

Ranolazine Associated With Cardiovascular, Metabolic Improvement

Results are from a retrospective analysis of the CARISA study.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

The investigational drug ranolazine improved glycemic control and increased exercise tolerance in patients with diabetes and stable angina, according to a retrospective analysis.¹

Ranolazine, an investigational agent, is a novel antianginal and antiischemic agent that has neutral hemodynamic properties, according to investigators reporting in the *European Heart Journal*. Adam D. Timmis, MD, FRCP, professor of clinical cardiology at the London Chest Hospital, and colleagues studied the efficacy and safety of the agent in diabetic and nondiabetic patients included in the Combination Assessment of Ranolazine In Stable Angina (CARISA) trial.

Glycemic control was also analyzed in this long-term, open-label extension study of CARISA. Patients enrolled in CARISA had chronic angina; 189 had diabetes and 634 did not. Background therapy included atenolol, diltiazem or amlodipine. Patients were randomized to ranolazine (750 mg or 1,000 mg twice daily) for 12 weeks or placebo. Exercise tolerance, angina frequency, nitroglycerin usage, glucose, HbA1c and lipid levels were measured.

After patients completed the randomized portion of the trial, they were eligible for enrollment in the ongoing, open-label extension study and were evaluated every 3 months. Professor Timmis and colleagues reported that ranolazine produced similar improvements in exercise parameters, nitroglycerin use and angina frequency in diabetic and nondiabetic patients. The occurrence of adverse events was similar between the groups. Fasting glucose and lipid levels remained unaltered in diabetic patients following 12 weeks of therapy.

"In a posthoc analysis, ranolazine 750 mg and 1,000 mg reduced HbA1c versus placebo by $0.48 \pm 0.18\%$ ($P=.008$) and $0.70 \pm 0.18\%$ ($P=.0002$), respectively; the HbA1c levels appeared to remain unchanged over time during long-term therapy," the investigators wrote.

Professor Timmis concluded that antianginal efficacy and safety of ranolazine for angina were similar for diabetic and

nondiabetic patients, and the agent significantly improved glycemic control in diabetic patients.

In an accompanying editorial,² Rhonda Cooper-DeHoff, PharmD, and Carl J. Pepine, MD, wrote that the mechanism of action of ranolazine is not completely understood.

"Emerging data suggest that ranolazine may be a potent and selective inhibitor of the late sodium current across the membrane of cardiomyocytes, which may result in improved diastolic function, microvascular flow and cardiac efficiency without altering blood pressure, heart rate or contractility," Dr. Pepine is professor of medicine and chief of the division of cardiovascular medicine and Dr. Cooper-DeHoff, is assistant director and clinical programs research assistant professor, both are at the University of Florida.

Antianginal and antihypertensive regimens often affect glucose metabolism and insulin sensitivity and may even promote diabetes, Dr. Pepine said. Because ranolazine may also improve metabolic function, the significant reduction in HbA1c seen in the study would make sense.

"I emphasize weight loss, diet and exercise," Dr. Pepine said in an interview with Reuters Health. "I aim for a blood pressure target of $<130/80$ mm Hg and LDL target of <70 mg/dL (with statins) while avoiding drugs with the potential to worsen glycemic control (eg, beta-blockers, thiazide diuretics and niacin) and emphasizing drugs with the potential to enhance insulin sensitivity (eg, thiazolidinediones, [angiotensin-converting enzyme] inhibitors/angiotensin receptor antagonists, aldosterone blockers and calcium antagonists)." ■

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1. Timmis AD, Chaitman BR, Crager M. Effects of ranolazine on exercise tolerance and HbA1c in patients with chronic angina and diabetes. *Eur Heart J*. 2006;27:42-48.

2. Cooper-DeHoff R, Pepine CJ. Ranolazine is associated with cardiovascular and metabolic improvement: A win-win for patients with diabetes. *Eur Heart J*. 2006;27:5-6.