Early Clopidogrel Can Improve MI Outcome

Benefit seen in patients with ST-segment elevation who undergo percutaneous coronary interventions.

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STOCKHOLM — Clopidogrel pretreatment markedly cut the rate of cardiovascular events in patients with ST-segment elevation myocardial infarction who underwent percutaneous coronary interventions in a study with more than 1,800 patients.

On the basis of these and previous findings, clopidogrel pretreatment should be considered the standard of care, both for patients with ST-segment elevation myocardial infarction (STEMI) and for all other patients who are undergoing percutaneous coronary intervention (PCI), Marc S. Sabatine, M.D., said at the annual congress of the European Society of Cardiology.

Until now, not all patients had received clopidogrel before PCI, Dr. Sabatine said in an interview. Usual care has been to administer a loading dose of clopidogrel when PCI begins. For every 23 patients in the study, pretreatment with clopidogrel prevented one major cardiovascular event. "That is an amazingly big benefit from one to three extra doses of clopidogrel," commented Christopher P. Cannon, M.D., a cardiologist at Brigham and Women's Hospital in Boston and a coinvestigator on the study.

Even if clopidogrel is not given at the initial presentation, it should be started once the decision is made to perform coronary angiography, said Dr. Sabatine, who is also a cardiologist at the hospital.

The study was sponsored by Sanofi-Aventis and Bristol-Myers Squibb, the companies that market clopidogrel (Plavix) worldwide. Dr. Sabatine and Dr. Cannon have received honoraria and research support and have served as advisers to both companies.

Clopidogrel pretreatment was effective both before and after PCI was performed, noted Keith Fox, M.B., professor of cardiology at the University of Edinburgh. "The most convincing evidence [of clopidogrel's efficacy] is the consistency of the clinical effect" across all subgroups examined in the study, he commented.

Up to 30 days after initial treatment, the rate of cardiovascular death, MI, or stroke was 3.6% in the clopidogrel group and 6.2% in the placebo group.

The new analysis was a prespecified substudy of the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) study.

Results from the parent study, which involved nearly 3,500 patients, were reported last March.

Those results showed that patients who had a STEMI and initially received thrombolytic therapy had better outcomes when a clopidogrel regimen (a 300-mg loading dose followed by 75 mg/day) was begun immediately, along with the first dose of aspirin and the thrombolytic agent (N. Engl. J. Med. 2005;352:1179-89).

All patients in the CLARITY study were scheduled to undergo angiography 2-8 days following thrombolytic treatment, and the PCI substudy focused on the more than 1,800 patients (53%) from this group who wound up having PCI after angiography.

Although the study did not randomize patients to PCI, the 933 patients from the clopidogrel group who had PCI were very similar in their baseline measures to the 930 patients from the placebo group who had PCI.

The study protocol recommended that all patients who received a coronary stent after angiography receive a loading dose of 300 mg of clopidogrel at the time of stent implantation followed by ongoing treatment with 75 mg/day.

PCI was done a median of 3 days after the start of fibrinolytic treatment—in some cases as quickly as within 6 hours, and in other cases after a delay as long as 8 days. During this phase, the incidence of MI or stroke was 4% in the clopidogrel-treated patients and 6.2% in the placebo group, a 38% relative reduction that was statistically significant.

After PCI, up to a total of 30 days after initial treatment, the rate of cardiovascular death, MI, or stroke was 3.6% in the clopidogrel group and 6.2% in the placebo group, a 46% reduction that was statistically significant.

Overall, patients who began clopidogrel treatment immediately and then had PCI had a 7.5% incidence of cardiovascular death, MI, or stroke, compared with a 12% rate in those who did not start on clopidogrel until their PCI began. The results were published on the same day that they were reported at the meeting (JAMA 2005;294:1224-32).

Clopidogrel pretreatment was safe. It was associated with a 0.5% rate of major bleeds and a 1.4% rate of minor bleeds, compared with a major bleed rate of 1.1% and a minor bleed rate of 0.8% in the placebo group. Clopidogrel pretreatment was also safe and effective in the one-third of patients who received a glycoprotein IIb/IIIa inhibitor at the time they got their stents.

A major issue left unresolved by the study is whether patients would fare even better with a larger loading dose.

Some physicians have used a 600-mg or even a 900-mg loading dose in order to produce a maximum antiplatelet effect more quickly.

"Clinicians should consider giving 600 mg of clopidogrel as a loading dose, even though this approach has not been formally tested with thrombolytic therapy," David J. Moliterno, M.D., and Steven R. Steinhubl, M.D., of the University of Kentucky, Lexington, wrote in an editorial that accompanied the published report (JAMA 2005;294:1271-3).

