lower mortality rate in the prasugrel cohort overall and at 30 days persisted after risk adjustment using EURO or STS Scoring. In spite of an increase in observed bleeding, platelet transfusion and surgical re-exploration for bleeding, patients treated with prasugrel prior to isolated CABG were observed to have a mortality that was significantly lower than patients administered clopidogrel prior to undergoing CABG, while enrolled in the TRITON-TIMI 38 study.

Acknowledgments

The authors would like to thank B Liu, MS (i3 Global) for statistical support and L.H. Muhlbaier, PhD (Duke University Medical Center) for his independent statistical replication of the analyses.

The authors also thank B.G. Utterback, MS and A.G. Leishman, PhD (both Eli Lilly and Company) for writing and project management support of the manuscript, and J A. Sherman, AAS (Eli Lilly and Company) for assistance with the figures.

Financial Support: This work was sponsored by Daiichi Sankyo, Inc., Parsippany, NJ and Eli Lilly and Company, Indianapolis, IN and is related to study protocol H7T-MC-TAAL, listed on ClinicalTrials.gov; NCT 00097591. Dr. Smith was supported by NHLBI U01-HL088953.

Abbreviations

ACS	acute coronary syndrome
CABG	coronary artery bypass grafting
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
EURO	European System for Cardiac Operative Risk Evaluation
MI	myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
STS	The Society of Thoracic Surgeons
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38

REFERENCES

1. Levine GN, Lincoff AM, Ferguson JJ 3rd, et al. Utilization of catheterization and revascularization procedures in patients with non-ST segment elevation acute coronary syndrome over the last decade. Catheter Cardiovasc Interv. 2005; 66:149–57. [PubMed: 16152646]
2. Aranki SF, Body SC. Antiplatelet agents used for early intervention in acute coronary syndrome: myocardial salvage versus bleeding complications. J Thorac Cardiovasc Surg. 2009; 138:807–10. [PubMed: 19769880]
3. Fox KA, Mehta SR, Peters R, et al. Clopidogrel in Unstable angina to prevent Recurrent ischemic Events Trial. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation. 2004; 110:1202–8. [PubMed: 15313956]
4. Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. Circulation. 2001; 103:363–8. [PubMed: 11157686]

5. Ebrahimi R, Dyke C, Mehran R, et al. Outcomes following pre-operative clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery: the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. J Am Coll Cardiol. 2009; 53:1965–72. [PubMed: 19460609]
6. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357:2001–15. [PubMed: 17982182]
7. Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol. 2011; 57:672–84. [PubMed: 21194870]
8. Montalescot G, Hulot JS, Collet JP. Antiplatelet therapy and coronary artery bypass graft surgery: A fallow land. J Am Coll Cardiol. 2010; 56:2003–5. [PubMed: 21126641]
9. Kim JH, Newby LK, Clare RM, et al. Clopidogrel use and bleeding after coronary artery bypass graft surgery. Am Heart J. 2008; 156:886–92. [PubMed: 19061702]
10. Chen L, Bracey AW, Radovancevic R, et al. Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2004; 128:425–31. [PubMed: 15354103]
11. Barnard J, Millner R. A review of topical hemostatic agents for use in cardiac surgery. Ann Thorac Surg. 2009; 88:1377–83. [PubMed: 19766855]
12. Bassand JP, Afzal R, Eikelboom J, et al. Relationship between baseline haemoglobin and major bleeding complications in acute coronary syndromes. Eur Heart J. 2010; 31:50–58. [PubMed: 19825809]
13. [Accessed August 8, 2011] Effient (Prasugrel) Acute Coronary Syndromes Managed by Percutaneous Coronary Intervention FDA Division of Cardiovascular and Renal Drugs Advisory Committee Briefing Document. Feb 03. 2009 Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm129219.pdf
14. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999; 16:9–13. [PubMed: 10456395]
15. Anderson RP. First publications from the Society of Thoracic Surgeons National Database. Ann Thorac Surg. 1994; 57:6–7. [PubMed: 8279920]
16. Wiviott SD, Antman EM, Gibson CM, et al. TRITON-TIMI 38 Investigators. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). Am Heart J. 2006; 152:627–35. [PubMed: 16996826]
17. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011; 57:e215–367. [PubMed: 21545940]
18. Kushner FG, Hand M, Smith SC Jr, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009; 120:2271–306. [PubMed: 19923169]
19. Mehta SR, Yusuf S, Peters RJ, et al. Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001; 358:527–33. [PubMed: 11520521]
20. Mehta RH, Chen AY, Pollack CV Jr, et al. Challenges in predicting the need for coronary artery bypass grafting at presentation in patients with non-ST-segment elevation acute coronary syndromes. Am J Cardiol. 2006; 98:624–27. [PubMed: 16923449]

