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Prasugrel Versus Clopidogrel in Patients With ST-Segment Elevation Myocardial Infarction According to Timing of Percutaneous Coronary Intervention

A TRITON–TIMI 38 Subgroup Analysis (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38)

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Objectives This study sought to evaluate the efficacy of prasugrel versus clopidogrel in ST-segment elevation myocardial infarction (STEMI) by the timing of percutaneous coronary intervention (PCI).

Background Treatment strategies and outcomes for patients with STEMI may differ when treated with primary compared with secondary PCI.

Methods STEMI patients in the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) were randomized to prasugrel or clopidogrel on presentation if primary PCI was intended or later during secondary PCI. Primary PCI was defined as within 12 h of symptom onset. The primary endpoint was cardiovascular death, myocardial infarction (MI), or stroke. Because periprocedural MI is difficult to assess in the setting of STEMI, we performed analyses excluding these events.

Results Reductions in the primary endpoint with prasugrel versus clopidogrel (hazard ratio [HR]: 0.79; 95% confidence interval [CI]: 0.65 to 0.97; p = 0.022) were consistent between primary and secondary PCI patients at 15 months (HR: 0.89; 95% CI: 0.69 to 1.13 vs. HR: 0.65; 95% CI: 0.46 to 0.93; p interaction = 0.15). However, a tendency toward a difference in treatment effect at 30 days (HR: 0.68; 95% CI: 0.54 to 0.87; p = 0.002) was observed between primary and secondary PCI patients (HR: 0.81; 95% CI: 0.60 to 1.09 vs. HR: 0.51; 95% CI: 0.34 to 0.76; p interaction = 0.06). When periprocedural MI was excluded, the efficacy of prasugrel remained consistent among primary and secondary PCI patients at 30 days (HR: 0.53; 95% CI: 0.34 to 0.81 vs. HR: 0.44; 95% CI: 0.22 to 0.88; p interaction = 0.68) and 15 months (HR: 0.76; 95% CI: 0.56 to 1.03 vs. HR: 0.75; 95% CI: 0.46 to 1.21; p interaction = 0.96).

Conclusions The efficacy of prasugrel versus clopidogrel was consistent irrespective of the timing of PCI, particularly in preventing nonprocedural events. (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38; NCT00097591) (J Am Coll Cardiol Intv 2014;7:604–12) © 2014 by the American College of Cardiology Foundation

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Primary percutaneous coronary intervention (PCI) is the preferred therapy for patients presenting with ST-segment elevation myocardial infarction (STEMI) (1,2). However, when mechanical reperfusion is unavailable in an expedited fashion, fibrinolysis for those presenting with acute STEMI is an alternative method of initial reperfusion routinely used worldwide (1–5). Alternatively, some patients with STEMI may delay presentation from symptom onset until they are outside of the recommended time window for primary PCI or fibrinolytic therapy (<12 h) but may remain symptomatic with chest discomfort secondary to myocardial ischemia or present with other high-risk features (hemodynamic instability, congestive heart failure, or arrhythmia) prompting a need for secondary PCI (1,2).

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The benefit of dual antiplatelet therapy with prasugrel, a potent thienopyridine, compared with clopidogrel, was demonstrated in moderate- to high-risk acute coronary syndrome (ACS) patients undergoing planned PCI in the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) (6) and appeared to have particular benefit within those patients presenting with STEMI (7). However, the value of more rapid, consistent, and effective P2Y12 receptor blockade among STEMI patients reperfused via primary compared with secondary PCI is not well established. The objective of this pre-specified subgroup analysis of the TRITON–TIMI 38 trial was to report the efficacy and safety of prasugrel compared with clopidogrel in STEMI patients according to the timing of PCI and to test the hypothesis that the comparisons between clopidogrel and prasugrel would be similar regardless of the timing of PCI.

Methods

Study patients. TRITON–TIMI 38 was a randomized, multicenter, double-blind, controlled trial for which the eligibility and exclusion criteria, methods, and results were previously reported (6–8). In brief, 13,608 patients with moderate- to high-risk ACS undergoing planned PCI were randomized to prasugrel (n = 6,813) or clopidogrel (n = 6,795) on a background of aspirin therapy. Among this cohort, 3,425 patients presented with STEMI and ultimately underwent PCI (Fig. 1). Patients who were enrolled and underwent PCI within 12 h of symptom onset (n = 2,340) were considered to have received primary PCI. Patients who were enrolled and underwent PCI between 12 h and 14 days after presentation for demonstrated recurrent myocardial ischemia or as part of routine medical management (n = 1,085) were considered as having received secondary PCI. Patients were excluded from the trial if they had an increased risk of bleeding, known intracranial pathology, ≥1 doses of a thienopyridine within 5 days before randomization, recent thrombolytic therapy (24 h for fibrin specific, 48 h for nonfibrin specific), or the inability or unwillingness to provide informed consent.

