Fondaparinux Lowers Bleeding Risk in Acute MI

‘It’s 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 reperfusion was not routine,” said Dr. Robert M. Califf in an editorial that accompanied the findings. “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.joe60038]).

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 1.2% 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 co-investigator 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 of the studies gave their individual takes on the pros and cons of the drugs, which both met their primary efficacy endpoints 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 improvement in patients who underwent a primary percutaneous coronary intervention (PCI), the preferred mode of 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 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 who underwent 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 safe when you cross from one antithrombin to another that you run into bleeding concerns,” Dr. Antman said.

‘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