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Cardiac Surgery

Mortality Benefit With Prasugrel in the TRITON–TIMI 38 Coronary Artery Bypass Grafting 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,‖ LeRoy A. LeNarz, MD‖

Durham, North Carolina; Stanford, California; Atlanta, Georgia; Tucson, Arizona; and Indianapolis, Indiana

Objectives The objective of this study was to characterize the bleeding, transfusion, and other outcomes of patients related to the timing of prasugrel or clopidogrel withdrawal before 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 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38), in which 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 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-h chest tube blood loss (655 ± 580 ml vs. 503 ± 378 ml; p = 0.050) was observed with prasugrel compared with clopidogrel, without significant differences in red blood cell transfusion (2.1 U vs. 1.7 U; p = 0.442) or the total donor exposure (4.4 U vs. 3.0 U; p = 0.463). All-cause mortality was significantly reduced with prasugrel (2.31%) compared with 8.67% with clopidogrel (adjusted odds ratio: 0.26; p = 0.025).

Conclusions Despite an increase in observed bleeding, platelet transfusion, and surgical re-exploration for bleeding, prasugrel was associated with a lower rate of death after CABG compared with clopidogrel. (A Comparison of Prasugrel [CS-747] and Clopidogrel in Acute Coronary Syndrome Subjects Who Are to Undergo Percutaneous Coronary Intervention; NCT00097591) (J Am Coll Cardiol 2012;60:388–96) © 2012 by the American College of Cardiology Foundation

Coronary artery bypass grafting (CABG) is one of the most frequently performed cardiac surgical procedures and affects 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 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 TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38), pra-

From the *Duke University Medical Center, Durham, North Carolina; †Stanford University, Stanford, California; ‡Emory University Hospital, Atlanta, Georgia; §University of Arizona School of Medicine, Tucson, Arizona; and ‖Lilly USA, LLC, Indianapolis, Indiana. This work was sponsored by Daiichi Sankyo, Inc. and Eli Lilly and Company and is related to study protocol H7T-MC-TAAL. Dr. Smith was supported by National Heart, Lung, and Blood Institute grant U01-HL088953. Ms. Short, Dr. Weerakkody, and Dr. LeNarz are employees of and report equity ownership or stock options in Eli Lilly and Company. Drs. Smith, Goodnough, Levy, and Poston have received honoraria as consultants for Eli Lilly and Company. Dr. Smith has also served as a consultant to Bayer Corporation, Baxter Corporation, and Cubist Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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sugrel was associated with an increased risk of CABG-related bleeding compared to clopidogrel (13.4% vs. 3.2%; $p < 0.001$) when adjudicated by using the TIMI criteria (6). However, a trend toward reduction in CABG mortality in those patients randomized to receive 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 uses the analysis of additional data, which were 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 before CABG. Supplementary data were also acquired to facilitate generation of risk-adjustment models for CABG (European System for Cardiac Operative Risk Evaluation score [EuroSCORE] [14] and The Society of Thoracic Surgeons [STS] score [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 the current analysis was to provide additional information to facilitate the assessment of risk benefit with respect to the pre-operative administration of thienopyridines.

Methods

The study design and principal results from the pivotal phase III TRITON–TIMI 38 trial have been published (6,16). Briefly, 13,608 patients with ACS to be managed with percutaneous coronary intervention (PCI) were randomized to receive a loading dose (60 mg of prasugrel or 300 mg of clopidogrel) followed by a daily maintenance dose (10 mg of prasugrel or 75 mg of 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 myocardial infarction (MI), or nonfatal stroke. Safety was assessed by using TIMI bleeding criteria (16) and based on a fall in hemoglobin levels 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 before 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 (EuroSCORE and STS scoring) mortality. Supplementary retrospective data collection was conducted by using chart review and was limited to the information captured during the patient's study participation.

