

TRITON Analysis: Prasugrel Curbs Second MI

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WASHINGTON — A new subanalysis of the TRITON-TIMI 38 trial shows that prasugrel significantly reduced the risk of death and subsequent heart attack in patients who had a first MI during the study.

Examining the full response of patients who have an event in any trial provides valuable information about a drug's total effect, Dr. Eugene Braunwald reported at a symposium sponsored by the Cardiovascular Research Institute at the Washington Hospital Center. Most patients who have a primary end point event will survive and stay in the study, although only that first event is included in the outcome analysis.

"The classical analysis we do in all clinical trials doesn't tell the whole story—the number of total events. A subanalysis of what happens to these patients tells you a lot about what the drug actually does," said Dr. Braunwald of Brigham and Women's Hospital, Boston, and chairman of the TIMI study group.

The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction) randomized 13,608 patients who had moderate- to high-risk acute coronary syndromes and were scheduled for percutaneous coronary intervention to either the investigational thienopyridine prasugrel (60-mg loading dose followed by

10-mg daily maintenance dosage) or clopidogrel (300-mg loading dose followed by 75-mg daily maintenance dosage), for up to 15 months.

Those taking prasugrel were 19% less likely to experience cardiovascular death, MI, or stroke; the number needed to treat was 46. However, Dr. Braunwald noted, "there was no free lunch." Prasugrel carried a 6% increased risk of major bleeding, with 35 more incidents than occurred in the clopidogrel group.

The new analysis concluded that even among those 1,424 patients who had a first primary end point event, prasugrel was significantly more effective than clopidogrel at reducing the risk of death and subsequent events.

"After the first event, patients who were assigned to clopidogrel had an additional 113 events, compared to an additional 56 events among those taking prasugrel," Dr. Braunwald said. "That was a highly significant difference. Additionally, there were 40 deaths after the initial event in the clopidogrel group, but only 14 in the prasugrel group, for a significant risk reduction of 34%."

He also presented analyses examining prasugrel's sustained reduction in the risk of secondary end point events in the entire

study group. Over the 15-month study period, prasugrel reduced urgent target vessel revascularization by 34%. This significant difference appeared within the first 30 days (47% reduction) and continued throughout the next 14 months (21% reduction).

Overall, prasugrel reduced stent thrombosis by 52%, compared with clopidogrel. That difference also emerged quite early, in the first 3 days of administration (51% reduction).

The TIMI study group continues to analyze prasugrel's effect in patients with either bare metal or drug-eluting stents, Dr. Braunwald said. "The analyses are not complete, but I think we can say that the 50% reduction in stent

thrombosis will be similar for both bare metal and drug-eluting stents."

Dr. Braunwald stressed that excess bleeding is the price for more effective platelet inhibition. "While there were no significant differences in the number of instrumented bleeds, there were significantly more spontaneous bleeds. Although the absolute number of events was small, the difference was significant."

Even the excess bleeding, however, doesn't significantly negate prasugrel's overall benefit, Dr. Deepak Bhatt said while commenting on Dr. Braunwald's

presentation. "The net clinical benefit was very significantly in favor of prasugrel even when you consider the bleeding episodes," said Dr. Bhatt of the Cleveland Clinic. Despite this, he said, it will be important to continue analyzing the incidences of bleeding in both groups.

"Other trials suggest a relationship between bleeding and mortality, apart from the obvious [death resulting from exsanguination]. Bleeding can lead to hypotension, transfusion that may or not be appropriate, and cessation of aspirin or any other form of antithrombotic therapy, either by the doctor or by the patient without the doctor's knowledge. By other pathways, bleeding may lead to ischemia, stent thrombosis, or inflammation, which may contribute to mortality."

The trial's finding of an attenuated bleeding risk among patients with diabetes (about 3,000) is an intriguing one, Dr. Bhatt noted. In this group, the rates of bleeding were not different between the two study drugs (2.6% prasugrel vs. 2.5% clopidogrel). "This could be a chance finding due to the small patient group, but an alternative explanation is that patients like diabetics, whose platelets are already 'revved up,' are most likely to derive benefit from prasugrel and least likely to suffer harm from it.

