Comparison of Prasugrel and Clopidogrel for Patients Undergoing PCI for ACS

More potent antiplatelet therapy with prasugrel reduced the rate of ischemic events compared with clopidogrel among patients with acute coronary syndromes (ACS) with planned percutaneous coronary intervention (PCI). TRITON-TIMI 38 showed that patients treated with the novel thienopyridine prasugrel had a significant net clinical benefit compared with clopidogrel, the standard therapy for patients undergoing PCI.

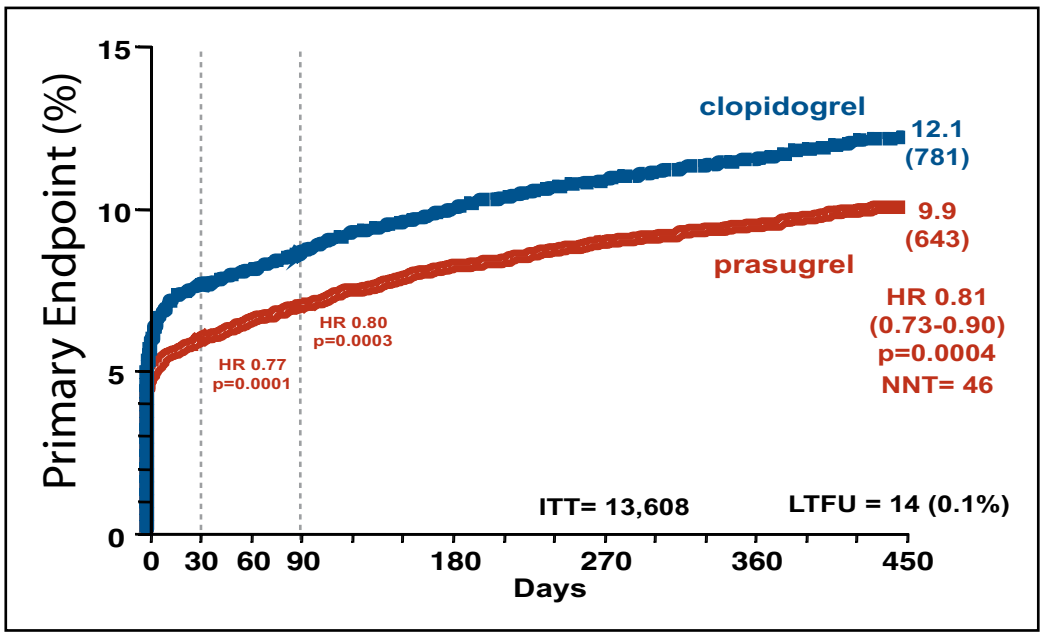
"There was an early and sustained benefit that was apparent across the ACS spectrum," said Elliott Antman, MD, Brigham and Women's Hospital, Boston, MA, who reported on the study. He added that the drug was associated with an increased risk of bleeding among specific subgroups of patients, indicating that the optimum use of the drug and its dosing are crucial issues to explore.

Dr. Antman explained that prasugrel produces rapid and high levels of platelet inhibition and that the trial was designed to test the hypothesis that a greater degree of platelet inhibition would reduce ischemic events as well as to evaluate the safety of prasugrel.

The multicenter trial enrolled 13,608 patients with ACS scheduled for PCI. Patients were randomly assigned to standard clopidogrel (300 mg loading dose and 75 mg daily for 6-15 months) or to prasugrel (60 mg loading dose and 10 mg daily for the same period).

Prasugrel was associated with a 19% reduction in the primary endpoint, a composite of cardiovascular death, nonfatal myocardial infarction (MI), or stroke (9.9% for prasugrel vs 12.1% for clopidogrel; p=0.0004). The benefit of prasugrel was evident both early (3 days) and late (450 days) (Figure 1). Mortality was similar for the two groups. The "most dramatic effect," said Dr. Antman, was a 52% reduction in stent thrombosis (1.1% for prasugrel vs 2.4% for clopidogrel; p<0.0001).

Figure 1. Cumulative Kaplan-Meier Estimates of the Rates of Key Study End Points During the Follow-Up Period.



