Primary Lytics Early in MI Still Have Key Role

Delayed access to percutaneous intervention often makes IV thrombolysis more timely and practical.

BY BRUCE JANCIN
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SNOWMASS, COLO. — The demonstrated superiority of primary percutaneous coronary intervention over fibrinolytics for acute MI in randomized trials has led to a "transfer mania" that is at times counterproductive, Dr. Bernard J. Gersh said at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

There is solid evidence that the first 2 hours after the onset of MI symptoms represent a golden window of opportunity. Achievement of reperfusion during this window provides far greater myocardial salvage and mortality benefits than it does at any later time, said Dr. Gersh, who is professor of medicine at the Mayo Medical School, Rochester, Minn.

Many studies showing fewer adverse events with PCI were done in small European countries, where transfer times are shorter than in the United States.

And the best way to accomplish this in patients who present to community hospitals during this early time period is by urgent administration of intravenous thrombolytic agents, Dr. Gersh said.

The delay inherent in transferring such patients to a facility capable of primary percutaneous coronary intervention (PCI) shuts the window of opportunity and moves them into the flatter part of the survival curve.

"I find that intellectually indefensible," he said.

He added that it has been known for at least 13 years that thrombolytic therapy is "extraordinarily effective" when given early after symptom onset. The Myocardial Infarction Triage Intervention (MITI) trial showed that 30-day mortality in patients treated within 70 minutes after symptom onset was 1.2%, compared with 8.7% in patients treated later, and that left ventricular infarct size following treatment within 70 minutes of symptom onset was only 4.9%, compared with 11.2% in patients treated later.

More recently, the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 (ASSENT-3) trial showed that 25% of aborted MIs, as defined by ECG and cardiac enzyme criteria, occurred in patients who received thrombolytic therapy within 1 hour of symptom onset; that rate decreased with time, to 10% at 3 hours.

The trouble is, a mere 3% of ASSENT-3 participants were treated within 1 hour of MI symptom onset; 27% received thrombolytics within 2 hours. Getting more patients to come to the hospital or call an ambulance early after symptom onset has proved a daunting task.

"So far every campaign to do that both here and abroad has failed," Dr. Gersh noted.

Transfer mania—the urge to transport everyone with an acute MI for primary PCI—is driven by half a dozen studies showing lower rates of death, stroke, and recurrent MI, he said. However, many of these trials were conducted in small European countries, including Denmark and the Czech Republic, where transfer times are so short that the applicability of the results to U.S. patients becomes questionable.

This point was driven home by a recent report from the U.S. National Registry of Myocardial Infarction (Circulation 2005;111:761-7). In analyzing nearly 4,300 MI patients transferred from one hospital to another for primary PCI during 1999-2002, the investigators found that only 4.2% had a less than 90-minute interval between time of arrival at the initial hospital to balloon inflation at the PCI center, as is recommended by current American College of Cardiology/American Heart Association guidelines for the use of primary PCI.

The Mayo Clinic has two helicopters and a fixed-wing airplane for transfer of MI patients from outlying hospitals. Here's what Mayo cardiologists recommend to physicians at community hospitals in their region without primary PCI capability: If a patient's duration of symptoms is less than 120 minutes, give full-dose thrombolytics and then transfer so the patient can undergo either routine elective angiography or, in the event of persistent ischemia, rescue PCI, Dr. Gersh said.

Beyond 2 hours, Dr. Gersh and his colleagues suggest direct transfer for primary PCI without preceding thrombolytics. This is a situation where facilitated PCI—that is, giving lytics and/or platelet glycoprotein IIb/IIIa inhibitors locally followed by transfer for PCI to maximize vessel opening—is very attractive.

The results of ongoing trials of this approach are eagerly awaited, Dr. Gersh said.

If facilitated PCI proves effective, it will be particularly advantageous when transfer delays occur. For instance, last year the Mayo Clinic's air transport service was grounded by severe weather for some part of 58 days.

"That's a fact of life in many parts of the United States," Dr. Gersh noted. ■

Bivalirudin May Reduce Need to Use IIb/IIIa Agents in ACS

BY MITCHEL L. ZOLER
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ATLANTA — Treatment of patients with moderate to high-risk acute coronary syndrome with the antithrombotic bivalirudin was as effective as regimens that also contained a glycoprotein IIb/IIIa inhibitor in a controlled study with more than 13,000 patients.

Treatment with bivalirudin without a IIb/IIIa inhibitor also led to significantly fewer major bleeding events, giving a regimen of bivalirudin alone an apparent advantage over the comparator regimens that used a IIb/IIIa inhibitor plus unfractionated heparin, the low-molecular-weight heparin enoxaparin, or bivalirudin, Dr. Gregg W. Stone reported at the annual meeting of the American College of Cardiology.

