Fondaparinux Lowers Bleeding Risk in Acute MI

'Its impact is as large as the difference between tissue plasminogen activator and streptokinase.'

BY MITCHEL L. ZOLER
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ATLANTA — The treatment of acute myocardial infarction with the antithrombotic drug fondaparinux produced significant reductions in death and new ischemic events without boosting the risk of major bleeds in a large trial with more than 12,000 patients.

"For the first time, we have an antithrombotic drug that lowers the risk for hemorrhage," Dr. Salim Yusuf said at the annual meeting of the American College of Cardiology.

Fondaparinux "is the only antithrombotic I know that saves lives, prevents new myocardial infarctions, and doesn't increase bleeding. No other antithrombotic has shown a mortality benefit," compared with the standard agent, unfractionated heparin, said Dr. Yusuf, professor of medicine at McMaster University, Hamilton, Ont. "Its impact is as large as the difference between tissue plasminogen activator and streptokinase" for fibrinolysis of MIs.

The only flaw in fondaparinux's performance was in patients treated with coronary catheterization and percutaneous coronary intervention (PCI). In this setting, fondaparinux was inferior to heparin for preventing clots from forming in catheters, which led to no efficacy advantage for fondaparinux, compared with heparin, in patients treated with primary PCI in the Organization to Assess Strategies for Ischemic Syndromes (OASIS) 6 trial.

Fondaparinux "looks very appealing for both unstable angina and ST-segment elevation MI, with excellent efficacy and reduced bleeding," said Dr. Christopher P. Cannon, a cardiologist at Harvard University and Brigham and Women's Hospital in Boston. For patients treated with primary PCI, "it looks like we'll need unfractionated heparin or a low-molecular-weight heparin, but for everyone else" fondaparinux looks good, he said in an interview.

A detailed analysis of the study's results showed that during the first 3 days after treatment with fondaparinux, patients who underwent PCI had a 2.8% rate of death or repeat MI, compared with a 2.2% rate in control patients treated with placebo or unfractionated heparin, a 30% increased risk with fondaparinux that was not statistically significant. By contrast, during the following 6 days, patients treated with fondaparinux had a 32% reduction in death or MI, compared with the control patients, which suggested that treatment with fondaparinux after primary PCI might be beneficial, said Dr. Yusuf, adding that the hypothesis would need to be tested in a future trial.

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DR. YUSUF

Overall, during the first 9 days after treatment, 30 days after treatment, and out to the end of the study (90-180 days after treatment), patients treated with fondaparinux who then underwent primary PCI had very similar outcomes, compared with control patients.

On the basis of these findings, "fondaparinux will be more preferred in settings in which the use of angiographic-based reperfusion is not routine," said Dr. Robert M. Califf in an editorial that accompanied online publication of the OASIS-6 results (JAMA 2006 Mar. 14 [E pub doi:10.1001/jama.295.13.jed60020]).

This caveat may make fondaparinux a harder sell in the United States, where "PCI has been established as the preferred treatment for STEMI [ST-segment elevation MI]," said Dr. Califf, a cardiologist and director of the Clinical Research Institute at Duke University, Durham, N.C. "The extra anxiety caused by the now-uncertain risk of catheter thrombosis casts a pall over the use of fondaparinux in patients for whom the intent is to use PCI to achieve reperfusion."

OASIS-6 enrolled 12,092 patients within 12 hours of the onset of symptoms of acute MI (the first 4,300 patients were enrolled within 24 hours of symptom onset) at 447 centers in 41 countries during September 2003–January 2006. According to Dr. Califf, only 33 of these patients were treated in either the United States or Canada. Although the study was sponsored by Sanofi-Aventis, Organon, and GlaxoSmithKline, which markets fondaparinux (Arixtra), it was run independently by the Population Health Research Institute of McMaster University. Dr. Yusuf has received honoraria from, has served as a consultant to, and has received research funding from GlaxoSmithKline.

The enrolled patients were managed in three different ways, depending on their clinical presentation and decisions by their physicians. Thrombolytic therapy was administered to about 45%, primary PCI was used to treat about 29%, and about 24% did not receive any reperfusion therapy.

