# Fondaparinux Cut Event, Bleeding Risk in ACS

BY BRUCE JANCIN
*Denver Bureau*

BARCELONA — The selective factor Xa inhibitor fondaparinux proved superior to enoxaparin or unfractionated heparin for the treatment of the full spectrum of acute coronary syndrome, from unstable angina through ST-elevation MI, in a weighty new combined analysis of two randomized trials totaling more than 32,000 patients, Dr. Shamir Mehta reported at a joint meeting of the European Society of Cardiology and the World Heart Federation.

In acute coronary syndrome (ACS) patients not undergoing percutaneous coronary intervention (PCI), fondaparinux conferred significantly lower rates of the composite end point of mortality, repeat MI, or stroke as well as less major bleeding than either enoxaparin or unfractionated heparin (UFH) in the combined analysis of the fifth and sixth Organization to Assess Strategies for Ischemic Syndrome (OASIS-5 and -6) trials. (See box.)

In those participants who did undergo PCI, fondaparinux (Arixtra) was as effective as enoxaparin (Lovenox, Clexane) and had a markedly lower associated risk of major bleeding, added Dr. Mehta of McMaster University, Hamilton, Ont.

Adding UFH in the catheterization lab at the time of PCI in patients treated upstream with fondaparinux essentially eliminates catheter thrombosis, a concern when patients went to PCI on fondaparinux alone. The incidence of catheter thrombosis was just 0.3% in patients on fondaparinux and UFH. Moreover, the incidence of abrupt or threatened abrupt closure in the cath lab was 6.2% with enoxaparin alone, 5.9% with fondaparinux alone, 4.3% with enoxaparin plus UFH, and comparably low with fondaparinux plus UFH.

"These data suggest that unfractionated heparin is a good anticoagulant for PCI and probably better than using enoxaparin or fondaparinux alone," the cardiologist said.

A caveat is that there were no primary PCIs in OASIS-5 and -6, Dr. Mehta noted, adding that he doesn't recommend using fondaparinux in that setting.

Fondaparinux is approved in the U.S and Europe for the prevention of venous thromboembolism in patients undergoing major orthopedic or abdominal surgery and for treatment of acute deep vein thrombosis and acute pulmonary embolism. It is not approved for ACS patients; however, GlaxoSmithKline reported in October that the Food and Drug Administration has accepted a supplemental new drug application based on OASIS-5 and -6 for priority review, for the use of fondaparinux in "a broad spectrum of patients with acute coronary syndromes."

The results of OASIS-5 were presented at the annual congress of the European Society of Cardiology in September 2005 and published in April 2006 (N. Engl. J. Med. 2006;354:1464-76); those of OASIS-6 were presented at the annual meeting of the American College of Cardiology in March 2006 and published in April (JAMA 2006;295:1519-30). The new combined analysis was performed in order to strengthen the power of the findings and address questions that had arisen when the individual studies were presented.

**OASIS-5 and -6 Combined 30-Day Major End Point Rates**

| | Enoxaparin or UFH | Fondaparinux | Relative risk reduction |
|---|---|---|---|
| Combined death/MI/stroke | 8.0% | 7.2% | 9% |
| Death | 4.3 | 3.8 | 11 |
| MI | 3.8 | 3.5 | 8 |
| Stroke | 1.0 | 0.8 | 18 |
| Major bleeding | 4.4 | 3.0 | 37 |

Note: Based on a study of more than 32,000 patients.
Source: Dr. Mehta

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One question many physicians asked when the individual OASIS studies were presented was this: Is fondaparinux safe in patients on clopidogrel or a glycoprotein IIb/IIIa inhibitor? The answer is now in: With more than 18,000 patients in the combined analysis on clopidogrel or ticlopidine, the rate of major bleeding at 9 days was 2.2% in fondaparinux-treated patients, vs. 3.8% treated with enoxaparin or UFH. And in more than 5,400 patients on a glycoprotein IIb/IIIa inhibitor, the major bleeding rate was 3.6% with fondaparinux and 5.6% in the comparator group.

Some interventional cardiologists had argued that comparing fondaparinux to enoxaparin plus UFH in the PCI setting was misleading because switching from enoxaparin to UFH in the cath lab resulted in increased bleeding, compared with rates with either alone. The combined analysis shows that's not so. When UFH was given at least 6 hours after the last enoxaparin dose as specified in the OASIS protocols, bleeding did not increase. The bleeding risk of fondaparinux is so low that unlike with enoxaparin, there is no need for a delay before giving UFH, Dr. Mehta said.

Fondaparinux costs less than half as much as enoxaparin, he said. "Plus you have lower rates of bleeding complications with all their related costs, plus the reductions in mortality, MI, and stroke."