This review was performed with the acknowledgment or approval of the ethics committee and 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.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CABG = coronary artery bypass grafting
CI = confidence interval
COPD = chronic obstructive pulmonary disease
CV = cardiovascular
EuroSCORE = European System for Cardiac Operative Risk Evaluation score
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
STS = Society of Thoracic Surgeons

Population. The initial study population included the 485 patients 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 (1 randomized to receive prasugrel but did not receive study drug; 1 randomized to receive clopidogrel and received drug before the procedure) failed to survive surgery and were included; the remaining 34 patients (11 in the prasugrel group and 23 in the clopidogrel group) with missing supplemental data were excluded, leaving 451 patients. Three additional patients were excluded due to an inability to determine the type of operative procedure performed, for a balance of 448 patients. Thus, the EuroSCORE 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-treated and 1 clopidogrel-treated 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 before 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 346 patients who underwent isolated CABG and received study drug before procedure.

Safety and mortality analysis. Selection bias may be introduced due to the nonrandomized 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 EuroSCORE (14) or STS score (15)

methods. For the purpose of calculating EuroSCORE 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 post-operative hours after CABG. Key secondary safety endpoints included incidence of surgical re-exploration for bleeding, mortality within 30 days after CABG, occurrence of CV death, nonfatal MI, or nonfatal stroke within 30 days after 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 (designated as CABG+). Statistical analyses and summaries are presented for isolated CABG procedures. Surgical characteristics, medical history, preoperative and postoperative (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 were guided according to the data type: comparison of distributions of nominal data by using the Cochran-Mantel-Haenszel general association test, comparison of medians by using the Cochran-Mantel-Haenszel row mean score test for ordinal data, comparison of medians by using the Kruskal-Wallis test, and comparison of means by using the 2-sample t test or analysis of variance, as appropriate, for interval scale data.

Average cumulative chest tube blood loss at 12 h after CABG was compared by using the Kruskal-Wallis test. Kaplan-Meier methods were used for estimating the time profiles of cumulative hazard. A Cox proportional hazards model was used for estimating the unadjusted hazard ratio for prasugrel versus clopidogrel. Comparison between time profiles were conducted by 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 by using the STS predicted mortality score and the EuroSCORE as covariates and produced similar results.

All analyses were conducted by using SAS version 9.1 (SAS Institute, Inc., 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 (e.g., con-

