Early and Late Benefits of Prasugrel in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention

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

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Objectives
We evaluated the relative contributions of the loading and maintenance doses of prasugrel on events in a TRITON–TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction) analysis.

Background
Prasugrel is superior to clopidogrel in preventing ischemic events in patients with an acute coronary syndrome who are undergoing percutaneous coronary intervention, but it is associated with an increased risk of major bleeding.

Methods
Landmark analyses for efficacy, safety, and net clinical benefit were performed from randomization to day 3 and from day 3 to the end of the trial.

Results
Significant reductions in ischemic events, including myocardial infarction, stent thrombosis, and urgent target vessel revascularization, were observed with the use of prasugrel both during the first 3 days and from 3 days to the end of the trial. Thrombolysis In Myocardial Infarction major non–coronary artery bypass graft bleeding was similar to clopidogrel during the first 3 days but was significantly greater with the use of prasugrel from 3 days to the end of the study. Net clinical benefit significantly favored prasugrel both early and late in the trial.

Conclusions
Both the loading dose and maintenance dose of prasugrel were superior to clopidogrel for the reduction of ischemic events. This result emphasizes the importance of maintaining high levels of inhibition of platelet aggregation via P2Y12 receptor inhibition, not only for the prevention of periprocedural ischemic events but also during long-term follow-up. The excess major bleeding observed with the use of prasugrel occurred predominantly during the maintenance phase. Approaches to reduce the relative excess of bleeding with prasugrel should focus on the maintenance dose (e.g., reduction in maintenance dose in previously reported high-risk subgroups, such as the elderly and those patients with low body weight). (A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects Who Are to Undergo Percutaneous Coronary Intervention; NCT00097591) (J Am Coll Cardiol 2008;51:2028–33) © 2008 by the American College of Cardiology Foundation

The use of dual antiplatelet therapy with aspirin and a thienopyridine is an essential aspect of the supportive pharmacologic regimen administered to patients with an acute coronary syndrome (ACS) who are undergoing percutaneous coronary intervention (PCI) (1–3). To achieve levels of the active metabolite sufficient to inhibit the P2Y12 receptor around the time of PCI, the thienopyridine dosing strategy begins with a loading dose (1–3) followed by long-term therapy with a daily maintenance dose that should not be discontinued prematurely to avoid ischemic complications (4). Despite its established effectiveness as the thienopyridine element of the dual antiplatelet regimen, clopidogrel has several limitations, including only a modest antiplatelet effect with a delayed onset of action and considerable interpatient variability (5–7). The active
metabolite is generated more efficiently after the administration of the novel thienopyridine prasugrel, allowing construction of a dosing regimen that consistently yields significantly greater levels of inhibition of platelet aggregation (IPA) after both the loading dose and the maintenance dose (8).

The TRITON–TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitionN with Prasugrel–Thrombolysis In Myocardial Infarction) trial demonstrated that a prasugrel regimen of a loading dose of 60 mg and daily maintenance dose of 10 mg was significantly superior to the standard regimen of clopidogrel (300-mg loading dose and 75-mg daily maintenance dose) in preventing the composite end point of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke during a median duration of therapy of 15 months (9). The reduction in the primary end point was driven by a significant 24% reduction in MI, significant reductions of 34% and 52% in urgent target vessel revascularization and stent thrombosis, respectively, also occurred (9). These benefits of prasugrel over clopidogrel in preventing ischemic events were achieved at the cost of an increased rate of Thrombolysis In Myocardial Infarction (TIMI) major non–CABG-associated bleeding. Net clinical benefit (death from any cause, nonfatal MI, nonfatal stroke, and nonfatal TIMI major non–CABG-related bleeding) significantly favored the use of prasugrel over the course of the trial (9).

Both the loading and maintenance doses of prasugrel studied in TRITON–TIMI 38 yield greater levels of IPA than a standard dose of clopidogrel. Therefore, it is important to assess their relative contributions to the benefits of prasugrel in the reduction of ischemic events and excess bleeding observed in the trial and to examine the effects of prasugrel on the net clinical benefit of these doses. In the present paper, we explored the impact of the loading and maintenance doses of prasugrel over a range of individual pre-specified efficacy end points. The current analysis also provides us the opportunity to assess the timing of prasugrel’s impact on the risk of major bleeding and net clinical benefit.

