The Efficacy and Safety of Prasugrel With and Without a Glycoprotein IIb/IIIa Inhibitor in Patients With Acute Coronary Syndromes Undergoing Percutaneous Intervention

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

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Objectives
We evaluated the efficacy and safety of prasugrel and clopidogrel in the setting of a glycoprotein (GP) IIb/IIIa inhibitor.

Background
Prasugrel reduced cardiovascular events as compared with clopidogrel in TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38) but with increased bleeding.

Methods
Researchers in the TRITON–TIMI 38 randomized 13,608 subjects with acute coronary syndrome undergoing percutaneous coronary intervention to prasugrel versus clopidogrel. The use of a GP IIb/IIIa inhibitor was at the physician’s discretion. For the current analysis, end points were examined at 30 days and were stratified by use of a GP IIb/IIIa inhibitor.

Results
A total of 7,414 subjects (54.5%) received a GP IIb/IIIa inhibitor during their index hospitalization. There was a consistent benefit of prasugrel over clopidogrel for reducing cardiovascular death, myocardial infarction, or stroke in patients who did (hazard ratio: 0.76; 95% confidence interval: 0.64 to 0.90) or did not receive a GP IIb/IIIa inhibitor (hazard ratio: 0.78; 95% confidence interval: 0.63 to 0.97, pinteraction = 0.83). Prasugrel significantly reduced myocardial infarction, urgent revascularization, and stent thrombosis irrespective of GP IIb/IIIa inhibitor use. Although subjects treated with a GP IIb/IIIa inhibitor had greater rates of bleeding, the risk of Thrombolysis in Myocardial Infarction major or minor bleeding with prasugrel versus clopidogrel was not significantly different in patients who were or were not treated with GP IIb/IIIa inhibitor (pinteraction = 0.19).

Conclusions
Prasugrel significantly reduces the risk of cardiovascular events in patients with acute coronary syndromes after percutaneous coronary intervention regardless of whether or not a GP IIb/IIIa inhibitor is used. The use of a GP IIb/IIIa inhibitor does not accentuate the relative risk of bleeding with prasugrel as compared with clopidogrel. (J Am Coll Cardiol 2009;54:678–85) © 2009 by the American College of Cardiology Foundation

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Prasugrel is a novel thienopyridine that has been shown to achieve greater, faster, and more consistent levels of platelet inhibition than clopidogrel (1–3). Like clopidogrel, prasugrel binds to the P2Y12 receptor on the platelet cell surface, leading to irreversible inhibition of platelet activation and aggregation (4). The TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes By Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) demonstrated that prasugrel significantly reduces the risk of cardiovascular (CV) death, myocardial infarction (MI), or stroke as compared with clopidogrel when given to patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) but at the cost of increased bleeding (5).

Glycoprotein (GP) IIb/IIIa inhibitors frequently are administered to patients with ACS undergoing PCI (6), a strategy supported by both the evidence-based (7,8) and clinical guidelines (9,10). Glycoprotein IIb/IIIa inhibitors have rapid onset of action and result in a high level of inhibition of platelet aggregation in most patients when measured in vitro (11). As such, the incremental benefit of prasugrel over clopidogrel in the setting of highly potent platelet inhibition with a GP IIb/IIIa inhibitor remains uncertain. Moreover, given the rapid onset of action of prasugrel, the safety of concurrent administration of prasugrel with a GP IIb/IIIa inhibitor has not been evaluated. For these reasons, we examined the relative efficacy and safety of prasugrel versus clopidogrel in patients who did and did not receive a GP IIb/IIIa inhibitor in the TRITON–TIMI 38 trial.

Methods

Patient population. The design and results of the TRITON–TIMI 38 trial have been previously reported (5,12). In brief, TRITON–TIMI 38 was a double-blind, phase 3 trial in which 13,608 patients with ACS (including unstable angina [UA], non–ST-segment elevation myocardial infarction [NSTEMI], and ST-segment elevation myocardial infarction [STEMI]) and undergoing PCI were randomized to either prasugrel (60-mg loading dose, 10-mg daily maintenance dose) or clopidogrel (300-mg loading dose, 75-mg daily maintenance dose). The study drug was to be administered within 1 h of completion of cardiac catheterization. The study drug could be administered before PCI only in subjects in whom the coronary anatomy was previously known or subjects in whom primary PCI for STEMI was planned. Subjects were to be treated with a standard loading dose of aspirin, if not on aspirin at the time of enrollment, followed by a daily aspirin dose of 75 to 162 mg. The choices of intracoronary stents used, vessels treated, and adjunctive medications administered (including the use of a GP IIb/IIIa inhibitor) were left to the discretion of the treating physician. Relevant exclusions to participation in the trial included individuals with an increased risk of bleeding, a history of anemia, thrombocytopenia, pathological intracranial findings, or the use of a thienopyridine within 5 days before randomization.