21. Lincoff AM, LeNarz LA, Despotis GJ, et al. Abciximab and bleeding during coronary surgery: results from the EPILOG and EPISTENT trials. Improve Long-term Outcome with abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibition in STENTing. Ann Thorac Surg. 2000; 70:516–26. [PubMed: 10969673]

22. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345:494–502. [PubMed: 11519503]

23. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361:1045–57. [PubMed: 19717846]

24. Goodnough LT, Despotis GJ, Smith PK, et al. Transfusion requirements and outcomes in the cohort of patients undergoing isolated CABG treated with prasugrel or clopidogrel: TRITONTIMI 38 retrospective data analysis. Blood. 2010; 116:482–483. (abstr).

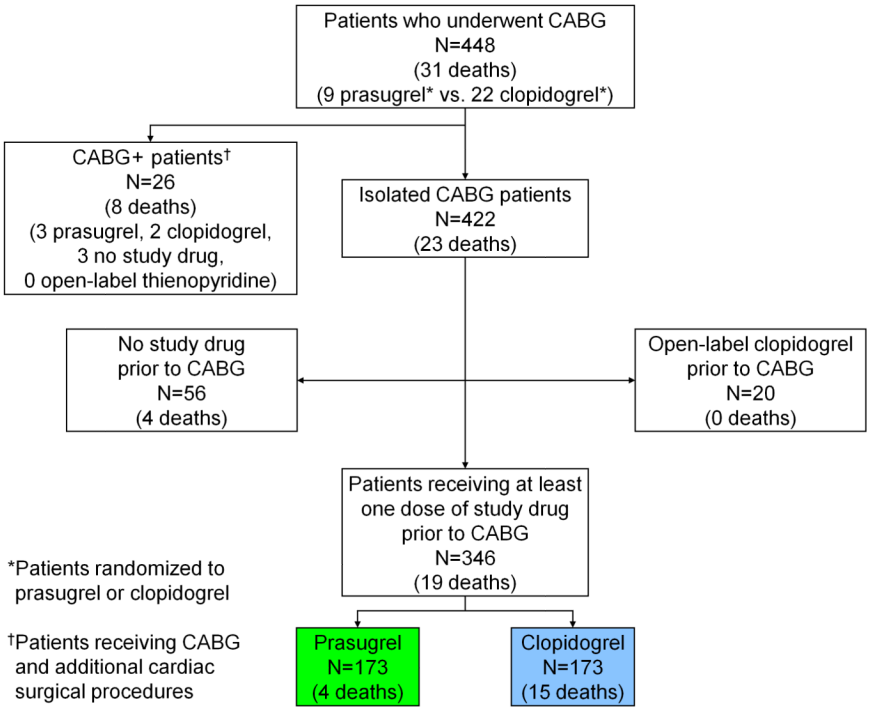

Figure 1.

Patient flow. CABG+ patients received additional cardiac surgical procedures. CABG=coronary artery bypass grafting, N=number of patients

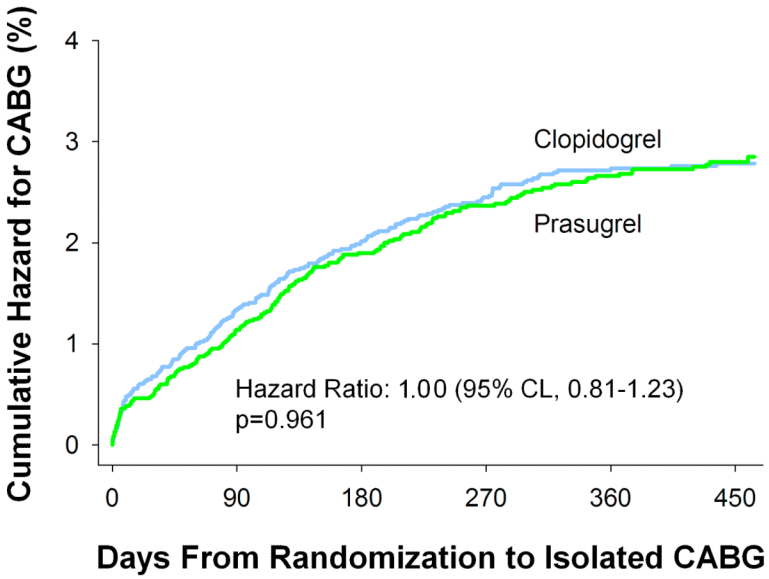

Figure 2.
Time from randomization to isolated CABG procedure. CABG=coronary artery bypass grafting, CL=confidence limit

