Enoxaparin Beats Heparin as Adjunct in Acute MI

BY MITCHEL L. ZOLER
Philadelphia Bureau

ATLANTA — The low-molecular-weight heparin enoxaparin was more effective than unfractionated heparin as an adjunct to fibrinolytic therapy in patients with an acute myocardial infarction in a study with more than 20,000 patients.

But enoxaparin's downside was a significant increase in the rate of major bleeding events, which rose from 1.4% in the unfractionated heparin (UFH) group to 2.1% in the enoxaparin group, a 50% relative increase, Dr. Elliott M. Antman reported at the annual meeting of the American College of Cardiology.

The increased bleeding risk with enoxaparin was, nonetheless, a substantial improvement over previous trials with this drug, which was accomplished largely by a modified regimen that eliminated bolus administration and pared the dosage administered to patients aged at least 75 years, as well as reduced the dosage given to patients with impaired renal function. These dosage adjustments brought the major bleeding rate down by a third, compared with the rate in previous studies, said Dr. Antman, director of the cardiac unit at Brigham and Women's Hospital, Boston.

Death or nonfatal MI occurred during the first 30 days after treatment in 9.9% of the enoxaparin group and 12.0% of the unfractionated heparin group.

On balance, even with the increased risk of major bleeds, treatment with enoxaparin cut the composite rate of death, nonfatal recurrent myocardial infarction, and nonfatal major bleeds to 11.0% at 30 days after treatment, compared with a 12.8% rate in the UFH group, a statistically significant difference.

The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction Study 25 (EXTRACT-TIMI 25) was sponsored by Sanofi-Aventis, which markets enoxaparin (Lovenox). Dr. Antman has received lecture fees and research grants from Sanofi-Aventis and also has served on paid advisory boards of the company.

The study enrolled 20,479 patients at 674 sites in 48 countries, including the United States. Patients had ST-segment elevation MI and entered the study within 6 hours of the onset of symptoms. All of the patients received aspirin and some form of thrombolytic therapy, and all were randomized to either a standard regimen of UFH for at least 48 hours, or enoxaparin. Patients in the enoxaparin arm who were younger than 75 years received a 30-mg intravenous bolus, followed by subcutaneous injections of 1.0 mg/kg twice a day until hospital discharge or for a maximum of 8 days. Smaller doses were administered on a similar basis to older patients and patients with an estimated creatinine clearance of less than 30 mL/min.

The study's primary end point was the rate of death or nonfatal MI during the first 30 days after treatment, which occurred in 9.9% of enoxaparin-treated patients and in 12.0% of patients treated with UFH, a 17% relative reduction with enoxaparin that was statistically significant. Enoxaparin treatment also led to a significantly reduced rate of urgent revascularization procedures during 30 days of follow-up.

Three different aspects of enoxaparin treatment may have been responsible for its improved efficacy compared with UFH, Dr. Antman said. First, enoxaparin has a superior antithrombotic effect; second, the convenience of subcutaneous, instead of intravenous, dosing led to enoxaparin being used for a longer time in the study's protocol than was the case for UFH; and third, use of enoxaparin helped prevent rebound increase in thrombotic events when treatment was stopped, which may have occurred in the patients treated with UFH. Treatment with enoxaparin was linked with an increased rate of major bleeds, but not with any rise in intracranial hemorrhages, which occurred in 0.7% of patients treated with heparin and 0.8% of those treated with enoxaparin. The major bleeding rate in the UFH group (1.4%) was substantially below the rates reported in several previous studies, which may be explained by the low use of open-label UFH before randomization, a conservative dosing strategy, and avoidance of double anticoagulation in patients who had coronary catheterization following fibrinolytic therapy, he said. ■