Endpoints. The primary efficacy endpoint of the trial as well as this analysis was the composite of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke at 15 months. We also provide results at 30 days of follow-up, a time period consistent with previous trials in STEMI and with primary PCI. Other efficacy endpoints included CV death, nonfatal MI, urgent target vessel revascularization at 30 days, definite or probable stent thrombosis (9), and other cardiovascular events. Key safety endpoints included Thrombolysis In Myocardial Infarction (TIMI) major bleeding that was unrelated to coronary artery bypass graft (CABG) surgery. A net clinical benefit endpoint was defined as the composite of all-cause death, nonfatal MI, nonfatal stroke, or nonfatal TIMI major bleeding unrelated to CABG surgery. Components of the primary endpoint and key safety endpoints were adjudicated by an independent clinical events committee whose members were blinded to the assigned treatment. We further characterized the diagnosis of recurrent MI by its timing and relationship to PCI according to the universal definition classification scheme into periprocedural and nonprocedural MI, as previously reported (10–12). Specifics of definitions were previously published (8). A sensitivity analysis excluding periprocedural MI was conducted because of the inherent challenge of delineating a recurrent MI using cardiac biomarkers in the setting of STEMI, in which a patient may

Abbreviations and Acronyms

ACS = acute coronary syndrome
CABG = coronary artery bypass graft
CI = confidence interval
CV = cardiovascular
HR = hazard ratio
IQR = interquartile range
MI = myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

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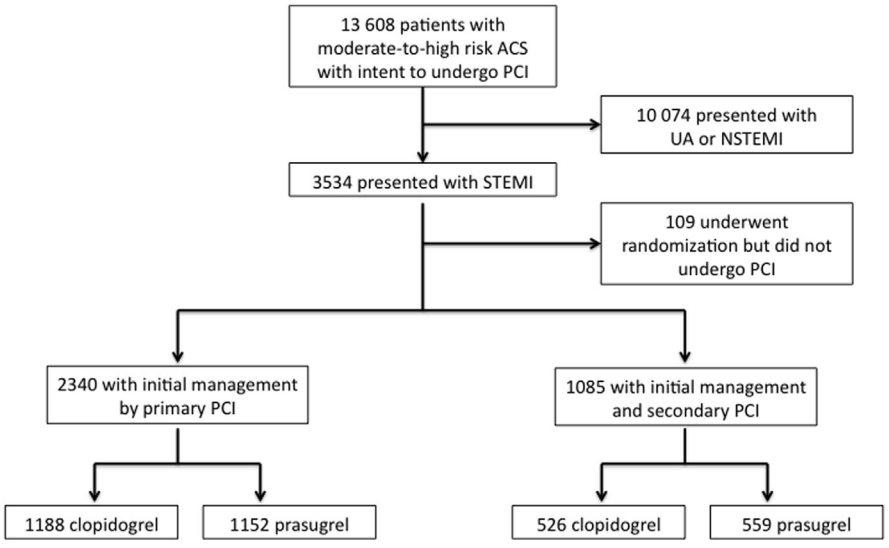

Figure 1. Study Flow Diagram

ACS = acute coronary syndromes; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

present early in the trajectory of an increase in cardiac biomarkers with limited additional clinical details or when myocardial injury may be due in part to reperfusion injury (13–16).

Statistical analysis. Baseline characteristics were summarized and compared between patient groups using frequencies and the Pearson chi-square test for categorical variables and medians with interquartile range (IQR) and the Wilcoxon rank-sum test for continuous variables. Cumulative event rates for clinical endpoints were determined using the Kaplan-Meier method and compared using the log-rank test. Efficacy comparisons were performed on an intention-to-treat basis with the use of a Cox proportional hazards model according to the time to the first event. To determine whether the randomized treatment effect was modified according to PCI timing, we assessed interaction terms to test for differential effect by PCI timing for each outcome. The event rates, hazard ratio (HR), 2-sided 95% confidence intervals (CIs), and p interaction terms are reported for each outcome according to PCI timing. Analyses of procedural and nonprocedural MI were performed according to the time to first MI. A landmark analysis of the primary endpoint from 3 days after randomization to the end of the study among surviving STEMI patients was performed as a further sensitivity analysis to exclude procedural MI events. All analyses were performed using STATA software (version 10.1, StataCorp, College Station, Texas). A threshold of $p < 0.05$ was considered statistically significant for all tests. Data analyses were conducted independent of the trial sponsors by the TIMI study group, which had full access to the data and take responsibility for its integrity.