But some experts were skeptical about whether the results from this large and complex study clearly established equal efficacy and a safety advantage for bivalirudin alone in moderate to high-risk patients with acute coronary syndrome (ACS) who are scheduled for angiography that may be followed by a percutaneous coronary intervention (PCI).

"Only 58% of patients were high risk, based on a positive biomarker," an elevated serum level of troponin, commented Dr. Eric D. Peterson, codirector of cardiovascular research at Duke University in Durham, N.C. Another indication that the study did not focus entirely on the types of high-risk patients enrolled in past studies was that their incidence of ischemic complications during the first 30 days after treatment was about 7.5%, substantially lower than the 12%-15% rates seen in high-risk patients in previous studies.

In other studies, treatment with a IIb/IIIa inhibitor involved a trade-off between a reduction in ischemic events and an increased risk of bleeding. "If 40% of the patients don't have high-risk ACS, then in those patients you get the risk [of increased bleeding] without the benefit," said Dr. Peterson in an interview. "It's not surprising that drugs that work by reducing ischemic events didn't benefit" patients.

Dr. Peterson said that despite the new results, treatment with a IIb/IIIa inhibitor remains the standard of care for high-risk ACS patients with an elevated level of serum troponin who undergo angiography and may be treated with PCI.

The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial was designed by Dr. Stone and his associates to address two questions. First, the study compared bivalirudin alone with two other antithrombotic regimens that included a IIb/IIIa inhibitor. Also, it examined whether, in patients who received a IIb/IIIa inhibitor, it made a difference if the drug was given early, to all patients, or was deferred and given only to the roughly 55% of patients who actually underwent PCI.

The study enrolled 13,819 patients at 448 centers in 17 countries. More than half of the patients were treated in the United States. The study was sponsored by The Medicines Company, which markets the synthetic direct-thrombin inhibitor bivalirudin (Angiomax). Dr. Stone is a consultant to The Medicines Company.

All the patients were treated with aspirin; clopidogrel treatment was recommended, but was administered according to local practices. The patients were randomized equally among the three treatment groups: bivalirudin alone, bivalirudin plus a IIb/IIIa inhibitor, and unfractionated heparin or enoxaparin and a IIb/IIIa inhibitor. Patients who received a IIb/IIIa inhibitor during initial treatment were treated with either epifibatide or tirofiban. Those who had their treatment deferred until they underwent PCI primarily received either epifibatide or abciximab, with a small percentage receiving tirofiban.

Primary end points were the incidence during the next 30 days of ischemic events (death, MI, or need for revascularization due to ischemia); the rate of major bleeding events; and the composite incidence of ischemic events and major bleeds.

The results showed no significant difference in ischemic events, which occurred in 7.3%-7.8% of patients, proving that bivalirudin alone is not inferior to treatments with a IIb/ IIIa inhibitor, said Dr. Stone, professor of medicine and director of cardiovascular research and education at Columbia University in New York. Major bleeding events occurred in 5.7% of patients treated with heparin or enoxaparin and a IIb/IIIa inhibitor, 5.3% of patients treated with bivalirudin and a IIb/IIIa inhibitor, and in 3.0% of patients treated with bivalirudin alone, a statistically significant reduced rate in the bivalirudin group.

The results of the second analysis, which compared upfront use of a IIb/IIIa inhibitor in all patients against deferred use only in the 55% of patients who underwent PCI, showed that the efficacy of both approaches was similar. The incidence of ischemic events was 7.1% in patients who received immediate treatment with a IIb/IIIa inhibitor, and 7.9% in patients who received the drug only before having PCI, a difference that was not statistically significant for superiority, but fell slightly short of proving that deferred use of a IIb/IIIa inhibitor was not inferior. The deferred strategy led to a 4.9% incidence of major bleeds, significantly less than the 6.1% rate in patients who got immediate treatment with a IIb/IIIa inhibitor. In the composite analysis of both major bleeds and ischemic events, the two strategies were completely equal, each producing an 11.7% event rate.

The "most important" implication from this analysis is that both strategies for administering a IIb/IIIa inhibitor were inferior to the net clinical outcome of bivalirudin alone, which had a composite event rate of 10.1% for major bleeds and ischemic events, Dr. Stone concluded.

"One thing that bivalirudin has done consistently [in prior studies] is reduce the rate of bleeding complications, so the difference in bleeding here is not surprising," said Dr. Kirk Garratt, director of interventional cardiovascular research at Lenox Hill Hospital in New York. ■