Low-Molecular-Weight Heparin Aids in Acute MI

Reviparin's protective effects extended to 30 days from the start of treatment in the multinational study.

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW ORLEANS — Antithrombotic treatment, in the form of the low-molecular-weight heparin reviparin, has been shown for the first time to safely improve the outcomes of patients with an acute MI.

"Although heparin is often routinely used to treat patients with an acute myocardial infarction, the incremental benefit from heparin or newer antithrombotics has been poorly defined," Jeffrey L. Anderson, M.D., said at the annual scientific sessions of the American Heart Association.

The new findings show that reviparin "clearly improves the outcomes of patients who undergo thrombolysis with streptokinase or urokinase," said Dr. Anderson, associate chief of the division of cardiology at LDS Hospital in Salt Lake City.

But the value of adding reviparin or a similar agent remains in doubt when patients are treated with the fibrin-specific drugs most often used for thrombolysis in the United States, such as alteplase (tissue plasminogen activator), reteplase, and tenecteplase. That's because this new trial, conducted in India, China, Pakistan, and several South American countries and involving 15,570 patients, included only about 100 patients treated with a fibrin-specific thrombolytic drug. Close to 80% of the patients received acute treatment to clear their coronary thrombus, but this treatment was primarily streptokinase in about 50% of patients, urokinase in about 23% of patients, and primary percutaneous intervention in about 6% of patients.

Despite this limitation, the results showed that "reviparin is a simple, inexpensive therapy that is globally applicable for treating acute myocardial infarction," said Salim Yusuf, D.Phil., director of the division of cardiology at McMaster University in Hamilton, Canada, and lead investigator for the study.

Reviparin is marketed by Abbott Pharmaceuticals under the name Clivarine in several countries in Europe and Asia, but is not approved for U.S. use. Abbott provided the reviparin, but otherwise, the study had no commercial funding.

The study enrolled patients with ST-segment–elevation MI or new bundle branch block who presented within 12 hours of symptom onset. All patients were to be treated with aspirin, and they could also be treated with a regimen designed to produce reperfusion in their blocked coronary arteries. The average age of the patients was 59 years, and the average time from symptom onset to treatment was 4.8 hours, with 61% of patients treated within 6 hours. Aspirin was used on 97% of patients, 72% received an ACE inhibitor, 66% received a lipid-lowering drug, 60% received a β-blocker, and 55% received a thienopyridine, most commonly clopidogrel.

Patients were randomized to treatment with reviparin or placebo by subcutaneous injection b.i.d for 7 days; 76% of patients received the full 7-day course.

'Reviparin is a simple, inexpensive therapy that is globally applicable' for treating MI.

DR. YUSUF

The study's primary end point was the incidence of death, repeat MI, or stroke during the 7 days of treatment. The rate of these outcomes was 11.0% in the placebo group and 9.6% in the reviparin group—a statistically significant relative reduction of 13%, Dr. Yusuf reported. Patients treated with reviparin also had a 13% relative reduction in the study's secondary end point, which included death, repeat MI, stroke, or ischemic ECG changes. Treatment with reviparin was also associated with a significant 11% relative reduction in death alone.

The protective effect from reviparin treatment extended to 30 days after the start of treatment. At that time, the rate of death, repeat MI, or stroke was 13.6% in the placebo group and 11.8% in the reviparin group, again a statistically significant 13% relative reduction. These results showed that "stopping therapy after 7 days was not associated with any rebound," Dr. Yusuf said.

Like all antithrombotic drugs, reviparin boosted the rate of bleeding events. The rate of life-threatening or major bleeds not included in the primary outcomes after 7 days of treatment was 0.1% in the placebo group, compared with 0.2% in the reviparin group. The increased risk of important bleeding events was small, compared with the overall benefit, he noted.

Another noteworthy finding was that the faster treatment with reviparin started the greater the benefit. Patients who started treatment within 2 hours of symptom onset had a 30% relative drop in the primary end point. This relative benefit fell to 20% when treatment began 2-4 hours and to 15% when treatment began within 4-8 hours. The benefit completely disappeared when treatment was delayed beyond 8 hours.

