

## Diabetes and Cardiovascular Events: Not a Straight Course

*A study of two drugs for the primary prevention of diabetes yielded disappointing results.*

One proposed strategy for reducing the risk for diabetes in individuals with glucose intolerance is preprandial use of nateglinide, a short-acting insulin secretagogue. In addition, some studies have suggested that renin-angiotensin inhibitors (such as angiotensin-converting-enzyme inhibitors and the angiotensin-receptor blocker valsartan) might decrease the risk for diabetes as well as risks for cardiovascular events (e.g., [JW Cardiol Nov 30 2001](#)); however, this conclusion is based on secondary endpoints, and the results have been inconsistent. To find out more, investigators conducted the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, an industry-sponsored, placebo-controlled, randomized trial with a 2x2 factorial design. They enrolled 9306 adults (50% women; mean age, 64) with fasting plasma glucose levels of 95–126 mg/dL and one or more cardiovascular risk factors. Median follow-up was 5.0 years for diabetes incidence and 6.3 years for a composite of cardiovascular outcomes.

In the valsartan arm, slightly fewer patients in the valsartan group than in the placebo group were taking a renin-angiotensin inhibitor other than the study drug at the last study visit (20.4% and 24.0%, respectively), and systolic blood pressure had decreased more in the valsartan group than in the placebo group (6.3 mm Hg vs. 3.8 mm Hg;  $P<0.001$ ). The composite cardiovascular outcome rate was similar in the two groups (14.5% and 14.8% in the valsartan and placebo groups, respectively; hazard ratio, 0.96;  $P=0.43$ ). Diabetes developed in 33.1% of patients in the valsartan group and 36.8% of patients in the placebo group (HR, 0.86;  $P<0.001$ ). This finding was consistent across subgroups. By study's end, fewer patients in the valsartan group than in the placebo group were taking antidiabetic medications, and the mean increase in fasting glucose level was 0.6 mg/dL lower in the valsartan group than in the placebo group.

In the nateglinide arm, the composite cardiovascular outcome rate was also similar in the nateglinide and placebo groups (14.2% and 15.2%, respectively; HR, 0.93;  $P=0.20$ ). The between-group difference in diabetes incidence was not significant (36% in the nateglinide group and 34% in the placebo group; HR, 1.07;  $P=0.05$ ). The mean increase in fasting glucose level was 0.5 mg/dL lower in the nateglinide group than in the placebo group. Adverse event rates were similar in the two groups.

**Comment:** In this trial, nateglinide did not benefit patients with glucose intolerance, and the valsartan results were mixed. Although the rate of progression to diabetes was 14% lower in the valsartan group than in the placebo group, no difference in cardiovascular events was seen during the 6-year follow-up, and the improvement in glycemic control was modest. Is the benefit gained substantial enough to justify adding valsartan to these patients' regimens?

— [Harlan M. Krumholz, MD, SM](#)

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