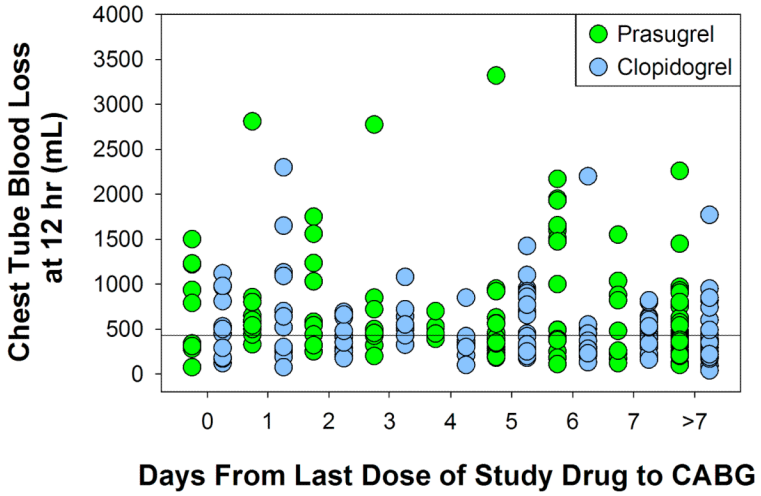

Figure 3.

Chest tube Loss at 12hr by days from last dose of study drug to CABG. Individual patient chest tube blood loss is indicated by patient in each treatment group. The solid line indicates the median blood loss=420 mL. CABG=coronary artery bypass grafting

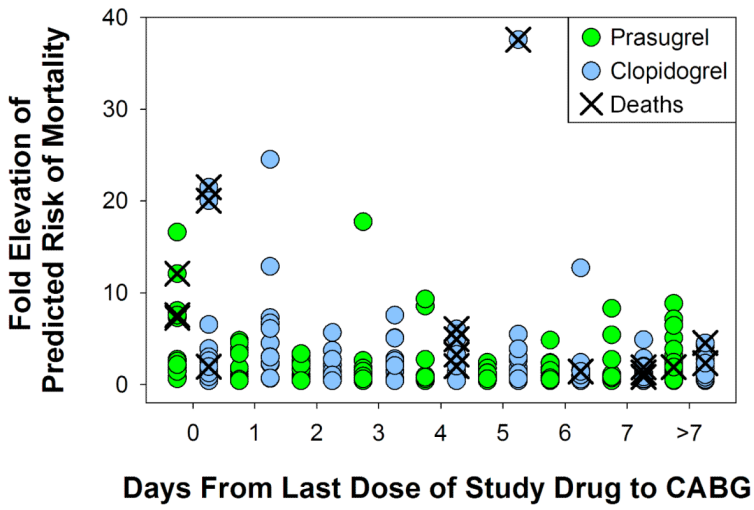

Figure 4.

Fold elevation of predicted risk of mortality based on EURO score by days from last dose of study drug to isolated CABG procedure. Individual patient elevation in predicted risk of mortality values by treatment group are indicated. Patient values indicated with an X are observed mortality in each treatment group. Zero is median risk for the population. Fold elevation of predicted risk of mortality refers to the predicted probability of death for a patient /median predicted probability for the entire group. CABG=coronary artery bypass grafting

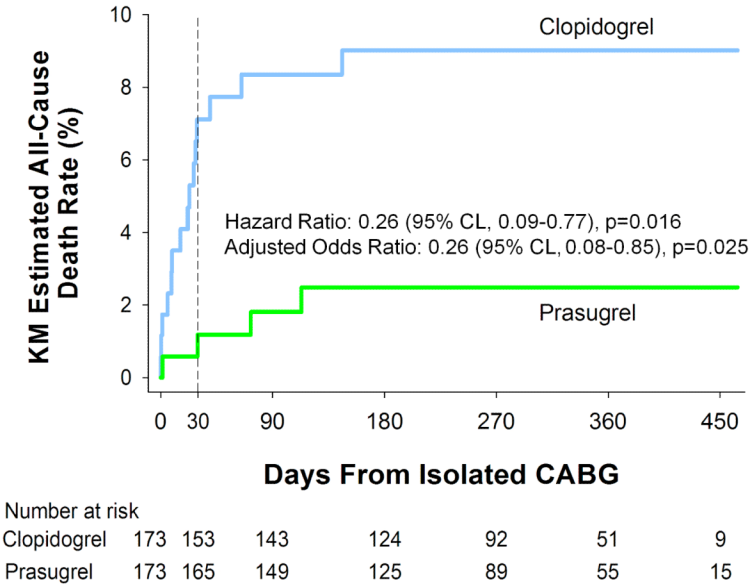

Figure 5.

