FUTURA/OASIS-8 Solves Fondaparinux Paradox

**BY BRUCE JANCIN**

FROM THE ANNUAL CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY

STOCKHOLM – The use of fondaparinux as an antithrombotic agent in percutaneous coronary intervention for acute coronary syndromes could get a major boost in clinical practice now that the optimal dose of adjunctive unfractionated heparin has been clearly defined in the large randomized FUTURA/OASIS-8 study.

It’s clear from the study that standard dose unfractionated heparin, not low-dose, is the right way to go for PCI in ACS patients treated with fondaparinux, Dr. Sanjit S. Jolly said at the congress. The investigators have fully baled up at using fondaparinux, a synthetic factor X inhibitor, despite its impressive performance in the earlier Organiztion to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial, in which it halved major bleeding and produced a 17% reduction in mortality compared with enoxaparin (N. Engl. J. Med. 2006;354:1464-76).

The concern among intervenional cardiologists has been that catheter thrombosis rates were higher with fondaparinux in OASIS-5. Although adjunctive unfractionated heparin will prevent that problem, the optimal dose of heparin needed to avoid catheter thrombosis and ischemic complications without compromising fondaparinux’s low rate of major bleeding has been unclear – until FUTURA/OASIS-8, said Dr. Jolly of McMaster University, Hamilton, Ont.

The FUTURA/OASIS-8 trial was a double-blind, randomized study involving 2,026 patients undergoing PCI within the next 72 hours for high-risk ACS at 179 hospitals in 18 countries. All patients received 2.5 mg of fondaparinux subcutaneously once daily; after entering the catheterization lab, they were randomized to adjunctive standard- or low-dose unfractionated heparin. Standard-dose heparin was defined as 60 U/kg, or in the event a glycoprotein IIb/IIIa inhibitor was used and 85 U/kg if not, with dosing guided by activated clotting time (ACT). Low-dose heparin was given at 50 U/kg regardless of glycoprotein IIb/IIIa inhibitor therapy, and was adjusted as needed.

The primary end point, major or minor bleeding or major vascular access complications within 48 hours after PCI, occurred in roughly 5% of both study arms. But there was a nominally significant difference between the two treatment groups in the key secondary end point: peri-procedural major bleeding and the 30-day rate of death, MI, or target vessel revascularization. This occurred in 3.9% of the standard-dose unfractionated heparin group, vs. 5.8% of those on low-dose heparin, representing a 51% increased risk with low-dose therapy.

The risk of major bleeding within 48 hours was 1.1% in the standard-dose unfractionated heparin arm and 1.2% with low-dose heparin in FUTURA/OASIS-8, vs. 3.4% with enoxaparin in OASIS-5, he noted.

“FUTURA/OASIS-8 will definitely improve uptake in the community and amongst interventional cardiologists,” he said.

Dr. Ralph Brindis, American College of Cardiology president, agreed. “This could be a paradigm change,” he predicted in an interview.

“We have been very leery, at least in the United States, in utilizing fondaparinux in ACS patients we’re going to take to the cath lab,” added the cath lab director during a press briefing shown in OASIS-5. “But they’ve shown in FUTURA/OASIS-8 that you can do so safely and effectively. I think this is going to be very helpful in the cath lab,” added Dr. Brindis, an interventional cardiologist and senior advisor for cardiovascular disease at the University of California Kaiser Permanente in Oakland.

Simultaneously with the Stockholm presentation, the study results were published online (JAMA 2010 Aug. 31 [doi:10.1001/jama.2010.1320]).

**Disclosures:** Dr. Jolly received honoraria and research grants from GlaxoSmithKline, the trial sponsor. Dr. Brindis said he had no financial conflicts.

---

**OCTOBER 2010 • WWW.ECARDIOLOGYNEWS.COM**

**INTERVENTIONAL CARDIOLOGY**

In the phase 3 diabetes trials, 637 (63%) patients had baseline fasting serum TG levels less than 200 mg/dL, 361 (35%) had baseline fasting serum TG levels between 200 and 499 mg/dL, and 111 (11%) had baseline fasting serum TG levels between 300 and 500 mg/dL, and 9 (1%) had fasting serum TG levels greater than or equal to 500 mg/dL. The median baseline fasting TG concentration for the study population was 172 mg/dL, the median post-treatment TG was 195 mg/dL should WELCHOL and 177 mg/dL in the placebo group.

WELCHOL, administered in a median placebo-corrected increase in serum TG of 5% compared to placebo WELCHOL resulted in a median increase in serum TG of 5% compared to placebo.

In the diabetes clinical trials, the incidence associated with hypertriglyceridemia. reported cases of acute pancreatitis primary hyperlipidemia, there were no clinical trials, including studies in patients with hepatic impairment.

In the phase 3 diabetes trials, 637 (63%) patients enrolled in the four diabetes studies, 696 (62%) had mild renal insufficiency (creatinine clearance [CrCl] <60–90 mL/min), 17 (3%) had moderate renal insufficiency (CrCl 30–50 mL/min), and none had severe renal insufficiency (CrCl <30 mL/min), as estimated from baseline serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation. No overall differences in safety or effectiveness were observed between patients with CrCl <60 mL/min and those with a CrCl ≥60 mL/min (n=705).

**10 OVERDOSAGE**

Doses of WELCHOL in excess of 4.5 g/day have not been tested. Because WELCHOL is not absorbed, the risk of systemic toxicity is low. However, excessive doses of WELCHOL may cause more severe local gastrointestinal effects (e.g., constipation) than recommended doses.

To date, no significant alteration of warfarin drug levels with warfarin and WELCHOL has been measured. In in vitro binding or in vivo drug interaction testing or a study published in the New England Journal of Medicine.

Dr. Sanjit S. Jolly said at the congress. A number of drugs have been tested for interaction with WELCHOL.

Dr. Jolly said at the congress. A number of drugs have been tested for interaction with WELCHOL.

- Cyclosporine levels should be monitored in postmarketing. Cyclosporine levels should be monitored in postmarketing.

Dr. Jolly said at the congress.

- Cyclosporine levels should be monitored in postmarketing.

Dr. Jolly said at the congress.

- Cyclosporine levels should be monitored in postmarketing.

Dr. Jolly said at the congress.

- Cyclosporine levels should be monitored in postmarketing.

Dr. Jolly said at the congress.

- Cyclosporine levels should be monitored in postmarketing.

Dr. Jolly said at the congress.

- Cyclosporine levels should be monitored in postmarketing.

Dr. Jolly said at the congress.

- Cyclosporine levels should be monitored in postmarketing.

Dr. Jolly said at the congress.