Results

Among the 3,425 STEMI patients who underwent PCI, 2,340 (68%) received primary PCI and 1,085 (32%) received secondary PCI (Fig. 1). The clinical characteristics of the STEMI patient population according to PCI timing are reported in Table 1. Overall, the median time from symptom onset to randomization for STEMI patients was 6.0 h (IQR: 2.9 to 28.0 h). Among the 68% of STEMI patients who were managed with primary PCI, that time was 3.7 h (IQR: 2.3 to 6.6 h), whereas among the 32% of patients who were managed with secondary PCI, that time was significantly longer, 47.3 h (IQR: 25.7 to 86.2) ($p < 0.0001$). Patients treated with primary PCI compared with secondary PCI were more frequently enrolled from Eastern Europe (35.9% vs. 14.0%), more frequently treated with study medication before PCI (30.1% vs. 18.8%), and more frequently treated with unfractionated heparin and glycoprotein IIb/IIIa inhibitor therapy (Table 1). As expected, patients managed with primary PCI less frequently had a history of diabetes mellitus (16.8% vs. 24.0%) and previous fibrinolytic therapy (2.4% vs. 29.0%). Among patients with previous fibrinolytic therapy, the timing of previous fibrinolysis was a median 1.7 days (IQR: 1.1 to 2.6 days) in primary PCI patients compared with secondary PCI patients with a median of 2.2 days (IQR: 1.5 to 4.1 days) ($p = 0.0002$). There were no meaningful differences in age,

Table 1. Baseline Characteristics

	PCI Timing		
	Primary (n = 2,340)	Secondary (n = 1,085)	p Value
Age, yrs	59 (52–68)	58 (50–67)	0.006
Female	548 (23.4)	224 (20.6)	0.07
Body weight, kg	80.0 (72.0–90.0)	81.0 (72.0–92.5)	0.02
Region			
North America	443 (18.9)	308 (28.4)	<0.0001
Western Europe	654 (27.9)	337 (31.1)	
Eastern Europe	841 (35.9)	152 (14.0)	
Other	402 (17.2)	288 (26.5)	
History			
Hypertension	1,140 (48.7)	563 (51.9)	0.08
Hypercholesterolemia	879 (37.6)	533 (49.1)	<0.0001
Diabetes mellitus	393 (16.8)	260 (24.0)	<0.0001
Tobacco use	1,053 (45.0)	513 (47.3)	0.21
Chronic renal disease	260 (11.4)	94 (8.8)	0.02
Myocardial infarction	245 (10.5)	104 (9.6)	0.43
Stroke or TIA	68 (2.9)	38 (3.5)	0.35
Anterior myocardial infarction	922 (39.4)	411 (37.9)	0.40
Treatment and procedures			
Time from symptom onset to randomization, h	3.7 (2.3–6.6)	47.3 (25.7–86.2)	<0.0001
Timing of study drug			
Before PCI	704 (30.1)	204 (18.8)	<0.0001
During PCI	1,571 (67.1)	863 (79.5)	
After PCI	28 (1.2)	8 (0.7)	
Concomitant medication at randomization			
Aspirin	2,256 (96.4)	1,044 (96.2)	0.78
Statin	1,618 (69.1)	819 (75.5)	0.0001
ACE inhibitor	896 (38.3)	568 (52.4)	<0.0001
Beta-blocker	1,339 (57.2)	790 (72.8)	<0.0001
Stent type during index PCI			
BMS (only)	1,554 (66.4)	545 (50.2)	<0.0001
DES	666 (28.5)	492 (45.3)	<0.0001
Antithrombin			0.0003
Unfractionated heparin	1,679 (71.8)	722 (66.5)	
Low-molecular-weight heparin	150 (6.4)	95 (8.8)	
Bivalirudin	23 (1.0)	25 (2.3)	
Other or a combination	438 (18.7)	220 (20.3)	
Glycoprotein IIb/IIIa inhibitor	1,549 (66.2)	651 (60.0)	0.0004
Fibrinolytic therapy	56 (2.4)	315 (29.0)	<0.0001
Multivessel PCI	150 (6.5)	118 (11.0)	<0.0001

Values are n (%) or median (interquartile range). Data for some characteristics are missing for some patients.