Methods

Study protocol. As described previously, a total of 13,608 patients with an ACS (both unstable angina/non–ST-segment myocardial infarction [UA/NSTEMI] and ST-segment myocardial infarction [STEMI]) were randomized in TRITON–TIMI 38 (9). Because the objective was to compare the use of prasugrel with clopidogrel in patients with ACS who were undergoing PCI, the coronary anatomy of all UA/NSTEMI and post-STEMI patients had to be known to be suitable for PCI before randomization (10). If the coronary anatomy was previously known or primary PCI for STEMI was planned, pre-treatment with study drug was allowed for up to 24 h before PCI. Randomization was to occur before the onset of PCI, and blinded study drug administration was to be administered as soon as possible after randomization. Decisions regarding the choice of vessels for PCI, the devices used, and the adjunctive medications were at the discretion of the treating physician. During the maintenance phase, patients were to receive a daily dose of aspirin of 75 to 162 mg and the blinded study drug. After hospital discharge, follow-up visits were conducted at 30-day, 90-day, and at 3-month intervals thereafter for a minimum of 6 months and maximum of 15 months (10).

End points. Details of the definitions of the end points are described in previous reports (9,10). In the analyses reported herein, we used the same definitions of MI, urgent target vessel revascularization, stent thrombosis (Academic Research Consortium definite or probable) (11), TIMI major non–CABG–associated bleeding, and net clinical benefit as in the main trial. All end points used in the analyses in this report were adjudicated by members of an independent clinical events committee that was blinded to the treatment assignment.

The investigators had free and complete access to the data used for these analyses. Members of the TIMI Study Group independently conducted the analyses, wrote the paper using a copy of the raw database for the main trial, and take full responsibility for this report. All analyses were performed with the use of STATA/SE 9.2 (STATA Corp., College Station, Texas).

Statistical analyses. All efficacy analyses were performed according to the intention-to-treat principle. Safety analyses were conducted in the cohort of patients who received at least 1 dose of the study drug. The time to first event in the 2 treatment groups was analyzed using Kaplan-Meier curves and compared using the log-rank test.

Landmark analyses were performed with the pre-specified windows of randomization to day 3 and from day 3 to the end of the trial (9). The landmark method of survival analysis uses a fixed time after the initiation of treatment to assess the response in treatment groups (12,13). Landmark analysis specifies the cutpoint in time after start of treatment without regard to patient response to therapy. Of importance, this specification provides us the opportunity to perform a separate statistical test to determine whether the response to treatment after the landmark time is different in the treatment groups (12,13). It should be noted that a limitation of landmark analysis is that the original effects of randomization at entry into the trial are no longer present because of deaths or dropouts before the time of the landmark cutpoint. There is a precedent for landmark analyses in both oncology and cardiology (12,13), but because of the observational nature of landmark methodology,
the findings should be interpreted in the context of cumulative survival analyses from randomization to the end of the study (as reported previously for TRITON–TIMI 38) (9).

The rationale for selection of the day 3 cutpoint for the landmark analyses was to separate, as much as possible, events that could be attributed to the loading dose (periprocedural events) and maintenance dose (events during long-term follow-up) phases of the study. On the basis of a previously reported pharmacodynamic and pharmacokinetic study of prasugrel and clopidogrel, a stable level of IPA attributable to the maintenance dose was evident by day 3 and was also independent of the loading dose of clopidogrel administered (14). When performing the landmark analyses from day 3 to the end of the trial, we ascertained that the number of patients at risk included all patients who were alive, regardless of whether a nonfatal event had occurred during the first 3 days, and had not withdrawn consent for follow-up. We considered $p < 0.05$ to indicate statistical significance. Hazard ratios (HRs) and associated 95% confidence intervals were calculated with a Cox proportional hazards survival model to evaluate the relative treatment effect. For subgroup analyses, an interaction term between the randomized treatment and subgroup was entered into a Cox model.

Results

A total of 13,608 patients were randomized and formed the intention-to-treat cohort. Of these, 99% underwent PCI and 94% received at least 1 stent. The safety cohort consisted of 13,457 patients who had received at least 1 dose of study drug.

