

Introduction

Welcome to this month's issue of PlateletNEWS Monthly, a newsletter dedicated to providing timely information in a concise format from the latest meetings and published research on topics related to the use of antiplatelet therapies in cardiology. In this issue, we report on 2 important trials presented at Transcatheter Cardiovascular Therapeutics (TCT) 2007 in Washington, DC, and at the American Heart Association (AHA) Scientific Sessions 2007 in Orlando, FL: the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) study and the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38, respectively.

Stay tuned for further updates on important issues related to antiplatelet strategies in subsequent issues.

Assessing Bivalirudin in AMI: Results of HORIZONS AMI

Results from the HORIZONS AMI study presented by principal investigator Gregg Stone, MD, at TCT 2007 indicate that the use of bivalirudin following primary angioplasty in ST-segment elevation myocardial infarction (STEMI) reduces 30-day net adverse clinical events and major bleeding compared with standard use of unfractionated heparin (UFH) plus a glycoprotein (GP) IIb/IIIa inhibitor.¹

The trial enrolled 3,602 patients undergoing primary angioplasty for STEMI and randomized them to receive either a standard regimen of UFH plus a GP IIb/IIIa inhibitor or the thrombin inhibitor bivalirudin alone. The primary endpoints were (1) net adverse clinical events, a composite of major bleeding and major adverse cardiovascular events (death, reinfarction, stroke, and ischemic target vessel revascularization) and (2) major bleeding at 30 days. At 30 days, bivalirudin-treated patients had a 24% reduction in the occurrence of the composite endpoint net adverse clinical events compared with patients who received UFH plus a GP IIb/IIIa inhibitor (12.1% vs. 9.2%; $P = 0.006$). Moreover, a significant 40% reduction in the incidence of major bleeding was demonstrated in patients who received bivalirudin alone (8.3% vs. 4.9%, $P < 0.0001$). Cardiac-related mortality at 30 days was reduced by 38% in the bivalirudin group (2.9% vs. 1.8%; $P = 0.035$). There was no significant difference in 30-day rates of stent thrombosis, but acute stent thrombosis within 24 hours was higher in the bivalirudin group (1.3% vs. 0.3%; $P = 0.0009$). Importantly, a second arm of this trial randomized the 3,000 patients who went on to stenting to receive either bare metal stents or TAXUS paclitaxel-eluting stents; results of the second phase of HORIZONS AMI are forthcoming.

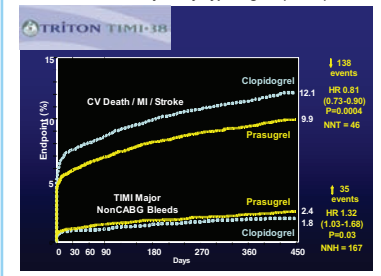
Landmark Results from the TRITON-TIMI 38 Trial

Results from the landmark TRITON-TIMI 38 trial were published² and presented³ on November 4, 2007, at the AHA Scientific Sessions. The trial enrolled 13,608 patients (including 3,534 patients with STEMI) with acute coronary syndromes scheduled for percutaneous coronary intervention.

The trial showed significant reductions in ischemic events, including stent thrombosis, but an increase in major bleeding, including fatal bleeding, in patients treated with the novel thienopyridine prasugrel compared with clopidogrel. Patients in TRITON-TIMI 38 were randomized to receive either a 60 mg loading dose of prasugrel (maintenance dose of 10 mg/day for 6 to 15 months) or a 300 mg loading dose of clopidogrel (maintenance dose of 75 mg/day for 6 to 15 months). The rate of the composite primary endpoint (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) was significantly reduced in the prasugrel group compared with the clopidogrel group (12.1% vs. 9.9%; hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.73 to 0.90; $P < 0.001$). This significant decrease was observed by the first prespecified timepoint (3 days) and persisted to the end of the study. The reduction in the primary endpoint was largely due to a reduction in MI in the prasugrel group (9.7% with clopidogrel vs. 7.4% with prasugrel; HR, 0.76; 95% CI, 0.67 to 0.85; $P < 0.001$).

The benefit of prasugrel was particularly robust among the prespecified subgroup of patients with diabetes ($N = 3,146$; 17.0% vs. 12.2%; $P < 0.001$) compared with patients without diabetes ($N = 10,462$; 10.6% vs. 9.2%; $P = 0.02$). There was also a notable 52% relative reduction in stent thrombosis in the prasugrel group (1.1% compared with the clopidogrel group (2.4%) ($P < 0.001$). However, prasugrel-treated patients demonstrated an increased risk of major TIMI hemorrhage compared with those who received clopidogrel (2.4% vs. 1.8%; HR, 1.32; 95% CI, 1.03 to 1.68; $P = 0.03$). This excess bleeding risk in the prasugrel group included a higher rate of life-threatening bleeding (1.4% vs. 0.9%; HR, 1.52; 95% CI, 1.08 to 2.13; $P = 0.01$) and fatal bleeding (0.4% vs. 0.1%; $P = 0.002$). Intracranial hemorrhage occurred in no patients in the clopidogrel group and 6 patients in the prasugrel group ($P = 0.02$). The figure to the right was presented by Elliott M. Antman, MD, to depict the balance between efficacy and safety in the trial.

Figure. Cumulative Kaplan-Meier estimates of the primary efficacy endpoint (death from cardiovascular causes, nonfatal myocardial infarction [MI], or nonfatal stroke) and thrombolysis in myocardial infarction (TIMI) major bleeding not related to coronary artery bypass graft (CABG)



Presented at: American Heart Association Scientific Sessions 2007. <http://www.sciencemanager.org/sessions2007/itinerary07/sessions/player.html?psid=071101/PS.01.2006>. Accessed November 16, 2007.

A prespecified analysis of net clinical benefit—including the efficacy and bleeding endpoints of death from any cause, nonfatal MI, nonfatal stroke, and TIMI major hemorrhage—favored prasugrel. This endpoint occurred in 13.9% of clopidogrel-treated patients vs. 12.2% of prasugrel-treated patients (HR, 0.87; 95% CI, 0.79 to 0.95; $P = 0.004$); thus, it is estimated that for every 1,000 patients treated with prasugrel, 23 MIs would be prevented, with an excess of 6 TIMI major hemorrhages. A post hoc analysis demonstrated net clinical harm in prasugrel-treated patients who had a previous stroke or transient ischemic attack (representing approximately 4% of the study population); these patients had more primary endpoint events and higher rates of bleeding with prasugrel compared with clopidogrel. Two other subgroups, representing approximately 16% of the study population (patients ≥ 75 years of age or those with a body weight < 60 kg), had fewer primary endpoint events but a higher incidence of bleeding, resulting in a net clinical benefit near unity.

References

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