Ivabradine Slashes Coronary Events in Angina

BY BRUCE JANCIN

BARCELONA — Ivabradine reduced hospitalizations for acute MI by 73% in patients with stable coronary artery disease and left ventricular systolic dysfunction who had limiting angina and a baseline resting heart rate of 70 bpm or more, according to a new analysis from the BEAUTIFUL trial.

Also, the need for coronary revascularization fell by 59% compared with placebo in this study population, Dr. Roberto Ferrari said at the annual congress of the European Society of Cardiology.

He noted that this was a nonprespecified post hoc analysis of the 1,507 participants in the double-blind, placebo-controlled trial who had limiting angina at baseline, so the results need to be tested in a large prospective clinical trial.

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DR. FERRARI

"This will be done in the SIGNIFY trial, which is now starting. However …the results we obtained are plausible, and they are in line with previous data for ivabradine," said Dr. Ferrari, ESC president and professor and chair of the department of cardiology at the University of Ferrara (Italy).

BEAUTIFUL (Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction) involved 10,917 patients with stable CAD and left ventricular systolic dysfunction from 34 countries who were randomized double-blind to ivabradine or placebo on top of conventional therapy and followed for a mean of 18 months.

The key findings were that a baseline resting heart rate of 70 bpm or more proved a strong risk factor for cardiovascular morbidity and mortality, and lowering an elevated resting heart rate with ivabradine significantly reduced those risks. The benefits were confined to ischemic outcomes; heart failure–related outcomes were unaffected (Lancet 2008; 372:807-16).

The new analysis, confined to individuals with baseline limiting angina symptoms, was undertaken because those with severe angina have a much higher risk of coronary events than do other CAD patients. Other antianginal drugs have not shown the ability to reduce coronary events, so demonstrating that ivabradine does sets it apart.

The substudy included 712 patients whose baseline resting heart rate was at least 70 bpm. Their rate of hospitalization for fatal or nonfatal acute MI was 1.7% if they received ivabradine and 6.3% on placebo. Their coronary revascularization rate was 2.0%, compared with 5.0% in controls. Ivabradine use resulted in a roughly 8 bpm greater reduction in resting heart rate than in the placebo group at 18 months.

Ivabradine is the first selective inhibitor of the sinus node I_f current. As such, it is a pure heart-rate-lowering drug that maintains myocardial contractility, atrioventricular contraction, and ventricular repolarization, avoiding the hypotension problems often seen with full-dose beta-blocker therapy.

Discussant Gerd Heusch of University Hospital, Essen (Germany), said he finds it "very difficult to reconcile" the modest heart rate reduction provided by ivabradine with the drug's profound protection against ischemic events. He hypothesized that ivabradine has pleiotropic effects including antioxidant activity and reduction of intracardiac sodium-calcium exchange.

Ivabradine is marketed in Europe and other countries but is not available in the United States. An official at Servier said that the French company is looking for an American pharmaceutical company partner to help bring the drug to this country.

Dr. Ferrari and Dr. Heusch disclosed having received honoraria from Servier for lectures. In addition, Dr. Ferrari received payment for serving on the executive committee of the Servier-sponsored BEAUTIFUL trial. ■