Tailored Clopidogrel® Loading Dose for PCI: A New Way to Achieve Optimal Platelet Reactivity

By Caroline Helwick

New Orleans — A tailored approach to dosing the antiplatelet agent clopidogrel significantly reduced the rate of adverse events without nonmerger of importance in 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 Florence (France).

“The response to clopidogrel is unpredictable, and there is a link between low response and thrombotic 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 measurement of platelet reactivity 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).

“Clopidogrel has shown a lot of promise in patients undergoing PCI. 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 nonemergency 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 some patients received a fourth loading dose until their VASP index fell below 50%. Despite the use of 2,400 mg 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 patients in each group, with a rate of 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 treated with additional clopidogrel loading; and resistant patients, who have a VASP above 50% despite receiving up to 2.4 g of clopidogrel.

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Eptifibatide Increased Bleeding, Added No Benefit in ASSIST

By Jeff Evans

Washington — The adjective use of eptifibatide in antithrombotic regimens that are given to patients undergoing primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction significantly increased 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 the Transcatheter Coronary Therapeutics 2008 conference.

The tail 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 terms of safety and efficacy of the drug. The study results “support the argument that reperfusion necrosis is a major component of infarct size after prolonged ischemia and reperfusion,” said Dr. Christopher Pot of Hôpital Armand de Villemeuve, Montpellier, France, and associates (N Engl J Med 2008;359:473-81).

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 20%, 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. Christopher Pot of Hôpital Armand de Villemeuve, 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