Tailoring Clopidogrel Reduced CV Events

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Monitoring platelet response using a novel measuring tool allowed for tailored clopidogrel dosing and was associated with reduced major adverse cardiovascular events after percutaneous coronary intervention in a small, prospective study of 162 patients.

After 30 days of follow-up, none of the 78 patients whose therapy was adjusted using the vasodilator-stimulated phosphoprotein (VASP) index assay experienced a major adverse cardiovascular event (MACE), compared with 8 (10%) of the 84 patients in the standard-dosing group, lead investigator Dr. Laurent Bonello reported in a late-breaking clinical trial session at the Innovation and Intervention (i2) Summit. The between-group difference in MACE, defined as cardiovascular death, acute or subacute stent thrombosis, or revascularization, was significant.

Overall rates of MACE were driven by acute and subacute thrombosis, which was reported in 4 (5%) of the controls.

Thrombolysis in myocardial infarction (TIMI) major bleeding was reported in one patient in each group, and TIMI minor bleeding occurred in three patients in the control group and two in the VASP-guided group.

The VASP index is an assay that measures the degree of phosphorylation of the vasodilator phosphoprotein, which is directly dependent on the $P2Y_{12}$ and adenosine diphosphate (ADP) receptors. These receptors are targets for clopidogrel, making the assay highly specific to the response of clopidogrel, said Dr. Bonello, of the Hôpital Universitaire Nord, Marseilles, France.

The ability to tailor the loading dose of clopidogrel is valuable because there is a large interindividual variability in response to clopidogrel. Moreover, several studies have established a link between low response to clopidogrel and ischemic events, including stent thrombosis, he said at the meeting, cosponsored by the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions.

All patients in the study were undergoing elective PCI for unstable angina or non–ST-elevation acute coronary syndrome, and were defined as low responders to clopidogrel, based on a platelet reactivity of 50% or more using the VASP index after a standard loading dose of 600 mg clopidogrel and 250 mg aspirin.

Patients in the control group underwent PCI after the standard clopidogrel dose, whereas patients in the VASP tailored–therapy group could receive three additional 600 mg doses, up to a maximum of 2,400 mg, every 24 hours until platelet activity dropped below 50% before undergoing PCI.

The dose adjustment was effective in 67 (86%) patients. Despite having received 2,400 mg of clopidogrel, 11 (14%) patients remained low responders, he said. The average clopidogrel dose was 1,620 mg in the VASP tailored–therapy group.

Baseline characteristics were similar between the VASP and control groups. In both groups, the mean age was 66 years and the mean body mass index was mean 27 kg/m^2. Previous MI occurred in 22 of the VASP patients and 20 of the control patients, a nonsignificant difference.

The 50% cutoff value used in the study was based on previous work by the same group in which the negative predictive value of the VASP index to predict MACE after PCI was 100% using a cutoff value of 50% of platelet reactivity (J. Thromb. Haemost. 2007;5:1630-6).

The assay is commercially available, but its use is currently restricted to the research setting.

Dr. Bonello did not disclose any conflict of interest. The study was supported by a grant from the French Federation of Cardiology. ■

TRANSFER-AMI: In STEMI, Postlytic Transfer for PCI Is Best

BY BRUCE JANCIN
Denver Bureau

CHICAGO — Transfer of patients with ST-elevation MI to a center where they can routinely undergo percutaneous coronary intervention within 6 hours after getting thrombolytic therapy at a non-PCI hospital was superior to the conventional wait-and-see strategy.

"Transfer to PCI centers should be initiated immediately after thrombolysis without waiting to determine whether reperfusion will be successful or not. Regional systems should be developed to ensure timely transfers," Dr. Warren J. Cantor said at the annual meeting of the American College of Cardiology.

TRANSFER-AMI (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) involved 1,059 patients with STEMI. All had high-risk features and presented to hospitals without a cardiac catheterization facility. In accordance with guidelines, they received thrombolytic therapy along with aspirin, clopidogrel, and unfractionated heparin or enoxaparin.

Subjects were then randomized either to transfer for PCI and stenting within 6 hours of thrombolytic therapy or to transfer only for rescue PCI in the event of failed reperfusion, with elective PCI encouraged after 24 hours in successfully reperfused patients. The latter approach is standard in MI patients unable to undergo timely primary PCI.