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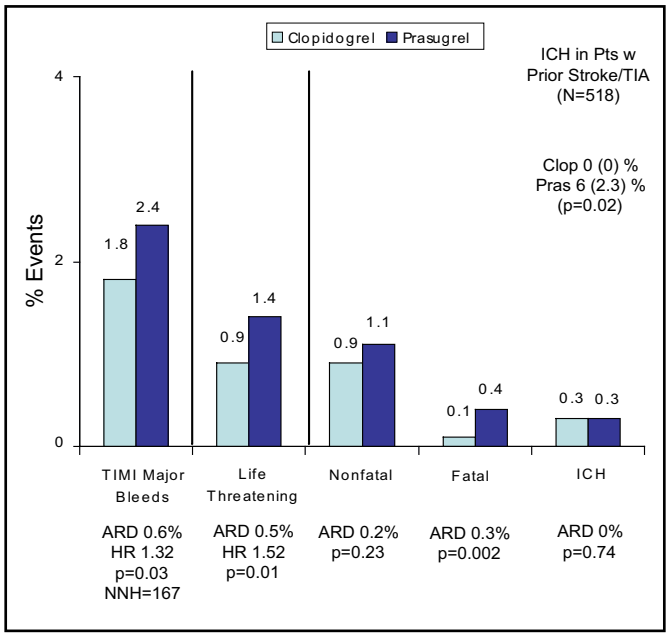
Significantly more TIMI major bleeding occurred with prasugrel (2.4%) than with clopidogrel (1.8%; p=0.03). Prasugrel use was also associated with significantly greater nonfatal, life-threatening, and fatal bleeding (Figure 2). The findings of a prespecified analysis of net clinical benefit significantly favored prasugrel (13.9% vs 12.2%; p=0.004).

Figure 2. Bleeding Events Safety Cohort (n=13,457).



The increased efficacy coupled with the increased risk for bleeding led the investigators to conduct post hoc exploratory analyses to identify subgroups of patients who did not have a net clinical benefit from prasugrel. These subgroups were found to be patients who were 75 years or older (HR, 0.99; p=0.92) or who weighed less than 60 kg (HR, 1.03; p=0.89). Patients with a history of cerebrovascular events also had no net clinical benefit as well as evidence of significant harm from prasugrel. Among patients with such a history, a composite endpoint of death from any cause, nonfatal MI, nonfatal stroke, or non-coronary artery bypass graft-related TIMI major bleeding was associated with a hazard ratio of 1.54 (p=0.04).

Further studies are needed to help define populations at increased risk for bleeding and determine optimal dosing. "Optimization of prasugrel maintenance dosing in a minority of patients may help improve the benefit-risk balance," said Dr. Antman.

The findings of this study have been published: [Wiviott et al. NEJM 2007;357:2001-2015].

Stem Cells for the Scarred Heart: A Mix of Positive and Negative Results

Skeletal Stem Cells Improve Heart Function

Intracoronary (IC) injection of skeletal muscle stem cells within days of myocardial infarction (MI) increases heart function after 1 year, according to findings of the Catheter-Based Delivery of Autologous Skeletal Myoblasts for Ischemic Cardiomyopathy: Feasibility, Safety and Improvement in Cardiac Performance (CAuSMIC) trial.

In the open-label, phase 1 trial, 23 patients with ischemic cardiomyopathy and EF ≤40% were randomly assigned to treatment with optimal medical therapy (OMT) alone (n=11) or OMT plus autologous skeletal myoblast (ASM) transplantation (n=12). Patients assigned to ASM therapy underwent a thigh muscle biopsy to harvest 2-5 g of skeletal muscle, representing 10,000-50,000 cells. Isolated myoblasts were grown until as many as 600 million cells were available for transplantation. Patients in the ASM group received one of four doses – 30, 100, 300, or 600 million cells – delivered to the heart with a catheter guided by an investigational three-dimensional mapping system.

Nabil Dib, MD, University of California, San Diego, CA, and colleagues determined that all ASM transplant procedures were performed successfully and without injection-related complications, meeting the primary endpoints of feasibility and safety. At 12 months follow-up, there were no deaths, MI, or cerebrovascular events in either treatment group, although one patient in each treatment group was hospitalized for congestive heart failure.

Functional capacity also improved in the transplantation group. Among ASM patients, mean NYHA class improved by roughly one class from baseline to 6 months (2.7 vs 1.5, respectively; p<0.0001) and 1 year (1.7; p<0.0001; Figure 1). Quality of life also appeared to improve in the ASM arm, as demonstrated by an improvement in Minnesota Living with Heart Failure Score from baseline to 6 months (p=0.02) and 1 year (p=0.002). By comparison, functional capacity and quality of life tended to worsen over time.