Tailored Clopidogrel Cut Adverse Events After PCI

BY CAROLINE HELWICK
Contributing Writer

New Orleans — A tailored approach to dosing the antiplatelet agent clopidogrel significantly reduced the rate of adverse events after nonemergent percutaneous coronary intervention with stenting, in a study by French investigators presented at the annual scientific sessions of the American Heart Association.

The results of the Tailored Clopidogrel Loading Dose According to Platelet Reactivity Monitoring to Prevent Stent Thrombosis trial were presented by Dr. Franck Paganelli, professor of medicine in the division of cardiology, Hôpital Nord, University of Marseille (France).

"The response to clopidogrel is unpredictable, and there is a link between low response and thrombolytic events," he noted. Investigators therefore aimed to develop an individualized approach to enhance the benefit of clopidogrel by lowering the patient's score on the vasodilator-stimulated phosphoprotein (VASP) index, a phosphorylation analysis that measures antiplatelet response to the drug. A cut-off value of 50% indicates lack of response and deems patients to be at high risk for major adverse cardiac events (MACE).

"Our aim was to demonstrate that a decrease in the VASP index may also reduce thrombosis," Dr. Paganelli said.

The multicenter prospective study included 429 patients with low responses to clopidogrel (VASP index of at least 50%) drawn from a cohort of 1,122 patients undergoing nonemergent PCI for ACS or stable angina. Of those, 215 were randomized to the control arm to receive usual care with one 600-mg dose of clopidogrel, and the remaining 214 were assigned to the VASP-guided loading dose arm, to receive up to three additional doses of clopidogrel every 24 hours. The primary end point was the rate of early definite stent thrombosis. Secondary end points were the rates of MACE, defined as MI, cardiovascular death, urgent revascularization, and bleeding events.

Platelet reactivity monitoring showed that after the first clopidogrel bolus, all patients in both arms still had a VASP response of at least 50%. After the second 600-mg bolus, 70% of patients achieved a VASP of less than 50%, and the remaining 30% went on to receive a third and sometimes a fourth 600-mg dose until their VASP index fell below 50%. Despite the use of 2,400 gm of clopidogrel, 17 patients (8%) remained unresponsive, with a VASP index that remained above 50%, Dr. Paganelli reported.

Tailored dosing significantly lowered the primary and secondary end points without significantly increasing bleeding. The primary end point—early definite stent thrombosis during 1 month of follow-up—was observed in only 1 patient (0.5%) in the experimental arm, compared with 10 (4.7%) receiving usual care. Subacute stent thrombosis also was significantly reduced, occurring in one patient (0.5%) vs. eight (3.7%). Major bleeding occurred in fewer than 1% of each arm and minor bleeding in about 2%-3%. There were no cases of intracerebral or fatal hemorrhages.

Importantly, rates of MACE also were significantly lower in the individualized treatment group, at 0.5%, compared with 8.9% in the control group. "When you decrease the VASP index, you decrease thrombosis," Dr. Paganelli noted.

"We also concluded that there are three kinds of patients," he added: good responders, who have a VASP below 50%; low responders, who have a VASP above 50% and who can be improved with additional clopidogrel loading; and resistant patients, who have a VASP above 50% despite receiving up to 2.4 g of clopidogrel.

The investigators creatively studied 'the optimum loading dose of clopidogrel in patients undergoing PCI.'

DR. ANTMAN

"Our message is 'yes, we can,' " he added. "We can develop a therapeutic window for antiplatelet therapy that will avoid MACE in patients undergoing PCI."

Dr. Elliott M. Antman, professor of medicine at Harvard Medical School and director of the Samuel A. Levine cardiac unit at Brigham and Women's Hospital, both in Boston, discussed the findings. "This is a very important observation," he told the media at a press conference. "The investigators have studied, in a creative fashion, the optimum loading dose of clopidogrel in patients undergoing PCI."

"There is considerable variation in response to clopidogrel, one reason being the patient's inability to convert the prodrug clopidogrel into the active form that inhibits platelets," he explained. "This involves a two-step reaction in the liver, which depends on the integrity of enzymes to convert clopidogrel to the active metabolite. There is marked genetic variation in this … and patients [unable to do this] have a marked increase in thrombotic events with stenting."

Regarding the tailored dosing approach described in the study, Dr. Antman commented that "giving iterative loading doses of clopidogrel takes some time. It could take 1-3 days to go through the iterative loading process, especially in patients who need to go to three or four doses."