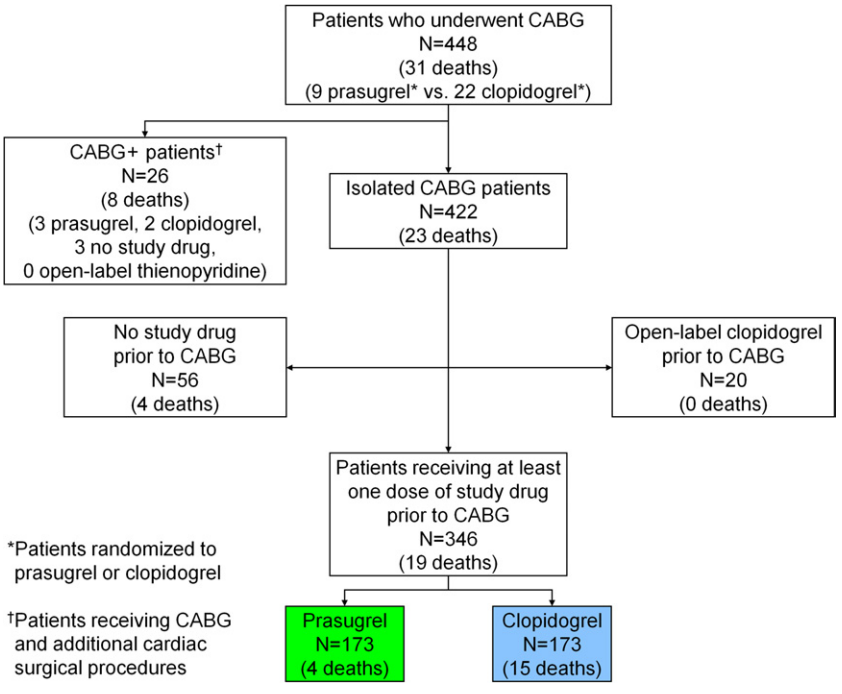

Figure 1 Patient Flow

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

comitant valve repair or replacement, aortic surgery, ventricular septal defect repair) 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 (83 ± 38 min for isolated CABG compared with 140 ± 46 min for CABG+) and had increased mortality (5.5% for isolated CABG compared with 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 before CABG without exposure to open-label clopidogrel before CABG.

There was no difference in time from randomization to isolated CABG procedure between treatment groups (Fig. 2). Demographic characteristics 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 >90 days after the enrolling unstable angina event. There was a significantly higher percentage of chronic obstructive pulmonary disease (COPD) 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 COPD, and no association of mortality with the choice of on-pump compared with 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

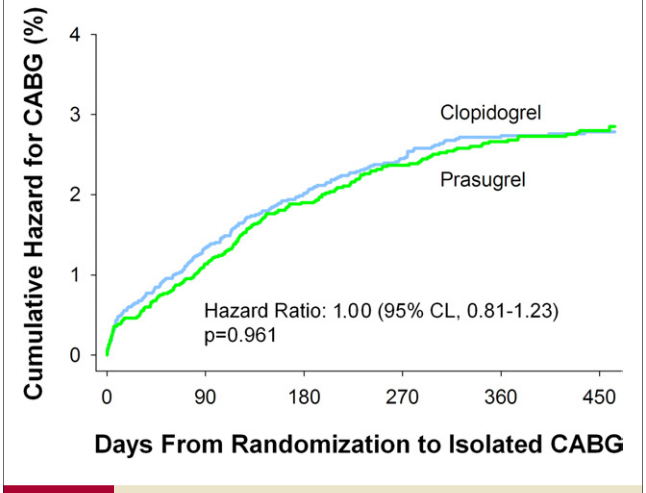

Figure 2 Time From Randomization to Isolated CABG Procedure

CABG = coronary artery bypass grafting; CL = confidence limit.

Table 1 Demographic Characteristics and Baseline TRITON–TIMI 38 Medical History for the Isolated CABG Cohort

Characteristic	Prasugrel (n = 173)	Clopidogrel (n = 173)	p Value*
Demographic			
Region of enrollment			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)	
Other†	31 (17.9)	25 (14.5)	
Age (yrs)	61.1 ± 9.3	60.9 ± 10.2	0.856
Age (yrs)	60.0 (54.0–69.0)	62.0 (54.0–69.0)	
Age ≥75 yrs	14 (8.1)	12 (6.9)	0.683
Male	130 (75.1)	135 (78.0)	0.526
Weight <60 kg	13 (7.7)	10 (5.9)	0.527
Medical history			
Cerebrovascular disease	14 (8.1)	13 (7.5)	0.841
Hypertension	115 (66.5)	107 (61.9)	0.370
Diabetes mellitus	51 (29.5)	47 (27.2)	0.633
TRITON baseline clinical presentation			0.823
UA/NSTEMI	110 (63.6)	112 (64.7)	
STEMI	63 (36.4)	61 (35.3)	

Values are n (%), mean ± SD, or median (25th–75th percentiles). *p values were calculated with Pearson's chi-square test (categorical variables) or analysis of variance (continuous variables). †Africa, Asia, and the Mideast.