Efficacy. The 3-day landmark analyses for the ischemic events of MI, stent thrombosis, and urgent target vessel revascularization are shown in Figure 1. A consistent pattern of significant reductions in each of these end points with prasugrel was found during the first 3 days and from 3 days to the end of the trial. The reduction in the HR for MI in favor of the prasugrel group was 19% in the first 3 days and 31% from 3 days to the end of the trial.

Reductions in the HR were observed with prasugrel for stent thrombosis (51% reduction by 3 days [$p = 0.006$] and 55% reduction from 3 days to the end of the trial [$p < 0.0001$]) and urgent target vessel revascularization (34% reduction by 3 days [$p = 0.047$] and 35% reduction from 3 days to the end of the trial [$p = 0.0003$]). Of the 300 episodes of urgent target vessel revascularization that occurred from 3 days to the end of the trial, glycoprotein IIb/IIIa inhibitors were used in 57 (19.0%) cases (14 [11.8%] with prasugrel and 43 [23.8%] with clopidogrel; $p = 0.01$).

During the maintenance phase, the absolute risk differences with prasugrel were 1.39%, 0.94%, and 1.03% for the end points of MI, stent thrombosis, and urgent target vessel revascularization, respectively. Inspection of the event curves shows a progressive widening of the differences between the 2 treatment groups for stent thrombosis and urgent target vessel revascularization during the first 3 days and for all 3 efficacy end points from 3 days to the end of the trial.

Interaction tests showed no significant effect of stent type at the index PCI (bare-metal stents vs. drug-eluting stents) on the treatment benefits of prasugrel in preventing urgent target vessel revascularization during the first 3 days ($P_{\text{interaction}} = 0.35$) or from 3 days to the end of the trial ($P_{\text{interaction}} = 0.17$). Similarly, there was no effect of stent type on prevention of stent thrombosis with prasugrel during the first 3 days ($P_{\text{interaction}} = 0.16$) or from 3 days to the end of the trial ($P_{\text{interaction}} = 0.64$).
Safety and net clinical benefit. The 3-day landmark analyses for TIMI major non-CABG bleeding and net clinical benefit are shown in Figure 2. Through the first 3 days, the rate of TIMI major non-CABG bleeding was numerically greater with the use of prasugrel (0.74%) compared with clopidogrel (0.61%), but this 0.13% absolute risk increase did not achieve statistical significance. From 3 days to the end of the trial, the rate of major bleeding was significantly greater with the use of prasugrel compared with clopidogrel (39% increase in the HR and 0.48% absolute risk increase). An interaction test of the treatment effect of prasugrel on major bleeding in the 0- to 3-day and >3-day periods was not significant (P<sub>interaction</sub> = 0.62). Inspection of the event curves for major bleeding does not suggest progressive widening of the differences between the treatment groups for the first 3 days, but there does appear to be a steeper increase in the rate of bleeding events over time with prasugrel compared with clopidogrel from 3 days to the end of the study. The net clinical benefit composite end point was significantly in favor of prasugrel both during the first 3 days and from 3 days to the end of the study. The reduction in the HR was 15% and 13% during the 2 time periods, respectively.

Discussion

The findings of the present analysis add considerably to the understanding of the profile of the clinical response to prasugrel compared with clopidogrel in patients with an ACS undergoing PCI. We previously reported in a landmark analysis that treatment with prasugrel was associated with significant reductions in the primary end point by the first pre-specified time point, 3 days as well as from 3 days to the end of the trial (9). The exploratory landmark analyses reported here show that there is a consistent significant benefit of prasugrel across multiple individual efficacy end points both early (loading dose phase) and late (maintenance dose phase) after randomization in TRITON–TIMI 38. There is internal consistency in that prasugrel prevented a range of ischemic events that are related to platelet activation and aggregation. The benefits of prasugrel in preventing ischemic events not only emerged rapidly (avoidance of periprocedural events) but continued to accrue during long-term treatment (avoidance of recurrent events). These efficacy observations support the concept that prasugrel is superior to the standard dose of clopidogrel as the thienopyridine both for acute pharmacologic support of PCI as well during the chronic phase of management after PCI (9).