Kaplan-Meier estimate of the cumulative incidence of all-cause death across time from isolated CABG. The 30 day timepoint is indicated by the dashed line. The 30 day all-cause mortality rate for prasugrel was 1.16% vs. 6.94% for clopidogrel. CABG=coronary artery bypass grafting, CL=confidence limit, KM=Kaplan-Meier

Table 1

Demographics and baseline TRITON-TIMI 38 medical history for the isolated CABG cohort.

	Prasugrel (N=173)	Clopidogrel (N=173)	p-Value*
Demographics			
Region of enrollment, n (%)			0.821
North America	28 (16.2)	34 (19.7)	
South America	6 (3.5)	8 (4.6)	
Europe	108 (62.4)	106 (61.3)	
Rest of World†	31 (17.9)	25 (14.5)	
Age in years, mean (SD)	61.1 (9.3)	60.9 (10.2)	0.856
Age in years, median (25^{th}-75^{th} percentiles)	60.0 (54.0-69.0)	62.0 (54.0-69.0)	
Age ≥75 years, n (%)	14 (8.1)	12 (6.9)	0.683
Male, n (%)	130 (75.1)	135 (78.0)	0.526
Weight <60 kg, n (%)	13 (7.7)	10 (5.9)	0.527
Medical History			
History of cerebrovascular disease, n (%)	14 (8.1)	13 (7.5)	0.841
History of hypertension, n (%)	115 (66.5)	107 (61.9)	0.370
Diabetes mellitus, n (%)	51 (29.5)	47 (27.2)	0.633
TRITON Baseline Clinical Presentation, n (%)			0.823
UA/NSTEMI	110 (63.6)	112 (64.7)	
STEMI	63 (36.4)	61 (35.3)	

*P-values were calculated with Pearson's chi-square test (categorical variables) or ANOVA (continuous variables)

†Africa, Asia, Mid-East

CABG=coronary artery bypass grafting, NSTEMI=non-ST-segment elevation myocardial infarction, SD=standard deviation, STEMI=ST-segment elevation myocardial infarction, TRITON-TIMI 38=Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction, UA=unstable angina

Table 2

Preoperative cardiac and procedural characteristics for the isolated CABG cohort.

	Prasugrel (N=173)	Clopidogrel (N=173)	p-Value*
Preoperative Characteristics			
Heart failure, n (%)	21 (12.2)	16 (9.3)	0.384
Ejection fraction ≤30%, n (%)	2 (1.2)	8 (4.6)	0.062
UA requiring pre-CABG IV nitrates, n (%)	20 (11.6)	17 (9.8)	0.602
Inotropic support, n (%)	5 (2.9)	7 (4.1)	0.550
Peripheral vascular disease, n (%)	13 (7.5)	11 (6.4)	0.672
Moderate to severe mitral valve regurgitation, n (%)	6 (3.5)	8 (4.7)	0.601
MI within 24 hr prior to CABG, n (%)	6 (3.5)	8 (4.6)	0.585
PCI within 6 hr of CABG, n (%)	12 (6.9)	6 (3.5)	0.146
History of CV surgery, n (%)	3 (1.7)	7 (4.1)	0.196
Chronic pulmonary disease, n (%)	8 (4.6)	20 (11.6)	0.017
Procedural Characteristics			
CABG occurred during TRITON index event, n (%)	8 (4.62)	7 (4.05)	0.792
CABG status (%)			0.931
Elective, %	84.4	85.0	
Urgent, %	13.9	12.7	
Emergent or salvage, %	1.7	2.3	
Thoracotomy, %	1.8	4.7	0.123
Intra-aortic balloon pump use, %	7.6	11.8	0.194
On-Pump, %	75.0	86.0	0.010
Total cross-clamp time minutes, mean (SD)	53 (27)	49 (23)	
Total cross-clamp time minutes, median (25^{th}-75^{th} percentiles)	46 (34-65)	47 (33-61)	0.500
Total heparin (U) during operation, mean (SD)	33012 (19177)	34500 (19700)	
Total heparin (U) during operation, median (25^{th}-75^{th} percentiles)	33250 (22000-40000)	32000 (25000-40000)	0.861
Protamine (mg), mean (SD)	315 (126)	336 (127)	
Protamine (mg), median (25^{th}-75^{th} percentiles)	300 (250-400)	325 (260-400)	0.232
ACT (highest recorded), sec, mean (SD)	633 (184)	653 (194)	
ACT (highest recorded), sec, median (25^{th}-75^{th} percentiles)	604 (495-735)	617 (506-800)	0.538
ACT (post-protamine), sec, mean (SD)	164 (130)	151 (88)	