CABG = coronary artery bypass grafting; NSTEMI = non–ST-segment elevation myocardial infarction; 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.

before the procedure, the most commonly used concomitant medication was aspirin (prasugrel 61%; clopidogrel 66%), as was the case at 1 day before 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 before 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 h. The data were highly variable, but there was a significantly higher overall mean chest tube blood loss at 12 h in the prasugrel group compared with the clopidogrel group (655 ± 580 ml [25th percentile 300 ml; 50th percentile 455 ml; 75th percentile 800 ml] vs. 503 ± 378 ml [25th percentile 250 ml; 50th percentile 395 ml; 75th percentile 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 the clopidogrel

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Table 2 Preoperative Cardiac and Procedural Characteristics for the Isolated CABG Cohort

Characteristic	Prasugrel (n = 173)	Clopidogrel (n = 173)	p Value*
Preoperative characteristics			
Heart failure	21 (12.2)	16 (9.3)	0.384
Ejection fraction ≤30%	2 (1.2)	8 (4.6)	0.062
UA requiring pre-CABG IV nitrates	20 (11.6)	17 (9.8)	0.602
Inotropic support	5 (2.9)	7 (4.1)	0.550
Peripheral vascular disease	13 (7.5)	11 (6.4)	0.672
Moderate to severe mitral valve regurgitation	6 (3.5)	8 (4.7)	0.601
MI within 24 h before CABG	6 (3.5)	8 (4.6)	0.585
PCI within 6 h of CABG	12 (6.9)	6 (3.5)	0.146
History of CV surgery	3 (1.7)	7 (4.1)	0.196
COPD	8 (4.6)	20 (11.6)	0.017
Procedural characteristics			
CABG occurred during TRITON index event	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 (min)	53 ± 27	49 ± 23	
Total cross-clamp time (min)	46 (34-65)	47 (33-61)	0.500
Total heparin (U) during operation	33,012 ± 19,177	34,500 ± 19,700	
Total heparin (U) during operation	33,250 (22,000–40,000)	32,000 (25,000–40,000)	0.861
Protamine (mg)	315 ± 126	336 ± 127	
Protamine (mg)	300 (250–400)	325 (260–400)	0.232
ACT, highest recorded (s)	633 ± 184	653 ± 194	
ACT, highest recorded (s)	604 (495–735)	617 (506–800)	0.538
ACT, post-protamine (s)	164 ± 130	151 ± 88	
ACT, post-protamine (s)	130 (120–146)	127 (121–141)	0.301
Off-pump, %	25.0	14.0	0.010
Heparin (U) loading dose	14,022 ± 8,678	15,444 ± 9,112	
Heparin (U) loading dose	13,750 (9,000–20,000)	10,000 (10,000–19,000)	0.938
Heparin (U) intraoperative	15,195 ± 8,972	30,833 ± 52,530	
Heparin (U) intraoperative	13,500 (10,000–22,500)	15,000 (10,000–20,000)	0.726
Protamine (mg)	169 ± 97	188 ± 112	
Protamine (mg)	150 (100–200)	150 (100–250)	0.683
ACT, post-protamine (s)	137 ± 17	123 ± 11	
ACT, post-protamine (s)	137 (125–146)	124 (117–131)	0.018
No. of diseased vessels			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			0.257
0	16 (9.2)	14 (8.1)	
1	15 (8.7)	13 (7.5)	
2	12 (6.9)	17 (9.8)	
3	12 (6.9)	10 (5.8)	
4	9 (5.2)	11 (6.4)	
5	24 (13.9)	34 (19.7)	
6	21 (12.1)	16 (9.2)	
7	13 (7.5)	25 (14.5)	
8–14	36 (20.8)	20 (11.6)	
>14	14 (8.1)	12 (6.9)	
Unknown or missing	1 (0.6)	1 (0.6)	

Values are n (%), mean ± SD, or median (25th–75th percentile). *p values were calculated by using Pearson's chi-square test (categorical variables) or Kruskal-Wallis test (continuous variables).

