Low-Molecular-Weight Heparin May Aid Acute MI

Reviparin improved patient outcomes in thrombolysis with streptokinase or urokinase.

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 myocardial infarction.

"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, and it also appears to be a useful adjunct for patients treated with primary percutaneous coronary intervention [PCI]," 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 PCI, in about 6% of patients.

The international study was not designed to evaluate heparin with the fibrin-specific drugs most often used for thrombolysis in the United States.

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 the drug is not approved for use in the United States. Abbott provided the reviparin that was used, 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 reviparin or placebo by subcutaneous injection b.i.d for 7 days; 76% of patients received the full 7-day course of treatment.

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 13% relative reduction that was statistically significant. The durability of reviparin's benefit out to 30 days showed that "stopping therapy after 7 days was not associated with any rebound," Dr. Yusuf said.

Like all antithrombotic drugs, reviparin boosted the incidence of bleeding events. The rate of life-threatening or major bleeds not included among 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.

An added 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 after symptom onset and to 15% when treatment began within 4-8 hours, and the benefit completely disappeared when treatment was delayed beyond 8 hours.

An inevitable question is whether the benefit from reviparin is a class effect that would also result from treatment with the low-molecular-weight heparins approved for use in the United States, such as enoxaparin (Lovenox) and dalteparin (Fragmin).

"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. ■

Heart Attack Outcomes Called 'Dismal' in Renal Disease Patients

BY BRUCE JANCIN
Denver Bureau

NEW ORLEANS — Mortality is extraordinarily high in the year after acute MI in patients with renal failure—and the explanation may lie largely in their strikingly different clinical characteristics as compared with the general MI population.

In this regard, dialysis patients and those with non–dialysis-dependent chronic renal insufficiency look much more alike as a group, and distinctly different from acute MI patients without a history of renal impairment, Charles A. Herzog, M.D., said at the annual scientific sessions of the American Heart Association.

Dialysis patients have a "dismal" 60% 1-year mortality following acute MI, noted Dr. Herzog, a cardiologist with the U.S. Renal Data System and Minneapolis Medical Foundation.

In an effort to understand why patients with renal failure fare so poorly after an MI, he and his colleagues constructed a unique database by cross matching the records of the U.S. Renal Data System and the National Registry of Myocardial Infarction-3, a large Genentech-sponsored registry of MI patients. This yielded a study population of 2,720 renal dialysis patients with MI; 35,950 MI patients with non–dialysis-dependent renal insufficiency; and 384,415 MI patients with no history of chronic renal disease. None of the patients was transferred for MI care.

Many statistically and clinically significant differences were apparent between the renal patients and those in the general population. (See box.)

One that may have had the greatest effect on poor long-term prognosis of patients with renal disease was their lesser likelihood of presenting with chest pain, in Killip class I, or with ST-elevation MI, as well as the lower diagnostic suspicion of MI upon presentation. By ECG criteria, a much lower percentage of renal failure patients were eligible for any sort of reperfusion therapy, Dr. Herzog continued.

There was no major difference between the groups in terms of prehospital delay, which averaged about 5.5 hours from symptom onset to hospital presentation, so an educational campaign aimed at increasing renal patients' awareness of MI signs and symptoms isn't likely to yield major improvements in long-term outcome, Dr. Herzog said.

In response to audience expressions of surprise that the patients with non–dialysis-dependent renal insufficiency fared as poorly post MI as patients requiring dialysis, Dr. Herzog replied that this appeared to be largely due to age. Advanced age has long been seen as an important predictor of worse outcome after an MI, he noted, and in this study the non–dialysis-dependent renal patients were significantly older than the other two groups, with a mean age of 75 years, compared with 68 years in the dialysis patients and 69 years in MI patients without renal disease. ■

Key Differences Between Renal and Nonrenal Patients With MI

	Dialysis patients (n = 2,720)	Patients with non–dialysis-dependent renal insufficiency (n = 35,950)	Nonrenal patients (n = 384,415)
History			
Diabetes	58%	52%	27%
Prior MI	26%	37%	24%
Heart failure	31%	45%	15%
Admission Characteristics			
ACS suspected at presentation*	21%	25%	44%
Chest pain	43%	44%	68%
Killip class I	58%	49%	76%
ST-elevation MI	25%	26%	40%
In-Hospital Characteristics			
Cardiac arrest	12.0%	8.7%	5.5%
Mortality	21.3%	21.9%	10.7%

*ACS is acute coronary syndrome.
Source: Dr. Herzog