ACE = angiotensin-converting enzyme; BMS = bare metal stent; DES = drug-eluting stent; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

body weight, infarct location, and previous stroke between groups.

Effect of prasugrel on 30-day outcomes according to PCI timing. The effect of prasugrel compared with clopidogrel with respect to 30-day outcomes is shown in Figure 2A and Online Table 1. Compared with clopidogrel, treatment with prasugrel for 30 days among STEMI patients resulted in a significant reduction in the primary endpoint (HR: 0.68; 95% CI: 0.54 to 0.87; p = 0.002) and CV death, nonfatal MI, or urgent target vessel revascularization (HR: 0.75; 95% CI: 0.59 to 0.96; p = 0.02). However, a tendency toward a difference in treatment effect was observed between primary and secondary PCI-managed patients for the primary endpoint (HR: 0.81; 95% CI: 0.60 to 1.09 vs. HR: 0.51; 95% CI: 0.34 to 0.76; p interaction = 0.06) and CV death, nonfatal MI, or urgent target vessel revascularization (HR: 0.91; 95% CI: 0.67 to 1.23 vs. HR: 0.53; 95% CI: 0.35 to 0.79; p interaction = 0.03), respectively. This difference was primarily driven by an observed reduction in risk of MI seen among secondary PCI-managed patients. Compared with clopidogrel, the risk of the development of MI was further reduced with prasugrel in patients managed with secondary PCI at 30 days (risk of MI among primary PCI–managed patients—HR: 0.92; 95% CI; 0.65 to 1.31; secondary PCI–managed patients—HR: 0.45; 95% CI: 0.29 to 0.71; p interaction = 0.01) (Fig. 2A).

Other individual cardiovascular endpoints, including stent thrombosis, showed consistent effects regardless of PCI timing (all other p interactions > 0.05). By 30 days, there was also no significant difference in the risk of major bleeding events unrelated to CABG surgery by PCI timing (p interaction = 0.68).

Effect of prasugrel on 15-month outcomes according to PCI timing. The primary endpoint, spontaneous CV events (primary endpoint excluding periprocedural MI), and primary safety endpoint for the entire study period by treatment group among both primary and secondary PCI-managed patients is shown in Figures 2B and 3. Major efficacy and safety endpoint results at 15 months are also presented in Online Table 1. Compared with clopidogrel, treatment with prasugrel resulted in a significant reduction in the primary endpoint among STEMI patients (HR: 0.79; 95% CI; 0.65 to 0.97; p = 0.022). When treatment effect was analyzed according to PCI timing, this reduction was consistent among both primary and secondary PCI–managed patients (HR: 0.89; 95% CI: 0.69 to 1.13 vs. HR: 0.65; 95% CI: 0.46 to 0.93; p interaction = 0.15) (Fig. 2B). In addition, treatment with prasugrel resulted in similar reductions in other major efficacy endpoints (all p interactions ≥ 0.05), except for MI (primary PCI–managed patients—HR; 0.91; 95% CI: 0.67 to 1.22; secondary PCI–managed patients—HR: 0.54: 95% CI: 0.36 to 0.82; p interaction = 0.046) (Fig. 2B).

With regard to safety, by 15 months, in STEMI patients overall, few non-CABG–related TIMI major bleeding events developed without a significant difference between randomized treatment groups (HR: 1.11; 95% CI: 0.70 to 1.77). Nevertheless, compared with clopidogrel, the risk of