End points. The primary efficacy end point of the TRITON–TIMI 38 trial was the composite of CV death, nonfatal MI, or nonfatal stroke during the follow-up period. Additional pre-specified efficacy end points included periprocedural MI (defined as occurring within 48 h of PCI), urgent target vessel revascularization, stent thrombosis, and the individual elements of the composite end point (12). Stent thrombosis was defined according to the Academic Research Consortium definitions for definite or probable stent thrombosis (13).

Key safety end points included Thrombolysis In Myocardial Infarction (TIMI) non-coronary artery bypass grafting (non–CABG)-related major bleeding, TIMI non–CABG-related major or minor bleeding, and TIMI non–CABG-related life-threatening (including fatal) bleeding (12). All efficacy and safety end points were adjudicated by an independent clinical events committee blinded to assigned treatment arm; however, the use of a GP IIb/IIIa inhibitor was not concealed.

Consistent with previous trials of GP IIb/IIIa inhibitors (14,15), end points were examined at 30 days to evaluate the short-term effects of randomized thienopyridine therapy concurrent with GP IIb/IIIa inhibitor administration. Subsequently, end points were also examined through long-term follow-up.

Statistical analysis. Baseline characteristics are presented as medians (interquartile ranges) for continuous variables and frequencies for categorical variables. Baseline characteristics were compared with the use of Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables. Patients were classified as having received...
a GP IIb/IIIa inhibitor if they were administered a GP IIb/IIIa inhibitor during the index hospitalization.

Because the decision to use a GP IIb/IIIa inhibitor could be made after randomization, no statistical comparisons were made regarding efficacy and safety end points between subjects who did or did not receive a GP IIb/IIIa inhibitor and instead were restricted to comparisons of prasugrel versus clopidogrel stratified by the use of a GP IIb/IIIa. Efficacy analyses comparing randomized therapies were conducted according to the intention-to-treat principle. Safety analyses were conducted for those subjects who received at least 1 dose of the study drug and included events occurring up to 7 days after discontinuation of drug therapy. Rates of end points are expressed as Kaplan-Meier estimates at 30 days. Hazard ratios (HRs) (95% confidence intervals [CIs]) were calculated with the use of Cox proportional hazard survival models. Effect modification was assessed by the inclusion of an interaction term in the model. All tests were 2 sided, with a p value <0.05 considered to be significant. Analyses were performed with use of Stata/SE version 9.2 (Stata Corp., College Station, Texas).

Results

Of 13,608 subjects enrolled in the TRITON–TIMI 38 trial, there were 7,414 subjects (54.5%) who received a GP IIb/IIIa inhibitor during the index hospitalization. Patients who received a GP IIb/IIIa inhibitor were more likely to be younger, male, Caucasian, current smokers, and have a previous history of hypercholesterolemia (Table 1). Subjects who were treated with a GP IIb/IIIa inhibitor were more likely to be enrolled at North American sites, have an index diagnosis of STEMI, and to have received drug-eluting stents or undergone multivessel PCI. Subjects who did not receive a GP IIb/IIIa inhibitor during the index hospitalization were more likely to have had a previous history of hypertension and a lower creatinine clearance.

