MERLIN Finds New Evidence of Ranolazine Safety

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NEW ORLEANS — Ranolazine may have earned a product labeling upgrade from second-line to first-tier status for treatment of chronic angina on the strength of its reassuring safety performance in the 6,560-patient MERLIN trial.

"Safety concerns have been at the forefront for this agent," Dr. David A. Morrow noted in presenting the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndrome–Thrombolysis in MI) results at the annual meeting of the American College of Cardiology.

Those concerns have focused on the fact that ranolazine (Ranexa) is associated with a roughly 5-millisecond prolongation of the QT interval at the doses used in chronic angina. Yet animal studies paradoxically suggest the drug suppresses markers of proarrhythmia, and the labeling warning concedes "the clinical significance of the QT prolongation … is unknown."

In MERLIN, ranolazine showed no increase over placebo in all-cause or sudden cardiac death, and the drug actually reduced clinically significant arrhythmias on Holter monitoring, said Dr. Morrow of Brigham and Women's Hospital, Boston.

MERLIN had three objectives. One was to provide additional safety information to guide clinical use of ranolazine. Another was to study the drug's efficacy as an antianginal agent in a far broader patient population than previously studied—and ranolazine did significantly reduce severe recurrent ischemia, with a 1-year incidence of 13.9%, compared with 16.1% for placebo. There was a 23% reduction in the rate of worsening angina and a 19% decrease in need for intensification of antianginal therapy in the ranolazine group, regardless of whether patients underwent coronary revascularization.

The trial's third aim was to determine if ranolazine reduces major cardiovascular events in patients with ACS or when used as secondary preventive therapy in patients with chronic stable angina. This was an attempt by the study sponsor, CV Therapeutics, to create a major new indication for the drug. On this score the trial was negative; the 1-year rate of cardiovascular death or MI was 10.4% with ranolazine, compared with 10.5% with placebo.

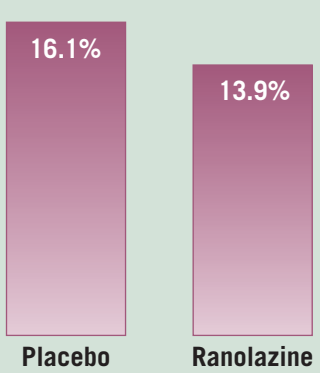
MERLIN participants had to have unstable angina or non–ST-elevation MI plus one or more indicators of moderate to high risk of recurrent ischemic events or death. About 24 hours after chest pain onset, they were randomized in double-blind fashion to intravenous ranolazine or placebo for up to 96 hours, followed by oral ranolazine at 1,000 mg b.i.d. or placebo for 1 year.

At 1 year there were 65 sudden cardiac deaths in the placebo arm and 56 in the ranolazine group. The incidence of clinically significant arrhythmia on Holter monitoring—defined as ventricular tachycardia, new-onset atrial fibrillation, supraventricular tachycardia, complete heart block, bradycardia, or a greater than 2.5-second pause—was 83.1% with placebo and 73.7% with ranolazine, a significant 11% relative risk reduction. All individual components of the Holter arrhythmia end point favored ranolazine, and the reduction in ventricular tachycardia reached statistical significance.

Cardiovascular Therapeutics announced MERLIN supports expansion of the existing ranolazine indication to include first-line antianginal therapy based upon a special protocol agreement the company made with the Food and Drug Administration.

Ranolazine is unique in that its antianginal and anti-ischemic effects occur without clinically significant impact on heart rate or blood pressure. Its novel mechanism of action involves inhibition of the late sodium current. ■

Incidence of Severe Recurrent Ischemia at 1 Year



Note: Based on the 6,560-patient MERLIN trial.
Source: Dr. Morrow

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