	Prasugrel (N=173)	Clopidogrel (N=173)	p-Value*
ACT (post-protamine), sec, median (25th-75th percentiles)	130 (120-146)	127 (121-141)	0.301
Off-Pump, %	25.0	14.0	0.010
Heparin (U) loading dose, mean (SD)	14022 (8678)	15444 (9112)	
Heparin (U) loading dose, median (25th-75th percentiles)	13750 (9000-20000)	10000 (10000-19000)	0.938
Heparin (U) intraoperative, mean (SD)	15195 (8972)	30833 (52530)	
Heparin (U) intraoperative, median (25th-75th percentiles)	13500 (10000-22500)	15000 (10000-20000)	0.726
Protamine (mg), mean (SD)	169 (97)	188 (112)	
Protamine (mg), median (25th-75th percentiles)	150 (100-200)	150 (100-250)	0.683
ACT (post-protamine), sec, mean (SD)	137 (17)	123 (11)	
ACT (post-protamine), sec, median (25th-75th percentiles)	137 (125-146)	124 (117-131)	0.018
Number of diseased vessels, n (%)			0.371
1	26 (15.0)	24 (13.9)	
2	108 (62.4)	105 (60.7)	
3	36 (20.8)	35 (20.2)	
Days from last dose to CABG, n (%)			0.257
0 days	16 (9.2)	14 (8.1)	
1 days	15 (8.7)	13 (7.5)	
2 days	12 (6.9)	17 (9.8)	
3 days	12 (6.9)	10 (5.8)	
4 days	9 (5.2)	11 (6.4)	
5 days	24 (13.9)	34 (19.7)	
6 days	21 (12.1)	16 (9.2)	
7 days	13 (7.5)	25 (14.5)	
8-14 days	36 (20.8)	20 (11.6)	
>14 days	14 (8.1)	12 (6.9)	
Unknown or missing	1 (0.6)	1 (0.6)	

* P-values were calculated with Pearson's chi-square test (categorical variables) or Kruskal-Wallis test (continuous variables)

ACT=activated clotting time, CABG=coronary artery bypass grafting, CV=cardiovascular, IV=intravenous, MI=myocardial infarction, PCI=percutaneous coronary intervention, SD=standard deviation, TRITON=Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction, U=units, UA=unstable angina

Table 3

Postoperative outcomes for the isolated CABG cohort.

	Prasugrel (N=173)	Clopidogrel (N=173)	p-Value*
Postoperative (In hospital)			
Deep sternal infection, n (%)	1 (0.6)	4 (2.3)	0.215
Respiratory dysfunction (vent >24 hrs), n (%)	10 (5.8)	9 (5.2)	0.824
Readmission within 30 days of CABG discharge			
Readmission to hospital within 30 days, n (%)	12 (6.9)	15 (8.7)	0.537
Readmission to hospital for deep sternal infection, n (%)	0 (0.0)	3 (4.0)	0.082
Readmission to hospital for other infection, n (%)	2 (2.8)	6 (8.1)	0.276
DAPT following CABG			
Resumed DAPT (open label or study drug) following CABG, n (deaths)	129 (1)	122 (7)	
-Study drug, n (deaths)	108 (0)	106 (3)	
-Open label clopidogrel, n (deaths)	21 (1)	16 (4)	
Did not resume DAPT (open label or study drug) following CABG, n (deaths)†	44 (3)	49 (7)	
Status unknown, n (deaths)	0 (0)	2 (1)	

*P-values were calculated with Pearson's chi-square test or Fisher exact test

†All deaths occurred in-hospital

CABG=coronary artery bypass grafting, DAPT=dual antiplatelet therapy