Metformin Lowered Mortality in Heart Failure

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MUNICH — Metformin-treated diabetic patients with heart failure had strikingly lower morbidity and mortality than did those on oral sulfonylureas, in a long-term observational study.

"Our data suggest metformin is probably safe—and potentially effective—in congestive heart failure patients compared to treatment with sulfonylureas alone," Dr. Chim C. Lang reported at the annual congress of the European Society of Cardiology.

The safety issue is key. Heart failure has long been considered a relative contraindication to metformin because of a supposedly increased risk of drug-related, potentially fatal, lactic acidosis. The concern has its origins in problems with phenformin, another insulin-sensitizing biguanide. But several lines of evidence suggest the concern over metformin has little or no merit, said Dr. Lang of Ninewells Hospital and Medical School, Dundee, Scotland.

How best to manage diabetes in patients with heart failure is a pressing issue, particularly in light of recent problems with the use of thiazolidinediones in this setting. Metformin could be a cheaper and safer alternative in this extremely common clinical situation. The incidence of heart failure in type 2 diabetic patients is 30.9 cases per 1,000 person-years, Dr. Lang noted.

He reported on all 774 type 2 diabetic patients who developed new-onset chronic heart failure in Tayside, Scotland, during 1994-2003. Ninety were managed with metformin monotherapy, 381 with sulfonylurea monotherapy, and 303 with both.

At 10 years of follow-up, 60% of patients in the metformin group were dead, compared with 77% who received sulfonylureas alone and 66% with combination therapy.

Patients managed with sulfonylureas alone tended to be older, to be sicker, and to have worse renal function, and were less likely to be on β-blockers and aspirin, so those differences were adjusted for in a Cox regression analysis. The result: an adjusted 28% relative risk reduction in mortality with metformin alone.

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The mortality curves diverged within the first year of follow-up. At 1 year, 90% of patients in the metformin group remained alive. They had an adjusted 55% relative risk reduction in 1-year mortality compared with the sulfonylurea-only group, while patients on both forms of therapy had a 34% relative risk reduction.

The combined risk of death or all-cause hospitalization was reduced by 26% in the metformin group compared with those on sulfonylureas alone. However, there was no significant difference between the sulfonylurea-only and combination therapy groups in the combined end point.

In an interview, Dr. Lang noted that he is conducting an ongoing, double-blind, placebo-controlled, randomized trial assessing whether 4 months of metformin improves exercise capacity, flow-mediated dilatation, and muscle enzyme activity in insulin-resistant patients with heart failure. It's a highly practical question, as poor exercise tolerance is one of the most debilitating aspects of heart failure.

The notion that metformin is safe in the setting of heart failure received a boost from a recent systematic review by investigators at the University of Alberta, Edmonton. They concluded, "Of the current antidiabetic agents, metformin is the only one not associated with any measurable harm in people with diabetes and heart failure and is associated with reduced mortality" (BMJ 2007;335:497).

In addition, the most recent Cochrane review concluded there were no cases of fatal or nonfatal lactic acidosis in 274 studies involving nearly 60,000 patient-years of metformin use (Cochrane Database Syst. Rev. Jan. 25, 2006 [epub doi:10.1002/14651858.CD002967.pub2]).

The observational Tayside study was funded by the British Heart Foundation. Dr. Lang's ongoing randomized trial is sponsored by the University of Dundee. ■