| Table 1 Baseline Characteristics Stratified by Use of a GP IIb/IIIa Inhibitor During Index Hospitalization |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Treated With a GP IIb/IIIa Inhibitor During Index Hospitalization (n = 7,414) | Not Treated With a GP IIb/IIIa Inhibitor During Index Hospitalization (n = 6,194) | p Value |
| Age (yrs), median (IQR) | 60 (52–69) | 62 (53–70) | <0.001 |
| Male | 75.9 | 72.0 | <0.001 |
| Caucasian race | 93.4 | 91.5 | <0.001 |
| BMI (kg/m²), median (IQR) | 27.9 (25.2–31.3) | 27.7 (25.1–30.8) | <0.001 |
| Current tobacco use | 40.2 | 35.8 | <0.001 |
| Hypertension | 61.5 | 67.6 | <0.001 |
| Hypercholesterolemia | 56.8 | 54.3 | 0.004 |
| Diabetes mellitus | 22.5 | 23.9 | 0.055 |
| Previous CABG | 7.7 | 7.5 | 0.67 |
| Creatinine clearance <60 ml/min* | 9.6 | 13.0 | <0.001 |
| Index event: NSTEMI or UA | 70.0 | 78.9 | <0.001 |
| Index procedure: ≥1 DES | 56.9 | 35.0 | <0.001 |
| Index procedure: multivessel PCI | 15.6 | 12.6 | <0.001 |
| Antithrombin during PCI | | | <0.001 |
| Unfractionated heparin | 70.5 | 59.7 | |
| LMWH | 10.2 | 6.6 | <0.001 |
| Bivalirudin | 1.4 | 5.4 | |
| Other or combination | 17.8 | 28.4 | |
| Region | | | |
| North America | 43.4 | 17.6 | |
| South America | 1.6 | 6.7 | |
| Western Europe | 26.7 | 25.4 | |
| Eastern Europe | 13.1 | 38.0 | |
| Rest of world | 15.2 | 12.3 | |
| Medications during hospitalization | | | |
| ACE-I or ARB | 73.6 | 77.7 | <0.001 |
| Beta-blocker | 88.8 | 87.5 | 0.02 |
| Statin | 92.2 | 92.0 | 0.63 |
| Aspirin | 99.5 | 99.0 | <0.001 |

Values are percentages unless otherwise indicated. *Creatinine clearance was estimated using the Cockcroft-Gault formula.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft surgery; DES = drug-eluting stent; GP = glycoprotein; IQR = interquartile range; LMWH = low-molecular-weight heparin; NSTEMI = non–ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; UA = unstable angina.
The baseline characteristics by treatment arm and within GP IIb/IIIa inhibitor cohorts are displayed in Table 2. Consistent with the overall trial, there were no significant differences in the baseline characteristics of subjects randomized to prasugrel versus clopidogrel for subjects who did or did not receive a GP IIb/IIIa inhibitor. The frequency of GP IIb/IIIa inhibitor use during index hospitalization did not differ significantly between randomized treatment arms.

**Efficacy outcomes.** There was a consistent benefit of prasugrel over clopidogrel in reducing CV death, MI, or stroke at 30 days in patients who did (HR: 0.76; 95% CI: 0.64 to 0.90) and did not receive a GP IIb/IIIa inhibitor (HR: 0.78; 95% CI: 0.63 to 0.97, $p_{\text{interaction}} = 0.83$) (Fig. 1). The effects of prasugrel for reducing CV death at 30 days were directionally consistent across each stratum. Prasugrel significantly reduced the risk of recurrent MI in subjects by approximately 25% regardless of the use of a GP IIb/IIIa inhibitor, including a comparable benefit toward a reduction in periprocedural MI across both subgroups (Fig. 2).

**Safety outcomes.** In the overall cohort, prasugrel significantly increased the risk of TIMI non-CABG-related
major or minor bleeding by 30 days as compared with clopidogrel (2.6% vs. 2.1%; HR: 1.26; 95% CI: 1.01 to 1.57; p = 0.04). The excess risk of TIMI non–CABG-related major or minor bleeding observed with prasugrel was comparable regardless of whether a GP IIb/IIIa inhibitor was used (HR: 1.63; 95% CI: 1.05 to 2.52, pinteraction = 0.19). The absolute excess in risk of TIMI non–CABG-related major bleeding with prasugrel versus clopidogrel was 0.1% in patients treated with a GP IIb/IIIa inhibitor (1.2% vs. 1.1%; HR: 1.06; 95% CI: 0.69 to 1.64) and 0.3% in subjects not treated with a GP IIb/IIIa inhibitor (0.9% vs. 0.6%; HR: 1.47; 95% CI: 0.81 to 2.66), a difference that was not statistically different between subgroups (pinteraction = 0.39) (Table 3). Similarly, the relative hazard of TIMI life-threatening bleeding with prasugrel compared with clopidogrel did not differ significantly in the presence or absence of a GP IIb/IIIa inhibitor (pinteraction = 0.19), including 10 fatal bleeds whose relative risk between treatment arms did not differ significantly in the presence or absence of a GP IIb/IIIa inhibitor (pinteraction = 0.26). The incidence of procedure-related TIMI major bleeding was similar for subjects treated with prasugrel or clopidogrel and was not significantly influenced by the use of a GP IIb/IIIa inhibitor. Consistent with the overall trial, there was no significant difference in the incidence of intracranial hemorrhage between treatment arms in either stratum (Table 3).