ACT = activated clotting time; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; IV = intravenous; MI = myocardial infarction; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

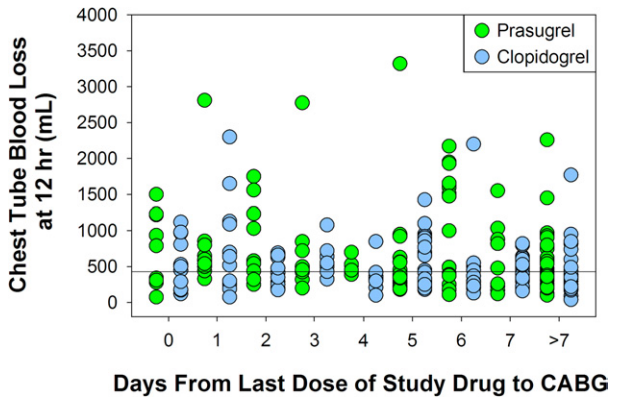

Figure 3 **Chest Tube Loss at 12 h by Days From Last Dose of Study Drug to CABG**

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.

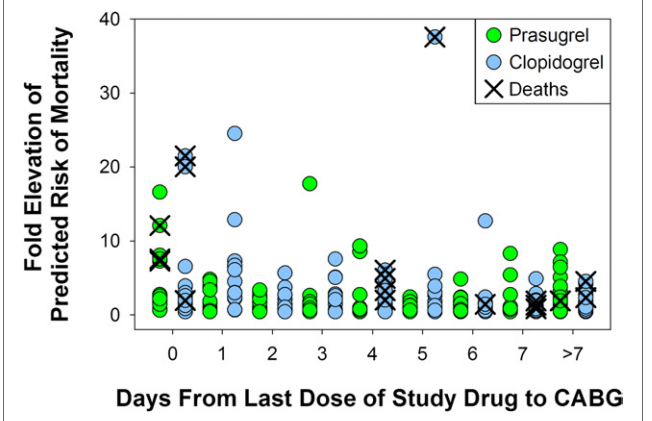

Figure 4 **Fold Elevation of Predicted Risk of Mortality Based on EuroSCORE by Days From Last Dose of Study Drug to Isolated CABG Procedure**

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; EuroSCORE = European System for Cardiac Operative Risk Evaluation score.

group (17.96% vs. 9.82%; p = 0.033) as was the mean number of platelet units transfused (0.78 U vs. 0.39 U; p = 0.047). However, there was no significant difference in packed red blood cell transfusion (2.1 U vs. 1.7 U; 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 U vs. 3.0 U; 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]).

Post-operative 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 EuroSCORE was 3.32 ± 2.9 and 3.62 ± 3.2, and the mean predicted probability of mortality according to EuroSCORE was 0.04 ± 0.06 and 0.05 ± 0.09, in the prasugrel and clopidogrel cohorts, respectively. The mean predicted probability of mortality according to the 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 using the EuroSCORE for each patient by day from last dose of study drug to isolated CABG procedure. Mortality was similar (3 of 16 prasugrel-treated patients; 3 of 14 clopidogrel-treated patients) when CABG was performed on the same day as last dose of study drug. These patients were at a higher predicted

Table 3 **Post-Operative Outcomes for the Isolated CABG Cohort**

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

Values are n (%). *p values were calculated by using Pearson's chi-square test or Fisher exact test. †All deaths occurred in hospital.
CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy.

risk of death according to the EuroSCORE (Fig. 4). When study drug was discontinued for ≥1 day, mortality was lower with prasugrel (1 of 156 prasugrel-treated patients; 12 of 158 clopidogrel-treated patients). There were no deaths in the 72 prasugrel-treated patients having CABG within 1 to 5 days of drug withdrawal and 6 deaths in the 85 clopidogrel-treated patients having CABG under the same conditions.