One means is to empirically give a higher dose, which is being evaluated in ongoing clinical trials. Another is to use a laboratory test, as was done in this study, he said. "We need much more information about the integrity of these tests and how to use them," he added. "In the future, we may have alternatives to clopidogrel, and this may make it simpler than the iterative dosing technique." ■

Eptifibatide Increased Bleeding, Added No Benefit in ASSIST

BY JEFF EVANS
Senior Writer

Washington — The adjunctive use of eptifibatide in antithrombotic regimens that are given to patients undergoing primary percutaneous coronary interventions for acute ST-segment elevation myocardial infarction significantly increases the rate of bleeding when compared with heparin alone, according to a small randomized trial.

This increased bleeding rate—plus a lack of any added benefit with eptifibatide—raises the question of whether treatment with a glycoprotein (GP) IIb/IIIa inhibitor is necessary in patients pretreated for primary PCI with a high loading dose of clopidogrel (Plavix), Dr. Michel R. Le May said at Transcatheter Coronary Therapeutics 2008.

The trial, called ASSIST (A Safety and Efficacy Study of Integrilin-Facilitated PCI in ST Elevation Myocardial Infarction), is the first randomized trial to compare eptifibatide against a control group in the setting of a high (600-mg) loading dose of clopidogrel, said Dr. Le May, director of the Coronary Care Unit Research Group at the University of Ottawa Heart Institute.

Previously, another GP IIb/IIIa inhibitor, abciximab (ReoPro), was shown to have no benefit over unfractionated heparin when patients with a ST-elevation MI (STEMI) were pretreated with a 600-mg loading dose of clopidogrel before undergoing primary PCI.

Dr. Le May noted that "in many U.S. centers, eptifibatide is now the preferred treatment for primary angioplasty, mostly because it's cheaper. It runs about $800, and abciximab is about twice the price."

'Eptifibatide is now the preferred treatment for primary angioplasty, mostly because it's cheaper.'

DR. LE MAY

In the open-label trial, 201 patients who took eptifibatide in addition to unfractionated heparin experienced a rate of events in the composite 30-day end point of death, reinfarction, or recurrent severe ischemia that was similar to the rate in patients who received unfractionated heparin alone (6.5% and 5.5%, respectively). At 6 months, the similarity persisted (8% and 7.1%, respectively).

Eptifibatide-treated patients experienced significantly more major and minor bleeding events combined in the first 30 days after PCI than did patients who received unfractionated heparin alone (22.4% vs. 14.6%). However, the differences between the groups in the rates of major bleeding alone or minor bleeding alone did not reach statistical significance, according to the TIMI (Thrombolysis in Myocardial Infarction) score.

All of the patients in ASSIST (mean age, about 60 years) were required to have felt symptoms less than 12 hours before admission. In the unfractionated heparin–only arm of the trial, 3% received eptifibatide and 4% received abciximab as a bail-out treatment.

ASSIST was funded by Schering-Plough Canada Inc., which has exclusive U.S. marketing rights to eptifibatide, and Medtronic of Canada. Dr. Le May said that he and his associates initiated the trial independently of industry. ■

Cyclosporine May Limit Infarct Size

Giving patients with ST-segment elevation myocardial infarction a cyclosporine bolus at the time of reperfusion appears to reduce infarct size by about 40%, researchers in a small proof-of-concept trial reported.

The study results "support the argument that reperfusion necrosis is a major component of infarct size after prolonged ischemia and reperfusion," said Dr. Christophe Piot of Hôpital Arnaud de Villeneuve, Montpellier, France, and associates (N. Engl. J. Med. 2008;359:473-81).

Cyclosporine has shown promise in limiting reperfusion injury in preclinical studies. The investigators conducted their prospective, multicenter trial in 58 patients with acute ST-segment elevation MI who were slated for percutaneous coronary intervention. Both the size of the infarct and the size of the area considered to be at risk were estimated by measuring the circumferential extent of abnormally contracting segments on angiography.

After coronary angiography was performed, but before stent placement, the patients were randomly assigned to receive a single IV bolus of either cyclosporine (30 subjects) or normal saline (28 control subjects).

Infarct size after reperfusion, as measured by release of serum creatine kinase, was significantly reduced in the cyclosporine group but not in the control group. The difference "represents a reduction in the infarct size of approximately 40%," the investigators said.

When the subjects were categorized according to the size of the area at risk, the infarcts that developed in those given cyclosporine were consistently smaller than those that developed in control subjects.

In a subgroup of 27 patients who underwent MRI, the absolute mass of the area of delayed hyperenhancement was 20% smaller in those given cyclosporine than in control subjects.

No adverse events were attributed to cyclosporine.

—Mary Ann Moon

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