The chemical structure of prasugrel leads to the more efficient conversion of the prodrug to its active metabolite with less dependence on specific cytochrome P-450 enzymes (8). As reported in studies of platelet function, there is a very rapid onset of substantial levels of IPA achievable with prasugrel, levels that are significantly greater than can be achieved by standard dosing with clopidogrel (8). The greater prevention of the periprocedural events of MI, stent thrombosis, and urgent target vessel revascularization during the first 3 days with prasugrel compared with standard dosing with clopidogrel is therefore likely the result of rapid attainment of much greater levels of IPA. The speed of onset of prasugrel’s antplatelet effect offers the clinician the opportunity to determine that the coronary anatomy is suitable for PCI before committing to irreversible P2Y<sub>12</sub> inhibition. This strategy overcomes the liability of a commonly used strategy of pre-treating with clopidogrel before PCI, which exposes patients to substantially increased risks of perioperative bleeding if urgent CABG surgery is required as well as non-CABG-related bleeding (15–17).

The 10-mg maintenance dose of prasugrel also produces significantly greater levels of IPA than the standard 75-mg maintenance dose of clopidogrel (8). Our landmark analyses and the shape of the event curves from day 3 through the end of the trial are consistent with an independent benefit of prolonged treatment with prasugrel compared with clopidogrel. The more consistent and greater levels of IPA with 10 mg of prasugrel reported in platelet function studies...
translated into prevention of more ischemic events in patients during the maintenance phase of therapy after PCI (8). Especially notable among these results was the large treatment effect on stent thrombosis, an infrequent but serious and often fatal complication after PCI (18).

The landmark analyses reported herein provide one important step in linking the greater levels of IPA achieved with the loading and maintenance doses of prasugrel compared with standard doses of clopidogrel in preventing early and late ischemic events. Of note, significantly greater levels of IPA were achieved with the loading and maintenance doses of prasugrel studied in the TRITON–TIMI 38 trial even when compared with higher-than-standard doses of clopidogrel (600-mg loading dose and 150-mg maintenance dose) in the PRINCIPLE–TIMI 44 (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis In Myocardial Infarction) trial (19). Furthermore, the ISAR-REACT 2 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) investigators reported that even pre-treatment with 600 mg of clopidogrel before PCI was inadequate antiplatelet therapy in patients with NSTEMI and additional treatment with abciximab was required to limit ischemic events (20).

Although formal interaction testing of the impact of prasugrel on early and late bleeding events was not significant, it should be noted that such interaction tests are relatively weak and may fail to detect important quantitative differences if the number of events is small, as is the case for bleeding within the first 3 days. On the basis of the absolute and relative event rates, our landmark analysis suggests the period from 3 days to the end of the trial as the major risk period for excess bleeding with prasugrel. As noted in several Food and Drug Administration guidance documents, the relationship between exposure and response to a drug may place certain subsets of the population at increased risk of toxicity (21,22). This relationship can be assessed through population-pharmacokinetic studies embedded within a large trial (21). Modeling can be used to predict modified dosing regimens for special populations to maintain efficacy and reduce risk (21). We previously identified several high-risk patient subsets of the TRITON–TIMI 38 trial population for whom net clinical benefit analyses were neutral (i.e., reduction in primary end point events was offset by an increase in bleeding events) and who may be candidates for a reduced maintenance dose (9). These subsets include individuals ≥75 years of age and those weighing <60 kg (together representing approximately 16% of the patients studied in TRITON–TIMI 38). Although the elderly and low body weight patients tended to have fewer primary end point events with prasugrel versus clopidogrel, this result was offset by a greater rate of major bleeding, resulting in a neutral net clinical benefit end point (9). Our landmark analyses of major bleeding suggest that the focus of ongoing population-pharmacokinetic analyses in TRITON–TIMI 38 should be on modeling to identify a suitable reduction of the maintenance dose in such high-risk groups.

Clinical implications. The superiority of both the loading dose and maintenance dose of prasugrel compared with the standard dose of clopidogrel emphasizes the benefits of high levels of IPA via P2Y₁₂ receptor inhibition not only for prevention of periprocedural ischemic events but also during long-term follow-up. The greatest risk of the more aggressive antiplatelet regimen with prasugrel is excess major bleeding, especially during chronic therapy. Efforts to minimize the risk of excess bleeding with prasugrel are needed. A logical approach in this regard is reduction of the maintenance dose (e.g., 5 mg) in previously reported high-risk subgroups (elderly, low body weight) (9).

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