Both Dr. Braunwald and Dr. Bhatt reported receiving grants from Daiichi Sankyo Co. and Eli Lilly & Co., sponsors of the TRITON-TIMI 38 study. ■

Bypassing Emergency Dept. Speeds Door-to-Balloon Times

BY MARY ANN MOON
Contributing Writer

A citywide program that relies on patient referral by paramedics dramatically shortened door-to-balloon times and halved in-hospital mortality among patients with ST-segment elevation myocardial infarction.

Launched in May 2005 in Ottawa (population 800,000), the program allows specially trained paramedics to triage and transport STEMI patients directly to a percutaneous coronary intervention (PCI) center, bypassing the emergency department. The program was developed after researchers had shown that paramedics there could accurately interpret prehospital ECGs and identify STEMI, Dr. Michel R. Le May and his associates reported.

Paramedics with advanced training in cardiac life support perform and interpret 12-lead ECGs at the scene, then triage and transport patients with STEMI to the city's designat-

ed PCI center at the University of Ottawa Heart Institute, bypassing the city's four EDs. The paramedics also use a dedicated phone line to notify the cardiology team to anticipate the patient's arrival and assemble near the catheterization laboratory.

During the first year of the program, 135 STEMI patients were thus referred directly from the field by paramedics, said Dr. Le May of the heart institute and his associates (N. Engl. J. Med. 2008;358:231-40).

Another 209 STEMI patients went through the usual process of presenting to one of the four EDs either on their own or by ambulance not staffed by specially trained paramedics. These patients were triaged by an ED nurse, evaluated by an ED physician, and immediately transferred to the designated PCI center by ambulance. All the EDs were within a 10-minute ambulance ride of the PCI center. The median door-to-balloon time was significantly shorter for patients referred from the

field (69 minutes) than for those transferred from EDs (123 minutes).

Door-to-balloon times of less than 90 minutes, as recommended in current guidelines, were achieved in 80% of patients referred from the field, compared with only 12% of those transferred from EDs, the investigators said.

"Before implementation of this approach, these patients (almost 40% of the entire cohort) would have been brought to the nearest hospital ED and considered for fibrinolysis. In this respect, the change in referral practice clearly benefited a substantial proportion of patients," Dr. Le May and his associates noted.

In-hospital mortality was 3% for patients referred directly by paramedics, compared with 6% for those transferred from EDs. "Before we re-engineered our strategies, in-hospital mortality [for STEMI] was 10% for patients presenting to our city's EDs between 2002 and 2004," they said. ■

'Rebound' Effect in MI Patients Found After Ending Clopidogrel

The risk of myocardial infarction or death spikes during the 90 days after clopidogrel therapy is discontinued among patients treated for acute coronary syndromes, especially those treated medically.

Clustering of adverse coronary events has been reported after cessation of long-term aspirin and heparin therapy in acute coronary syndrome (ACS) patients. Dr. P. Michael Ho of the Denver Veterans Administration Medical Center and his associates assessed whether clopidogrel withdrawal was associated with a similar "rebound" effect.

The investigators analyzed data on all patients with acute MI or unstable angina who were discharged from any of 127 VA medical centers throughout the country between 2003 and 2005 with prescriptions for clopidogrel. A total of 1,568 of these patients who had been treated medically and 1,569 who had undergone PCI took the drug for a mean of 302 and 203 days, respectively, then discontinued the treatment.

In the medically treated patients, the combined end point of all-cause mortality or ACS occurred in 268 patients (17%) after they stopped taking clopidogrel. Significantly more (163) of those events occurred with-

in 90 days of clopidogrel discontinuation than occurred at 91-180 days (57) or 181-270 days (26).

In PCI-treated patients, who took clopidogrel for an average of 278 days after their procedure, death or ACS occurred in 124 (8%) after discontinuation. As with the medically treated patients, significantly more of the primary end point events occurred within 90 days of cessation (73), compared with days 91-180 (29) and days 181-270 (8).

"We found a clustering of death or acute MI in the initial 90-day period after stopping treatment with clopidogrel, compared with later follow-up intervals," the investigators said (JAMA 2008;299:532-9).

The incidence rate of adverse events was higher by far in the medically treated patients within 90 days of drug cessation, at 1.31 per 1,000 patient-days, than in those patients during days 91-180 (0.69) or in the PCI group during the same period (0.57).

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—Mary Ann Moon