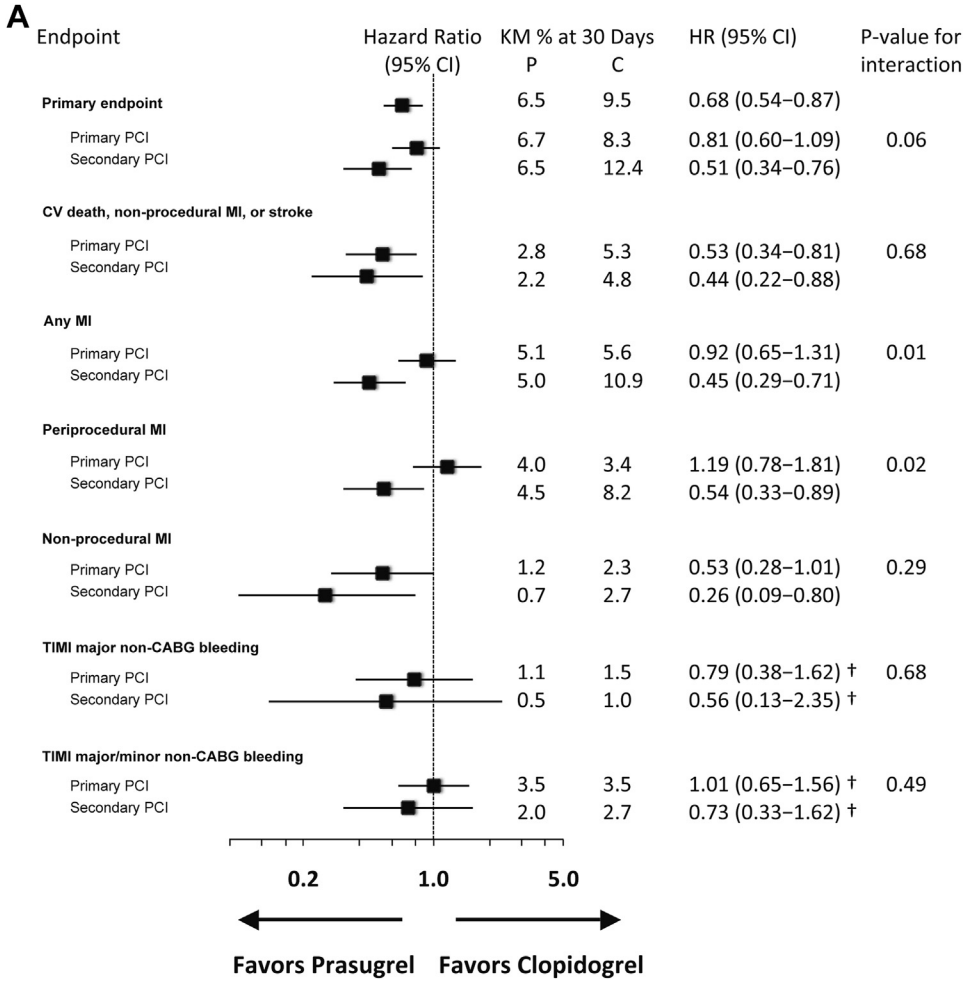

Figure 2. Forest Plot of the Effect of Therapy on Major Efficacy and Safety Endpoints Among STEMI Patients Managed by Primary or Secondary PCI

Shown are Kaplan-Meier estimates of the rate of major efficacy and safety endpoints, **(A)** at 30 days, **(B)** at 15 months, according to study-group assignment stratified by PCI timing at randomization. See Figure 1 for numbers of patients in the prasugrel, clopidogrel, all STEMI, primary PCI, and secondary PCI cohorts. †Odds ratio. p Values for interaction are shown next to the respective event rates for each endpoint. C = clopidogrel; CABG = coronary artery bypass grafting; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; KM = Kaplan-Meier; MI = myocardial infarction; P = prasugrel; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

TIMI major bleeding events observed with prasugrel was lower among patients managed with secondary PCI (HR: 0.39: 95% CI: 0.14 to 1.11) compared with primary PCI (HR: 1.52; 95% CI: 0.87 to 2.65; p interaction = 0.02) (Fig. 3).

Effect of prasugrel on nonprocedural CV events according to PCI timing. When the type of MI was further delineated, a significant interaction according to PCI timing between the effect of prasugrel compared with clopidogrel was apparent only for procedural MI events (primary PCI—HR: 1.19; 95% CI: 0.78 to 1.81; secondary PCI—HR: 0.54; 95% CI: 0.33 to 0.89; p interaction = 0.02 at 30 days [Fig. 2A]; p interaction = 0.03 at 15 months [Fig. 2B]). In contrast, a reduction in nonprocedural MI was consistent among both primary and secondary PCI–managed patients (30-day and 15-month p interaction was 0.29 and 0.57, respectively) (Fig. 2). As a result, when the treatment effect was analyzed post-hoc focusing on spontaneous primary endpoint events according to PCI timing (CV death, nonprocedural MI, stroke), significant differences in risk reduction among primary and secondary PCI–managed patients were no longer present (30-day and 15-month p interactions were 0.68 and 0.96, respectively (Fig. 2). Consistent findings were seen in landmark analyses of the primary endpoint from day 3 to day 30 (primary PCI—HR: 0.47; 95% CI: 0.26 to 0.83; secondary PCI—HR: 0.55; 95% CI: 0.27 to

