Excessive Dosing of Tirofiban Common in Women

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DALLAS — Women with acute coronary syndrome treated with a platelet glycoprotein IIb/IIIa inhibitor are nearly four times more likely than men to receive excess dosing—and that goes a long way toward explaining their sharply increased risk of major bleeding complications, Dr. Karen P. Alexander said at the annual scientific sessions of the American Heart Association.

She reported on 14,170 patients with non-ST elevation acute coronary syndrome (ACS) who received an intravenous platelet glycoprotein IIb/IIIa inhibitor during 2004 at 400 U.S. sites participating in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/AHA Guidelines) registry.

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The incidence of excess dosing, as defined in the drug labeling, was 19.2% among men and 46.4% in women. After the investigators adjusted for age, heart failure, diabetes, renal insufficiency, and body mass index, women were 3.8-fold more likely than men to receive tirofiban or eptifibatide in excessive doses.

The incidence of major bleeding was 6.6% among men treated with a IIb/IIIa inhibitor and 14.1% among treated women.

National guidelines recommend the use of the IIb/IIIa inhibitors in patients with ACS because the drugs have been shown to reduce mortality or MI. The package labeling for the drugs calls for dose adjustment based on renal function. The excess dosing problem results when physicians rely on the serum creatinine level as a guide to renal function, when in fact serum creatinine is affected by body size.

A calculation of creatinine clearance avoids this pitfall. It's also the method of adjustment for renal function specified in the Physicians' Desk Reference, which calls for a dose reduction of tirofiban when creatinine clearance is less than 30 cc/min and of eptifibatide at less than 50 cc/min, noted Dr. Alexander of Duke University, Durham, N.C.

"This study goes beyond describing gender-based differences in outcomes to suggesting a possible way to improve them. Specifically, correct dosing of IIb/IIIa inhibitors is important in both sexes, but women may afford a greater relative benefit with appropriate dosing and safe use than men," she added.

Excess dosing didn't explain all of the difference in major bleeding between treated men and women, because the major bleeding rate among CRUSADE participants with correct dosing of their IIb/IIIa inhibitor was 5.3% in men but 10.9% in women. Moreover, while men subjected to excess dosing had a 13.2% incidence of major bleeding, the rate was 18% in excessively dosed women. After investigators adjusted for gender differences in age, systolic blood pressure, body mass index, and heart failure, however, patients of either gender exposed to excessive doses of a IIb/IIIa inhibitor had a 43% increased relative risk of major bleeding.

The CRUSADE investigators undertook this study in part because a metaanalysis of six clinical trials involving the use of IIb/IIIa inhibitors in ACS had suggested a net clinical benefit in men but a net harm in women.

AHA's immediate past president, Dr. Alice K. Jacobs, called the CRUSADE analysis "an important study for those of us who treat women with these agents and are always worried about bleeding.

"A normal serum creatinine may be misleading in a smaller patient. A serum creatinine of 0.8 mg/dL—normal in a man—might be indicative of abnormal renal function in a woman, so we're increasingly turning to creatinine clearance," added Dr. Jacobs, professor of medicine and director of interventional cardiology at Boston University.

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