"I think that there is evidence that the 600-mg dose is effective and safe, especially if given less than 6 hours before PCI. If it's going to be 6 or more hours before PCI is done, then I'd use 300 mg," Dr. Sabatine told this newspaper. ■

CLINICAL CAPSULES

Thrombolytic Tx in Kidney Patients

Thrombolytic therapy is delayed in patients with kidney disease who develop MI, which is "particularly unfortunate" in this patient population because of their large burden of cardiovascular disease and high CVD mortality, according to Britt B. Newsome, M.D., of the Birmingham (Ala.) Veterans Affairs Medical Center, and associates.

The researchers analyzed data from 109,169 MI patients who were treated at more than 6,000 U.S. acute-care hospitals, and found that "door-to-needle time" increased as severity of kidney disease worsened.

They also found that patients with kidney disease were no more likely than those with normal kidney function to develop bleeding complications from thrombolytic therapy (Am. J. Kidney Dis. 2005;46:595-602).

The treatment delay may be due to clinicians' perception that kidney patients are more frail, less likely to benefit from treatment, or more likely to develop adverse effects, particularly bleeding complications, than other patients. But the study results suggest that such concerns are not warranted.

This study also disproved another possible explanation for the treatment delay, namely that patients with kidney disease have more comorbidities than other patients, which complicates their medical care and increases the time needed to make treatment decisions. Also, the subjects with kidney disease did have more comorbidities, but comorbidities did not correlate with treatment delays, the investigators noted.

Statins: Benefits Outweigh Hazards

Statin therapy doesn't raise the risk of cancer or any specific cause of death, and it carries an extremely low risk of rhabdomyolysis, according to investigators in the Cholesterol Treatment Trialists' collaborative study.

The CTT collaborators will report on periodic metaanalyses of morbidity and mortality data from all the large randomized trials of lipid therapies. In the first such report, which involved 14 statin trials, the CTT found a direct linear relationship between reductions in LDL cholesterol level and reductions in coronary and other vascular events (Lancet 2005;366:1267-77).

Although previous research had suggested that statin use might raise the risk of nonvascular causes of death, particularly cancer, this concern was not borne out in the metaanalysis.

The safety of statins was further confirmed by the finding of an excess risk of rhabdomyolysis of only 0.01% after 5 years of treatment.

"The potential hazards of lowering LDL cholesterol with these statin regimens seemed to be extremely small in relation to the clear benefits in many circumstances," the CTT researchers said.

Endocarditis Rate Remains Stable

The incidence of infective endocarditis hasn't changed over the past 30 years in many areas of the United States, and Streptococci—not *Staphylococcus aureus*—continue to be the most common cause of infection, reported Imad M. Tleyjeh, M.D., of the Mayo Clinic, Rochester, Minn., and associates.

In a community surveillance study, all 107 cases of infective endocarditis treated in one Minnesota county between 1970 and 2000 were reviewed. The incidence remained stable throughout the study, with annual rates ranging from 5.0 to 7.0 cases per 100,000 person-years (JAMA 2005;293:3022-8).

Other researchers have reported an increasing frequency of *S. aureus* endocarditis or a drop in streptococcal endocarditis, "leading to a general consensus that *S. aureus* has surpassed viridans group streptococci as the leading cause" of the infection.

"In contrast, we found that viridans group streptococci continue to be the most common cause of infective endocarditis in the study population and that its incidence rate is approximately twice that of *S. aureus*," they noted.

Drug Treatment Mismatched in HF

Among patients hospitalized with heart failure, those who are at the highest risk of death are the least likely to be given drugs of proven benefit, according to Douglas S. Lee, M.D., Ph.D., of the University of Toronto, and his associates.

They assessed drug treatment in relation to predicted 1-year mortality risk, using data from a study of 1,418 heart-failure patients treated at 103 acute-care hospitals across Ontario.

The number of prescriptions written at hospital discharge for ACE inhibitors, angiotensin II–receptor blockers, and β-adrenoreceptor antagonists decreased as mortality risk increased, the investigators said (JAMA 2005;294:1240-7).

The mismatch between mortality risk and drug prescriptions persisted even in patients who had no perceived contraindications to the drugs and no life-limiting comorbidities that could confound a risk-benefit assessment. It seems likely that clinicians undertreated these patients because either they didn't appreciate the benefits of therapy or they mistakenly believed that high-risk patients are more susceptible to the medications' adverse effects, Dr. Lee and his associates said.

—Mary Ann Moon