Fondaparinux Bests Enoxaparin Overall in ACS

BY BRUCE JANCIN
Denver Bureau

STOCKHOLM — The antithrombotic agent fondaparinux provided similar short-term efficacy compared with enoxaparin, but dramatically greater safety and superior long-term outcomes in the largest-ever clinical trial involving patients with acute coronary syndrome.

Key findings in the Organization to Assess Strategies for Ischemic Syndromes (OASIS-5) trial were that fondaparinux (Arixtra) was associated with a 47% reduction in major bleeding compared with enoxaparin (Lovenox), and this led to reduced overall mortality in the fondaparinux group at 6 months, Salim Yusuf, M.B., said at the annual congress of the European Society of Cardiology.

OASIS-5 was a double-blind, randomized trial involving more than 20,000 patients with unstable angina/non–ST-segment elevation MI. They received subcutaneous injections of 2.5 mg of fondaparinux once daily for up to 8 days, or enoxaparin at 1 mg/kg twice daily.

The primary efficacy end point in OASIS-5 was the rate of the composite of death, MI, and refractory ischemia by day 9. It was similar in the two groups at roughly 5.8%.

The primary safety end point was the rate of major bleeding. Key secondary end points included the rates of death, MI, and stroke at 1 and 6 months; these results significantly favored fondaparinux, as did the safety outcomes. (See box.)

More than 6,000 study participants underwent percutaneous coronary intervention (PCI); their 30-day combined rate of death, MI, and major bleeding was 10.1% with enoxaparin, compared with 8.1% with fondaparinux, a highly significant (20%) difference. Among 1,732 patients who underwent PCI within the first 24 hours, the major bleeding rate was 4.7% with enoxaparin and 39% lower with fondaparinux. In fact, there was no patient subgroup in OASIS-5 who did better with enoxaparin.

The clinical implications of OASIS-5 are that for every 1,000 patients with acute coronary syndrome (ACS) treated with fondaparinux instead of enoxaparin, there will be 10 fewer cases of death or MI, 4 fewer strokes, and 25 fewer major bleeds, according to Dr. Yusuf, professor of medicine and director of the Population Health Research Institute at McMaster University, Hamilton, Ont.

"The OASIS-5 trial clearly demonstrates that fondaparinux is the preferred anticoagulant for treatment of ACS," said Dr. Yusuf, principal investigator in the trial.

Fondaparinux is the first selective inhibitor of factor Xa. It is already approved worldwide for prevention of venous thromboembolic events in patients undergoing orthopedic or abdominal surgery, as well as for treatment of acute pulmonary embolism and deep vein thrombosis. In North America, it is priced lower than enoxaparin, further increasing its attractiveness as a therapeutic alternative to low-molecular-weight heparin, which has been shown superior to unfractionated heparin in the treatment of ACS, the physician said.

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DR. YUSUF

A spokesman for GlaxoSmithKline, cosponsor of OASIS-5 together with Sanofi-Synthelabo and Organon, said the company plans to apply to the Food and Drug Administration and European authorities for an indication for use of fondaparinux in ACS.

Discussant Robert M. Califf, M.D., said the OASIS-5 investigators had identified an excellent regimen for anticoagulation in ACS. "With all the previous antithrombotics I've worked with, as the dose goes up you get more bleeding but fewer ischemic events. That's the classic tradeoff. Apparently with fondaparinux it's a different story. There's a dose-related increase in bleeding but no dose-related reduction in ischemic events. That means we have the delightful situation—if it holds up—that the lowest effective dose is also the most effective dose," noted Dr. Califf, professor of medicine and vice-chancellor for clinical research at Duke University, Durham, N.C.

He added that he strongly suspects there was a dosing problem with enoxaparin, particularly in older patients who tend to have mildly reduced renal function. He pointed to the finding that the 30-day combined rate of death, MI, refractory ischemia, and major bleeding was virtually identical in the two study groups in patients younger than 65 years, whereas in patients above that cutoff, the rate was 23% lower with fondaparinux.

Yet in fairness to the OASIS investigators, they used enoxaparin exactly as recommended in the product labeling, which calls for a dose adjustment only in patients with a creatinine clearance below 30 mL/min.

"Really, the burden is on the manufacturer now to clarify whether in patients with a creatinine clearance above 30 but below 60 mL/min there's a problem that needs to be addressed," the cardiologist said.

