Stent Patients Need to Take Their Aspirin Daily

BY MITCHEL L. ZOLER
Philadelphia Bureau

STOCKHOLM — Less than 1% of patients who receive a drug-eluting coronary stent develop late stent thrombosis during the first 1.5 years after implantation, on the basis of a study in more than 2,000 patients.

While these and earlier findings showed that drug-eluting stents are "relatively safe" during the long term, they also highlighted the need for patients who receive a drug-eluting stent to unceasingly remain on daily aspirin therapy, Andrew T.L. Ong, M.D., said at the annual congress of the European Society of Cardiology.

Stopping aspirin is an "absolute contraindication," he said in an interview. "In today's day and age there is no surgery that requires stopping aspirin," said Dr. Ong, a cardiologist at Thoraxcenter Rotterdam (the Netherlands).

"Every patient who gets a drug-eluting stent should receive a 'passport' " that tells all of the patient's other physicians not to stop aspirin without consulting the ones who placed the stent, commented Luis Gruberg, M.D., director of the division of invasive cardiology at the Rambam Medical Center in Haifa, Israel.

The link between late stent thrombosis and stopping aspirin and other antiplatelet therapy was underscored by the new incidence data, collected on all 2,006 patients who received a drug-eluting, coronary stent at Thoraxcenter since April 2002. The total included 1,017 patients who received a sirolimus-eluting stent (Cypher), and 989 who received a paclitaxel-eluting stent (Taxus).

During an average follow-up of 1.5 years, seven patients (0.35%) developed late stent thrombosis, defined as an abrupt stent occlusion that developed more than 30 days after stent placement. One patient had two stents that each had late thrombosis.

When analyzed statistically, the upper 95% confidence interval on the rate of late thrombosis was 0.72%, which means that it is very likely that the "real" rate of late thrombosis is 0.72% or less, said Dr. Ong. The rate in this series was strikingly similar to a 0.7% rate reported last May for a series of 2,229 patients who were treated at three hospitals in Germany and Italy (JAMA 2005;293:2126-30).

That study and the one presented by Dr. Ong are the first two reports to calculate a rate of late thrombosis in a large, well-defined number of patients who got drug-eluting stents. This rate is also similar to what has been reported for bare metal stents, said Dr. Ong.

Of the eight stents with late thrombosis in the Thoraxcenter series, three were in patients who had stopped both aspirin and clopidogrel (Plavix) treatment, while the other five were in patients who had stopped clopidogrel but had continued aspirin.

Clinicians at Thoraxcenter now usually prescribe clopidogrel for 6 months following stent implantation. The drug can be continued longer, but in the Netherlands most insurers will only pay for a 6-month course.

All seven patients had ST-segment elevation MIs as a result of the stent thrombosis; two patients also had shock and died.

Following Dr. Ong's talk, several in the audience spoke about the need for patients with drug-eluting coronary stents to stay on daily aspirin, and how to best get this message to primary care physicians who care for these patients with stents. Many spoke in favor of giving each patient a "passport" reviewing their medical history that patients would be told to show to all of their other physicians. ■

Fondaparinux Betters Enoxaparin in Acute Coronary Syndrome

BY BRUCE JANCIN
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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.

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, four 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.

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

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 the low-molecular-weight heparin, which in turn has previously been shown superior to unfractionated heparin in the treatment of ACS, the physician said.

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. It's something you'd only dream about in most situations," 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, even though it's more effective than enoxaparin for prevention of venous thromboembolism," 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.

An ongoing companion trial, OASIS-6, involves the randomization of 12,000 ST-segment elevation MI patients—including many undergoing primary PCI—to fondaparinux or unfractionated heparin. ■