Median time from symptom onset to administration of the thrombolytic tenecteplase was 2 hours. Median time from thrombolysis to PCI was 4 hours in the early transfer group, compared with 27 hours in the roughly 60% of patients in the wait-and-see group who eventually underwent PCI, explained Dr. Cantor of Southlake Regional Health Centre, Newmarket, Ont.

The primary end point in TRANSFER-AMI was a composite of 30-day death, reinfarction, heart failure, cardiogenic shock, or recurrent ischemia. The end point occurred in 10.6% of patients given the pharmacoinvasive strategy and in 16.6% who received the standard approach, for a 46% relative risk reduction. Rates for 30-day moderate and major bleeding were similarly low in both groups.

STEMI patients should be sent to PCI centers after thrombolysis without waitng to see if reperfusion is successful.

DR. CANTOR

Discussant Dr. Dariusz Dudek said TRANSFER-AMI mainly differed from prior similar trials, which had contradictory results, in its use of state-of-the-art medications and stents.

In particular, dual antiplatelet therapy was used to blunt the coagulation cascade that peaks roughly 90 minutes after thrombolysis and was key to making early PCI safe. Also, using an age-adjusted clopidogrel loading dose (75 mg in patients older than age 75 years, 300 mg in others) was very smart, added Dr. Dudek of the Institute of Cardiology, Kraków, Poland.

In an interview, Dr. William W. O'Neill predicted that TRANSFER-AMI will change management for the roughly 50% of U.S. patients with MI who come to hospitals without catheterization labs.

"There's been a lot of reluctance at small hospitals to routinely transfer patients after lytic therapy. Now we're saying, give lytics and then routinely send everybody. I think this is really going to change the way that small community hospitals practice," said Dr. O'Neill, professor of medicine and executive dean of clinical affairs at the University of Miami.

Dr. Cantor has served as a consultant to Roche, which, together with the Canadian Institutes of Health Research, funded TRANSFER-AMI. ■

Blood Stored Over 2 Weeks Linked to Risks After Heart Surgery

BY SUSAN BIRK
Contributing Writer

Transfusions of red blood cells stored for 15 days or more increase the risk of serious complications and both short- and long-term mortality following cardiac surgery, according to a retrospective study of more than 6,000 patients.

"The relative risk of postoperative death is increased by 30% in patients given blood that has been stored for more than 2 weeks," wrote Dr. Colleen Gorman Koch and her colleagues at the Cleveland Clinic Foundation.

Earlier studies comparing older and newer blood have yielded conflicting results. These studies examined small or heterogeneous samples, did not control for confounding factors, and used end points that did not reflect specific organ function, such as length of hospital stay.

The present study analyzed data on 3,130 cardiac surgery patients transfused with 10,782 units of blood stored for more than 14 days and 2,872 patients transfused with 8,802 units of blood stored for 14 or fewer days during cardiac surgery at Cleveland Clinic between 1998 and 2006. It excluded patients whose transfusions consisted of both newer and older blood and those with trauma and chronic diseases. Patients underwent coronary artery bypass graft surgery, cardiac valve surgery, or both. The older and newer blood groups shared similarities on most baseline and operative variables. The primary end point was a composite of in-hospital adverse events defined by the Society of Thoracic Surgeons. Follow-up survival status was obtained from the Social Security Death Index (N. Engl. J. Med. 2008;358:1229-39).

The study found a significant association between blood storage time and the serious adverse events composite end point, which occurred in 22.4% of the patients who received newer blood and 25.9% of those who received older blood. The link remained after adjusting for coexisting conditions and other risk factors. Patients transfused with older blood, compared with those who received newer blood, had significantly higher rates of in-hospital mortality (2.8% vs. 1.7%), prolonged ventilation (9.7% vs. 5.6%), renal failure (2.7% vs. 1.6%), septicemia or sepsis (4.0% vs. 2.8%), and multisystem organ failure (0.7% vs. 0.2%).

Risk of death was significantly lower among patients who received newer units of blood; 1-year death rates were 7.4% and 11.0% for the newer and older blood groups, respectively.

The mortality increase with older blood was most pronounced within 6 months of surgery. "The adverse effects of transfusing older blood persisted even after adjustment for perioperative factors known to be associated with an adverse outcome in this population," the researchers wrote (data were not presented). Further study is needed before any broad-based changes in blood banking practices are made, they said. The study's results, while important, are not enough to change blood supply practices, said Dr. John W. Adamson of the University of California, San Diego, in an accompanying editorial. Because the study population had a median age of 70 years, "by definition, the patients had a substantial number of coexisting illnesses." ■