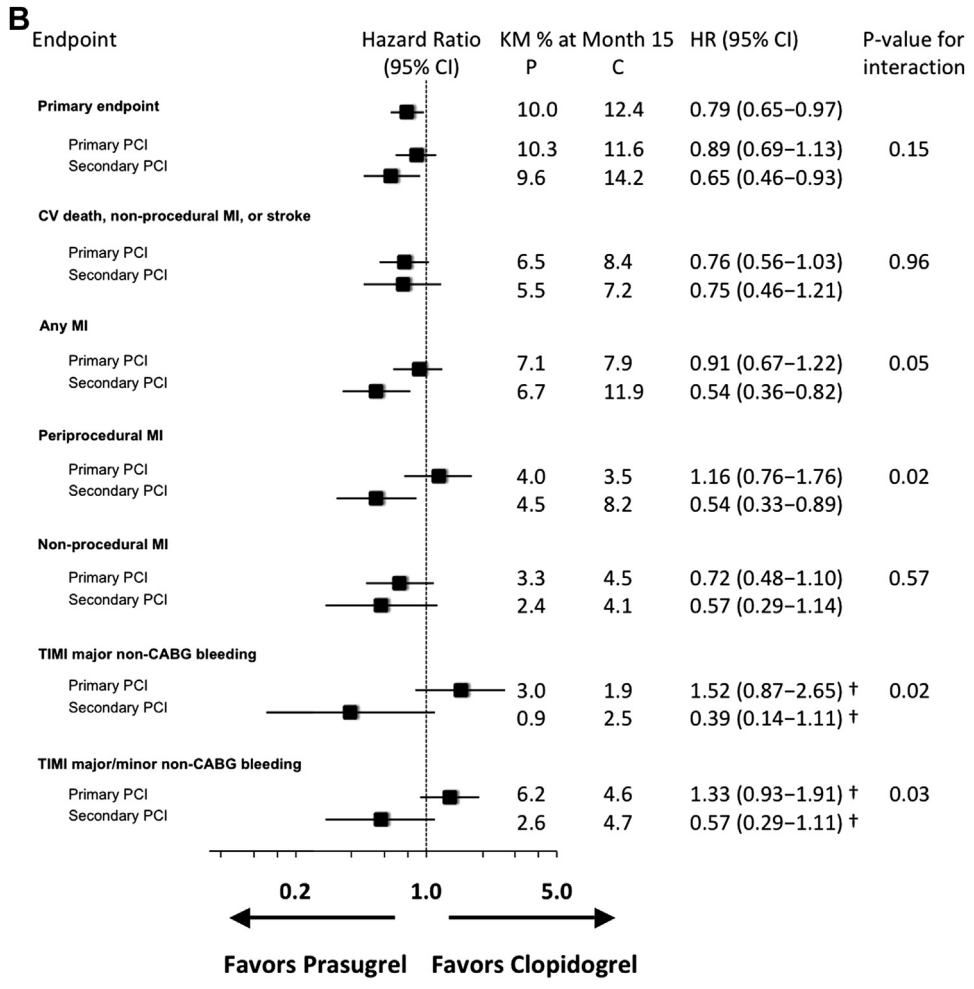

Figure 2. Continued

1.14; p interaction = 0.72) and to the end of study (primary PCI—HR: 0.79; 95% CI: 0.56 to 1.11; secondary PCI—HR: 0.84; 95% CI: 0.51 to 1.38; p interaction = 0.84).

Discussion

The pathophysiology of STEMI is characterized by extensive thrombosis, and patients with STEMI tend to be at high risk of recurrent thrombotic complications after PCI. Therapeutic strategies may differ depending on the timing and indication for PCI. Thus, understanding the consistency of benefit of prasugrel according to the timing of PCI is clinically relevant (1,2,17). Overall, we observed a benefit of prasugrel compared with clopidogrel in patients with STEMI.

The diagnosis of a recurrent MI is particularly difficult in STEMI patients managed with primary PCI because of reliance on cardiac biomarkers, which are often increased at the time of presentation or as a result of reperfusion injury (14,16,18,19). The recognition of a periprocedural MI requires disentangling a recurrent pattern of increased biomarkers of myocardial ischemia from the evolution of the patient's initial cardiac biomarker pattern (14,15). As a result, recommendations for the classification of a periprocedural MI have evolved (10). Procedural MIs were observed less frequently among primary PCI patients and appeared to have less of a treatment effect. Many of these recurrent events may be less clearly discernible from the index MI and represent nonmodifiable events or "noise" during early follow-up. However, when nonprocedural MI events were evaluated by either exclusion of procedural events or landmark analyses at day 3 after randomization, composite efficacy endpoints showed a consistent benefit of prasugrel. This secondary analysis of the TRITON–TIMI 38 trial is therefore informative because perception of a difference in treatment effect by PCI timing involving