The patients were also divided by their treating physicians into two categories: those judged not to need antithrombotic therapy (about 47%) and who were randomized to treatment with either fondaparinux or placebo, and those who needed antithrombotic treatment (about 53%) and who were randomized to treatment with either unfractionated heparin or fondaparinux. The fondaparinux dosage was 2.5 mg subcutaneously once daily, which was continued for up to 8 days or until hospital discharge. Treatment with heparin was continued for 24-48 hours.

The study's primary end point was the incidence of death or MI by 30 days after initial treatment, which occurred in 9.7% of patients treated with fondaparinux and in 11.2% of those treated with placebo or heparin, a 14% relative difference that was statistically significant. The results were published online concurrent with the report at the meeting (JAMA 2006 Mar. 14 [Epub doi:10.1001/jama.295.13.joc60038]).

The rate of major bleeds during the first 9 days of treatment was 1.8% in patients treated with fondaparinux and 2.1% in the control patients, a difference that was not significantly different.

The analysis also included a net clinical benefit calculation that totaled the rate of death, MI, stroke, and severe hemorrhage by the end of the study. This rate was reduced by 12% in the fondaparinux group, compared with the control patients, a significant difference. For every 1,000 patients treated, fondaparinux prevented 16 episodes of death, MI, strokes, and severe bleeds, compared with placebo or heparin, Dr. Yusuf reported.

Fondaparinux is a synthetic inhibitor of factor Xa, an early step in the coagulation cascade, and uses a different mechanism than do unfractionated heparin and the low-molecular-weight heparins, which block other coagulation factors. This difference in activity seems to be linked to the reduced hemorrhage risk posed by fondaparinux, and use of the drug may have resulted in fewer deaths because bleeding was reduced.

"We believe that when a patient has a bleeding event, it leads to worse long-term outcomes, including increased long-term mortality," said Dr. Christopher B. Granger, a coinvestigator of OASIS-6 and cardiac care unit director at Duke University. ■

Researchers Give Pros, Cons for Fondaparinux, Enoxaparin

BY MITCHEL L. ZOLER
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ATLANTA — Comparisons between enoxaparin and fondaparinux were perhaps inevitable when findings from two major clinical trials that evaluated the two different antithrombotic drugs as adjuncts to fibrinolytic therapy for acute MI were reported back-to-back at the annual meeting of the American College of Cardiology.

Such comparisons are also dangerous, cautioned many experts, who noted that across-study comparisons are notoriously untrustworthy.

Nonetheless, the two lead investigators for the studies gave their individual takes on the pros and cons of the drugs, which both met their primary efficacy end points of proven superiority to the standard antithrombotic drug, unfractionated heparin (UFH).

The biggest selling point for fondaparinux was safety, with a significantly reduced rate of major bleeding events, compared with UFH, in the Organization to Assess Strategies for Ischemic Syndromes (OASIS) 6 trial, said Dr. Salim Yusuf, professor of medicine at McMaster University, Hamilton, Ont.

The biggest problem with fondaparinux seemed to be its lack of improved efficacy in patients who underwent a primary percutaneous coronary intervention (PCI), the preferred mode for treating MIs in the United States.

In fact, a detailed analysis suggested that treatment with fondaparinux showed a trend toward inferior outcomes during the first 3 days after PCI, then seemed to become more beneficial during continued treatment.

That raised the possibility that in the PCI setting, the best approach might be to use UFH or a similar drug first and then switch to fondaparinux, a strategy that will need testing in a new study, Dr. Yusuf said.

Enoxaparin's profile was almost a mirror image of that of fondaparinux, in that its Achilles' heel was safety, causing 50% more major bleeds than UFH. But the advantage of low-molecular-weight heparin is versatility, with no apparent downside in patients undergoing PCI. Although no patients in the new enoxaparin study were treated with primary PCI, the drug was used for rescue PCI without problems, and its efficacy in primary PCI was proved in an earlier study, said Dr. Elliott M. Antman, director of the cardiac unit at Brigham and Women's Hospital, Boston.

"You can take enoxaparin to the cath lab without having to switch drugs, and we know it's when you cross from one antithrombin to another that you run into bleeding concerns," Dr. Antman said. ■

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'Physicians are like big ships. By the time you can see that they are sinking, it's too late.'

Dr. Dan Shapiro, on stress, burnout, and depression in physicians, p. 70