When efficacy and safety were combined (death, MI, stroke, or TIMI major non–CABG-related bleeding), there was a similar overall net clinical benefit for prasugrel over clopidogrel in patients who did (HR: 0.79; 95% CI: 0.67 to 0.92) or did not (HR: 0.85; 95% CI: 0.69 to 1.04, pinteraction = 0.57) receive a GP IIb/IIIa inhibitor during their index hospitalization.

**Key subgroups.** There was a consistent benefit of prasugrel versus clopidogrel for reducing CV events, irrespective of index diagnosis. For patients admitted with NSTEMI or UA, prasugrel as compared with clopidogrel reduced CV death, MI, or stroke in patients who did (HR: 0.84; 95% CI: 0.69 to 1.04) and those who did not (HR: 0.77; 95% CI: 0.60 to 0.98, pinteraction = 0.56) receive a GP IIb/IIIa inhibitor. Similarly, in STEMI patients, there was a consistent benefit for prasugrel reducing CV death, MI, or stroke regardless of whether subjects did (HR: 0.63; 95% CI: 0.47 to 0.84) or did not (HR: 0.84; 95% CI: 0.55 to 1.28, pinteraction = 0.27) receive a GP IIb/IIIa inhibitor. The relative risk of TIMI major bleeding with prasugrel versus clopidogrel did not differ significantly regardless of whether they received a GP IIb/IIIa inhibitor for patients with NSTEMI or UA (pinteraction = 0.50) or those with STEMI (pinteraction = 0.59).

We also examined the safety of prasugrel compared with clopidogrel in the setting of a GP IIb/IIIa inhibitor in key subgroups that had been found to have either less efficacy or greater absolute levels of bleeding, thereby resulting in less net clinical benefit or in clinical harm with prasugrel. The relative hazard of TIMI major bleeding with prasugrel versus clopidogrel was comparable regardless of whether or not they received a GP IIb/IIIa inhibitor, including patients whose body weight was <60 kg (HR: 1.42; 95% CI: 0.38 to 5.31 vs. HR: 1.92; 95% CI: 0.46 to 8.05, pinteraction = 0.76), those whose age was ≥75 years (HR: 1.37; 95% CI: 0.60 to 3.12 vs. HR: 1.17; 95% CI: 0.36 to 3.85, pinteraction = 0.89), or those with a previous history of transient ischemic attack or stroke (HR: 3.30; 95% CI: 0.67 to 16.3 vs. HR: 2.90; 95% CI: 0.30 to 28.2, pinteraction = 0.91).

**Discussion**

The current findings suggest that prasugrel compared with clopidogrel significantly reduces the risk of CV events in patients undergoing PCI after ACS, regardless of whether a GP IIb/IIIa inhibitor is used during index hospitalization. Importantly, the use of a GP IIb/IIIa inhibitor does not appear to accentuate the relative increase in bleeding observed with
prasugrel versus clopidogrel when a loading dose of thienopyridine is administered shortly before or at the time of PCI. Both prasugrel and clopidogrel are prodrugs that rely on cytochrome P450-dependent pathways to form their active metabolites (16). When compared with clopidogrel, prasugrel demonstrates more rapid, more potent, and more consistent inhibition of platelet aggregation (2,3). When a 60-mg loading dose is used, prasugrel significantly inhibits in vitro platelet aggregation within 30 min of administration (17). In contrast, clopidogrel requires several hours to achieve a significant antiplatelet effect when a 300-mg loading dose is used (18,19). These differences may in part be explained by a more efficient hepatic metabolism and conversion of prasugrel to its active metabolite (20).

These pharmokinetic and pharmacodynamic properties of prasugrel have been shown to result in improved clinical outcomes for patients with ACS undergoing PCI. In TRITON–TIMI 38, prasugrel significantly reduced the risk of recurrent CV events as compared with clopidogrel, both in the periprocedural period and during long-term follow-up (5,21). In particular, prasugrel significantly reduced the risk of nonfatal MI by 24% and reduced the risk of stent thrombosis by 52% during the course of the study. Consistent with a more potent antiplatelet effect, prasugrel significantly increased the risk of bleeding, including fatal bleeding, during long-term follow-up.