Lars Wallentin, M.D., a pioneer in the development of low-molecular-weight heparin for use in ACS, told this newspaper he found OASIS-5 persuasive, and that—on the basis of the findings of equivalent efficacy but enhanced safety—he was strongly considering switching from enoxaparin to fondaparinux.

"Less bleeding is very important to patients. A large hematoma that we'd traditionally classify as a 'moderate' bleed often seems catastrophic from the patient's perspective," added Dr. Wallentin, professor of cardiology at Uppsala (Sweden) University Hospital.

Freek Verheugt, M.D., told this newspaper OASIS-5's impact will vary locally depending on the price of fondaparinux. "In Holland, where fondaparinux was developed, it's so expensive the orthopedic surgeons don't use it at all," said Dr. Verheugt, professor and chairman of cardiology at University Medical Center, Nijmegen (Netherlands).

For him, the most important thing about OASIS-5 is that it showed that factor Xa inhibition is very safe, a finding he considers extremely reassuring. There are half a dozen or more selective oral Xa inhibitors in the developmental pipeline. They will be far cheaper than injectable anticoagulants, and it will be possible to use them for months rather than days. ■

Selected OASIS-5 End Points Significantly Favor Fondaparinux

	Enoxaparin	Fondaparinux	Relative Risk Reduction
Mortality at day 30	3.5%	2.9%	17%
Stroke rate at 6 months	1.6%	1.3%	19%
Mortality at 6 months	6.3%	5.6%	11%
Combined rate of death/MI/stroke at 6 months	12.3%	11.1%	10%

Source: Dr. Yusuf

ACE Inhibitor Blocks Left Ventricular Remodeling in Elderly

BY MITCHEL L. ZOLER
Philadelphia Bureau

STOCKHOLM — Treatment with the ACE inhibitor perindopril cut the incidence of left ventricular remodeling in elderly patients after myocardial infarction in a study with more than 1,200 patients.

As a result, treatment with the study drug, perindopril at a dosage of 8 mg/day, "may be suggested as standard treatment in this clinical setting," Roberto Ferrari, M.D., said at the annual congress of the European Society of Cardiology.

On the basis of these results and the findings of seven previous studies, "we now have convincing evidence that all patients with coronary artery disease should get treated with an ACE inhibitor," commented Nicolas Danchin, M.D., a professor of medicine at the European Hospital Georges Pompidou in Paris.

The latest trial, the Perindopril Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) study, tested the efficacy of ACE inhibitor therapy in a very specific population: patients aged 65 or older with preserved left ventricular function following an MI.

The study enrolled 1,252 patients at 109 centers in five European countries. All patients had to have a left ventricular ejection fraction of at least 40%; the average ejection fraction was 59%, and their average age was 72 years. About 80% of patients had New York Heart Association class I heart failure. Patients were enrolled 7-20 days (a mean of 11 days) after their MI. Patients who had already begun treatment with an ACE inhibitor were withdrawn from the drug for at least 24 hours before entering the study. Almost three-quarters of the patients were on a β-blocker, which they continued to take.

Patients were randomized to treatment with either 4 mg of perindopril daily or placebo for the first month of the study, after which the dosage was raised to 8 mg daily. Patients were followed for 12 months.

The primary end point was the combined incidence of death, hospitalization for heart failure, or left ventricular remodeling. Remodeling was defined as at least an 8% rise in left ventricular and diastolic volume. Echocardiographs suitable for assessing remodeling were available a year after treatment started for 455 patients on perindopril and 441 on placebo.

The incidence of the primary end point was cut by 38% in patients treated with perindopril, compared with those on placebo, a statistically significant difference, reported Dr. Ferrari, head of cardiology at the University of Ferrara (Italy).

But the result was driven entirely by a 46% relative drop in the rate of ventricular remodeling in the perindopril-treated patients, compared with the controls. Remodeling occurred in 51% of the placebo patients and in 28% of the test group. There was no difference between the two groups in the mortality rate. And although perindopril was linked with a 27% cut in the rate of hospitalization for heart failure, this difference was not significant.

The drug was well tolerated. Its activity in reducing remodeling is probably a class effect of all ACE inhibitors, Dr. Ferrari said.

The study was sponsored by Servier, which markets perindopril (Coversyl) in Europe and elsewhere. In the United States, perindopril is marketed as Aceon by a partnership of Solvay Pharmaceuticals Inc. and CV Therapeutics Inc. ■