Dr. Mehta has served as a consultant for and on the speaker's bureau of GlaxoSmithKline, which sponsored the OASIS trials. ■

# Thrombolysis Is Unexpected Flop in Out-of-Hospital Cardiac Arrest Study

BY BRUCE JANCIN
*Denver Bureau*

BARCELONA — Routine thrombolytic therapy in patients with refractory out-of-hospital cardiac arrest failed to show even a glimmer of benefit in the 1,050-patient Thrombolysis in Cardiac Arrest trial, the first major randomized double-blind study to examine the issue.

"These results are very unexpected," a disappointed TROICA Chairman Dr. Bernd W. Boettiger admitted at the joint meeting of the European Society of Cardiology and the World Heart Federation. "Cardiac arrest remains a high-mortality syndrome with no specific treatment," added Dr. Boettiger, professor of anesthesiology at the University of Heidelberg (Germany) and chairman-elect of the European Resuscitation Council.

TROICA involved 1,050 patients in 10 European countries with witnessed cardiac arrest of presumed cardiac origin who didn't experience prompt return of spontaneous circulation after initiation of CPR. Following administration of atropine in accord with standard CPR protocol, patients were randomized to fibrinolytic therapy with tenecteplase or placebo given in the field by EMS personnel or physicians as CPR continued.

The primary end point was 30-day survival. It was 18.2% in the tenecteplase arm and 20.2% with placebo, a nonsignificant difference.About 59% of both groups were admitted to the hospital. The two groups did not differ significantly in any other outcomes, including symptomatic intracranial hemorrhage or major bleeding.

The rationale for TROICA, a Boehringer Ingelheim–funded trial, lies in the well-established fact that 65%-70% of all out-of-hospital cardiac arrests are due to underlying acute MI or pulmonary embolism, both of which are approved indications for thrombolytic therapy. Cardiac arrest also entails activation of a cascade of systemic coagulation, and thrombolytic therapy dissolves blood clots. Roughly a half dozen prior small, nonrandomized studies suggested benefit for thrombolysis during CPR.

One possible explanation for the negative results in TROICA is that thrombolytic therapy was administered either too early or too late. Another is that the tenecteplase was rendered less effective by the derangements in pH and blood glucose, and other changes that characterize cardiac arrest, or perhaps by having vasopressors on board.

"I am still convinced the rationale is sound for a thrombolytic approach during CPR, maybe combined with an adjunctive anticoagulant like heparin," Dr. Boettiger said in an interview.

For now, he will consider using thrombolysis in out-of-hospital cardiac arrest on a case-by-case basis, mainly in patients with suspected pulmonary embolism. There was a suggestion in TROICA that thrombolysis produced better outcomes in that patient subset.

Dr. Frans Van de Werf, professor of cardiology at the University of Leuven (Belgium), speculated that another possible explanation for TROICA's failure might be that the blood flow generated during prolonged CPR was insufficient to bring the thrombolytic agent to the thrombus. He stressed that the TROICA results have absolutely no bearing on the currently approved indications for thrombolytic therapy: ST-elevation MI, pulmonary embolism, and ischemic stroke. ■

# *Study Finds Link Between Psoriasis and Risk of MI*

Psoriasis appears to be an independent risk factor for myocardial infarction, conferring the same magnitude of risk as other major cardiac risk factors, according to Dr. Joel M. Gelfand of the University of Pennsylvania, Philadelphia, and his associates.

Noting that the immunologic abnormalities that give rise to psoriasis may also put patients at risk for other diseases associated with systemic inflammation, including heart disease, Dr. Gelfand and his associates assessed the risk of MI in a population-based cohort study. They used data on nearly 131,000 psoriasis patients treated in the United Kingdom between 1987 and 2002, who were matched with 557,000 control subjects.

After a mean of 5 years, patients with psoriasis had a significantly higher incidence of MI than controls. In those younger than 50 years, psoriasis conferred a similar degree of risk as standard cardiac risk factors. Patients with the most severe psoriasis had the highest MI rate. These findings are consistent with the hypothesis that greater immune activity in psoriasis is related to a higher risk of MI (JAMA 2006;296:1735-41).

The link between psoriasis and MI persisted after the data were adjusted for smoking, diabetes, hyperlipidemia, hypertension, and body mass index, and also appeared to be independent of psoriasis treatments, such as oral retinoids, cyclosporine, and methotrexate. The researchers were not able to examine the role of NSAIDs.

"The link between psoriasis and MI may be mediated by other factors beyond inflammation, such as psychological stress, sedentary lifestyle, or possibly poor compliance with management of CV risk factors," Dr. Gelfand and his associates noted.

**—Mary Ann Moon**