An inevitable question is whether treatment with the low-molecular-weight heparins approved for use in the United States would confer the same benefits. "It's a tricky issue, because low-molecular-weight heparins are very heterogeneous compounds. You need to know the exact dosage to use." Dr. Yusuf said. ■

Ischemia Algorithm Could Reduce the Need for Stress Tests

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — In some patients being evaluated for chest pain, stress tests might be avoided through the use of an algorithm designed to predict the probability of cardiac ischemia, David D. Moyer-Diener and his associates said at the annual meeting of the American College of Emergency Physicians.

In a prospective, observational cohort study of consecutive patients evaluated at a chest pain center, investigators obtained Acute Coronary Ischemia–Time Insensitive Predictive Instrument (ACI-TIPI) scores and conventional chest pain work-ups on 1,478 low- or intermediate-risk patients for whom acute myocardial ischemia had been ruled out. The treating physicians were blinded to the ACI-TIPI scores, and patients underwent conventional evaluations including serial enzyme tests and provocative cardiac testing.

Among 400 patients who had ACI-TIPI scores of 20 or less, 265 were men younger than age 35 years or women younger than age 45 years, and 217 underwent provocative cardiac testing. None of the 265 patients developed an acute coronary syndrome within 30 days, as determined by phone calls to patients and reviews of records and the Social Security Death Index.

If clinicians had used an ACI-TIPI score of 20 or less in these subsets of young patients to exclude provocative cardiac testing and had sent these patients home, 15% of all stress tests in the study cohort could have been avoided without causing any harm, said Mr. Moyer-Diener, a medical student at the University of Michigan, Ann Arbor, who conducted the study with Michael G. Mikhail, M.D., and associates at the university.

At the meeting, physicians on a separate panel discussing cutting-edge research both praised and criticized the study.

"There's been a lot of debate about just how useful" an ACI-TIPI score is, said Charles V. Pollack Jr., M.D., chair of emergency medicine at Pennsylvania Hospital, Philadelphia. Many emergency physicians would rather not have a quantitative number related to the risk of ischemia on a patient's chart, he said, because if the case sparks a lawsuit, they would rather defend their clinical impression that the patient didn't have ischemia.

The ACI-TIPI was designed to predict the probability of cardiac ischemia on a 0- to 100-point scale, to serve as support or a "second opinion" in clinical decision making. The way ACI-TIPI was used in the study to identify patients who don't need further tests "is not really the use for which it was designed," but the idea is intriguing, Dr. Pollack said.

Jerome R. Hoffman, M.D., lauded the investigators for trying to identify a strategy to cut down on the many unnecessary tests performed for chest pain evaluation that are not backed by evidence-based medicine. "It's very hard to get us out of that rut," said Dr. Hoffman, professor of emergency medicine at the University of California, Los Angeles.

In practical terms, however, physicians are unlikely to adopt these criteria for avoiding stress tests. An ACI-TIPI score of 20 or less is associated with a 19% risk of acute myocardial ischemia, Dr. Hoffman explained. For medicolegal reasons, physicians will not feel comfortable sending patients home if that number appears on a patient's chart.

"That, more than anything, makes me question the value of an ACI-TIPI— other than as a research tool," Dr. Hoffman said.

Previous studies have shown that physicians were from two to three times more likely to admit patients if given an ACI-TIPI score to include in the patient's chart, said Ian G. Stiell, M.D., of the University of Ottawa. On the other hand, it's "refreshing" to hear skepticism about widespread use in the United States of stress tests, chest pain units, and prolonged cardiac monitoring, he added.

Dr. Pollack noted that the current study claimed to exclude patients with acute myocardial ischemia. "I think that's a dangerous statement," he said, "because ordinarily that is done in a chest pain center by measuring serial troponin levels, which excludes only necrosis. It doesn't exclude ischemia." ■

2004 IN REVIEW

The revelation in September that the popular arthritis drug rofecoxib (Vioxx) more than doubles the risk of myocardial infarction led to its withdrawal by Merck and to a reevaluation of the safety of other cyclooxygenase-2 inhibitors. In the aftermath, many have questioned why the Food and Drug Administration and Merck had not paid more attention to earlier results that also raised safety concerns.

Regardless of the conclusions reached by the various investigators, "More safety experience is going to be required, and there may be more cautionary labels not for what has been seen but for what is not known.

"The issues brought forth by Vioxx will ultimately drip down to almost everything we do. But we mustn't overlook the fact that a huge number of patients have taken the drug and been exposed to increased risk," Barry Massie, M.D., chief of cardiology at the Veterans Affairs Medical Center, San Francisco, told CARDIOLOGY NEWS.

—From staff reports