All-cause mortality was 2.31% in the prasugrel cohort compared with 8.67% in the clopidogrel cohort (adjusted odds ratio [OR]: 0.26 [95% confidence interval (CI): 0.08 to 0.85]; p = 0.025). The mortality rate at 30 days adjusted for imbalances at baseline, when analyzed by using logistic regression per EuroSCORE, remained statistically significant (adjusted OR: 0.17 [95% CI: 0.04 to 0.79]; p = 0.024). Similar results were observed when mortality was adjusted for STS mortality risk score. CV death within 30 days after CABG was 0.58% for the prasugrel cohort compared with 5.78% for the clopidogrel cohort (OR: 0.11 [95% CI: 0.01 to 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 to 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 for baseline differences with predicted EuroSCORE mortality risk. In-hospital mortality rate for prasugrel and clopidogrel was 3 of 173 patients and 8 of 173 patients, respectively. The mortality benefit observed in the prasugrel cohort seemed to be similar regardless of whether dual antiplatelet therapy treatment was resumed after the CABG procedure (Table 3).

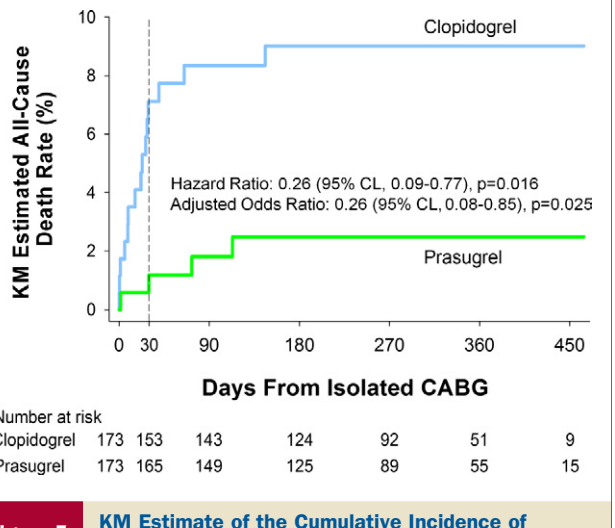

Figure 5 KM Estimate of the Cumulative Incidence of All-Cause Death Across Time From Isolated CABG

The 30-day time point is indicated by the dashed line. The 30-day all-cause mortality rate for prasugrel was 1.16% versus 6.94% for clopidogrel. KM = Kaplan-Meier; other abbreviations as in Figure 2.

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 PCI is anticipated (17,18). The guidelines also recommend delaying elective CABG for ≥5 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/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 MI 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 with clopidogrel. Multivariate analyses and standard mortality risk-adjustment methods indicate 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 in which 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 with aspirin alone, whereas ticagrelor had similar bleeding and transfusion rates compared with clopidogrel (23). The observation of increased bleeding, transfusion, and re-exploration 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 resuscitation, platelet therapy, or other hemostatic therapy for those patients who develop life-threatening bleeding after cardiac surgery.

Similar to prasugrel in the current study, abciximab (21) and ticagrelor (7) have been associated with improved CABG survival versus the comparator. As with these 2 agents, the survival differences are noted primarily in the first 30 days, suggesting that perioperative events related to

surgery are affected 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, to the best of our knowledge, to use standard risk-adjustment methods to confirm that the comparative risk is not related to other potential confounding factors.

Study limitations. First, this study was 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 used. 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 affected by cardiopulmonary bypass and will be further explored, but mortality outcome is not similarly affected. 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 decision, 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 that was based on knowledge of the coronary anatomy before randomization, resulted in a CABG population enriched with 1- and 2-vessel coronary artery disease. Thus, the results are less generalizable to the typical population of patients referred for bypass surgery in whom 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.

Conclusions

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 before 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 the EuroSCORE or the STS score. Despite an increase in observed bleeding, platelet transfusion, and surgical re-exploration for bleeding, patients treated with prasugrel before isolated CABG were observed to have a mortality rate that was significantly lower than patients administered clopidogrel before undergoing CABG while enrolled in the TRITON–TIMI 38 study.

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Reprint requests and correspondence: Dr. Peter K. Smith, Box 3442, Duke University Medical Center, Erwin Road, Durham, North Carolina 27710. E-mail: smith058@mc.duke.edu.

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Key Words: acute coronary syndrome ■ clopidogrel ■ coronary artery bypass grafting ■ mortality ■ prasugrel.