Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 51, No. 21, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.04.002

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 $P2Y_{12}$ 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 $P2Y_{12}$ 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

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Manuscript received January 17, 2008; revised manuscript received March 7, 2008, accepted April 7, 2008.

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 InhibitioN 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 noncoronary artery bypass grafting (CABG)–related 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).

Abbreviations and Acronyms

ACS = acute coronary syndrome
CABG = coronary artery bypass graft
HR = hazard ratio
IPA = inhibition of platelet aggregation
MI = myocardial infarction
PCI = percutaneous coronary intervention
TIMI = Thrombolysis In Myocardial Infarction
UA/NSTEMI = unstable angina/non–ST-segment myocardial infarction

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,