It has been previously shown that there is an added benefit for administering a GP IIb/IIIa inhibitor after a...
treated with clopidogrel had a greater number of recurrent ischemic events during index hospitalization. However, the frequency of GP IIb/IIIa use did not differ significantly between randomized treatment arms, and baseline characteristics were comparable for subjects randomized to prasugrel versus clopidogrel across both subgroups. In addition, the type of GP IIb/IIIa inhibitor that was used was not uniformly captured; therefore, we are unable to assess for consistency across different GP IIb/IIIa inhibitor subtypes. Finally, tests for heterogeneity are conservative, and the trial was not powered to examine outcomes within individual subgroups.

Conclusions

Prasugrel appears to be both safe and effective in the setting of GP IIb/IIIa inhibitor use in patients with ACS undergoing PCI. These data also support the concept that inhibition of platelet activation and aggregation are complementary and that there is additive value for enhanced targeting of the P2Y12 receptor in the setting of GP IIb/IIIa receptor blockade. Efforts should continue to be made to help identify those individuals who will have the potential to achieve the greatest benefit from treatment with prasugrel without a significant excess in bleeding.

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600-mg loading dose of clopidogrel in patients with non–ST-segment elevation ACS undergoing PCI (8). However, there are limited data examining whether there is any incremental benefit for administering a thienopyridine on a background of near-complete platelet aggregation inhibition with a GP IIb/IIIa inhibitor (22).

Why might there be additive value for administering a rapidly acting thienopyridine, such as prasugrel, in the setting of potent inhibition of platelet aggregation with a GP IIb/IIIa inhibitor? GP IIb/IIIa inhibitors prevent fibrinogen cross-linking and platelet aggregation by blocking the IIb/IIIa receptor on the activated platelet cell surface. In contrast, thienopyridines target the more upstream P2Y12 receptor, thereby inhibiting ADP-dependent platelet activation (4). In addition to stimulating the expression of GP IIb/IIIa receptors and promoting platelet aggregation, the P2Y12 receptor plays an important role in thrombus formation by promoting fibrinogen receptor activation, P-selectin expression, and the release of dense granules (23,24). As such, thienopyridines may influence multiple pathways related to thrombosis, including inflammation, endothelial function, and leukocyte–platelet interactions in addition to modulating platelet aggregation (25). In addition, because GP IIb/IIIa inhibitors are administered for a shorter duration of time, there may be incremental benefit of daily maintenance therapy with a thienopyridine that accrues during follow-up.

Our findings suggest that prasugrel significantly reduces the risk of CV events, irrespective of whether a GP IIb/IIIa inhibitor is used during the index hospitalization. In particular, prasugrel significantly reduced the risk of recurrent MI, urgent target vessel revascularization, and stent thrombosis both in subjects who were and were not treated with a GP IIb/IIIa inhibitor. These findings lend support to the concept that there is additional benefit for more potent GP IIb/IIIa receptor blockade. Randomized trials will be necessary to determine whether there is any incremental benefit for a GP IIb/IIIa inhibitor in the setting of prasugrel. Finally, despite the rapid onset of action of prasugrel, the use of a GP IIb/IIIa inhibitor did not appear to alter the relative risk of bleeding for patients treated with prasugrel versus clopidogrel when a thienopyridine loading dose is administered shortly before or at the time of PCI.

Study limitations. Limitations of the current analysis include that the use of a GP IIb/IIIa inhibitor was not randomized and was left to the discretion of the treating physician. Because the decision to treat with a GP IIb/IIIa inhibitor may be influenced by multiple variables including baseline characteristics and findings at coronary angiography, we did not compare efficacy and safety outcomes between subjects who did or did not receive a GP IIb/IIIa inhibitor. Similarly, although the trial was double-blinded, we cannot exclude the possibility that the decision to use a GP IIb/IIIa inhibitor may have been inadvertently influenced by randomized treatment arm because subjects...


Key Words: prasugrel • clopidogrel • thienopyridine • glycoprotein IIb/IIIa inhibitor • platelets • acute coronary syndrome • percutaneous intervention.