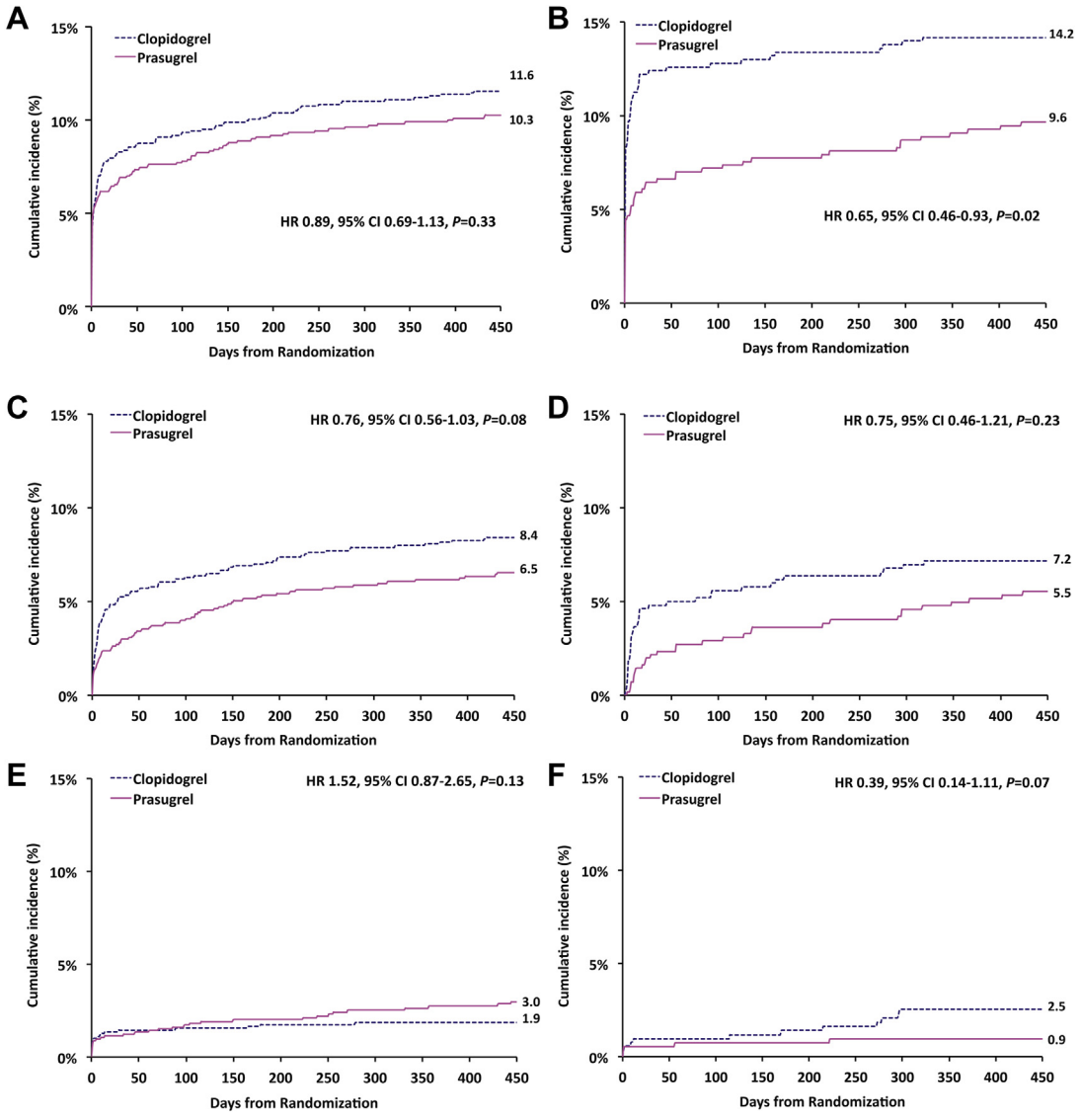

Figure 3. Kaplan-Meier Curves for Selected Endpoints Among Primary and Secondary PCI Patients Treated With Clopidogrel or Prasugrel

1) Primary study endpoint (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) among primary PCI patients **(A)** and secondary PCI patients **(B)**. 2) Spontaneous primary study endpoint (cardiovascular death, nonprocedural myocardial infarction, or nonfatal stroke) among primary PCI patients **(C)** and secondary PCI patients **(D)**. 3) Thrombolysis In Myocardial Infarction major bleeding unrelated to CABG surgery among primary PCI patients **(E)** and secondary PCI patients **(F)**. Abbreviations as in Figure 2.

endpoints that included nonfatal MI may have appeared as a result of the inherent difficulty in distinguishing a recurrent primary procedural MI from one that develops later in the course of therapy when the increase and decrease in cardiac ischemia biomarkers is well established after initial STEMI presentation.

Although it appears that the differential in assessment of procedural MIs explains any treatment differences observed, secondary PCI–managed STEMI patients may be a more select patient population who have greater benefit in the long term from more potent antithrombotic therapy at the time of PCI, with a more favorable risk balance for recurrent ischemia and spontaneous bleeding (17,20–22). This may in part reflect a treating physician's ability to select patients for invasive management who are at a low risk of bleeding; however, further prospective confirmation of this observation is required.

The *timing* of study drug administration was not randomized in TRITON–TIMI 38, in contrast to the ACCOAST (A Comparison of Prasugrel at PCI or Time of Diagnosis

of Non-ST Elevation Myocardial Infarction) trial, which compared 2 strategies of timing of prasugrel initiation among non–ST-segment elevation ACS patients (23). In TRITON, it was mandated that the coronary anatomy had to be known to be suitable for PCI before randomizing non–ST-segment elevation ACS patients or medically managed STEMI patients. In STEMI patients with either previously known coronary anatomy amenable to PCI or planned primary PCI, pre-treatment with study drug was permitted for up to 24 h before PCI. Although a small subgroup of the primary and secondary PCI STEMI patients were randomized to study drug before PCI, caution is advised in attempting to compare analyses of TRITON with the results of ACCOAST. With the exception of procedural events, a strategy of treatment with prasugrel after the coronary anatomy is defined or in select STEMI patients undergoing primary PCI resulted in consistent reductions in ischemic events at the expense of an increased risk of bleeding.

Study limitations. The limitations of this analysis warrant consideration. Patients with high-risk ACS enrolled in TRITON–TIMI 38 were intended for an invasive management strategy; however, the timing of PCI was not mandated, nor was justification of PCI timing completely characterized. As a result, PCI timing was not random, resulting in inherent heterogeneity between patients who received primary PCI compared with those who received secondary PCI. Nevertheless, randomized comparisons within each subgroup remain valid. In addition, the ~70% frequency of primary PCI management among our STEMI patients is similar to the frequency of use within the PLATO (Platelet Inhibition and Patient Outcomes) trial (24,25). Furthermore, because publication of the universal definition of MI occurred after completion of the TRITON–TIMI 38 trial, procedural MI was not evaluated using these new definitions (11). However, adjudicators remained blinded to study treatment assignment; thus, we would not expect bias in treatment effect comparisons of procedural or nonprocedural endpoint results. As well, a small sample of primary PCI patients received fibrinolysis >24 h before randomization, likely because either reperfusion failed and/or recurrent STEMI developed in these patients. Sensitivity analyses excluding these patients resulted in no material difference in either the primary or secondary results. Likewise, secondary PCI patients in routine clinical practice may be treated with clopidogrel at the time of fibrinolytic therapy; however, this was not standard of care at the time that TRITON–TIMI 38 was conducted (1). Because patients pre-treated with clopidogrel were excluded from TRITON, we cannot extrapolate our findings to that clinical scenario. Finally, this secondary analysis of the TRITON–TIMI 38 population involved further subgroup comparisons for STEMI patients receiving primary or subsequent PCI and treatment effect interactions; hence, these data should be interpreted with caution.

Conclusions

The majority of STEMI patients in an international trial comparing the efficacy and safety of more potent antiplatelet therapy were managed with primary PCI, whereas one-third of patients were managed with secondary PCI. Patients with STEMI who were managed with PCI late after presentation appeared to be a highly selected group who derived long-term efficacy from more potent antithrombotic therapy with a more favorable risk balance for spontaneous bleeding. Primary and secondary PCI–managed STEMI patients demonstrated consistent efficacy results when treated with prasugrel compared with clopidogrel, except regarding the development of procedural MI. When nonprocedural MIs were considered apart from procedural events, the benefit of prasugrel was consistent, irrespective of the timing of PCI.

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Key Words: antiplatelet therapy ■ myocardial infarction ■ periprocedural myocardial injury ■ prasugrel ■ primary percutaneous coronary intervention.

APPENDIX

For a supplemental table, please see the online version of this article.