NAVIGATOR Drugs Miss Prevention Targets

BY MARY ANN MOON

Nateglinide, an insulin secretagogue that lowers postprandial glucose, failed to prevent the development of diabetes and related cardiovascular events among high-risk patients in a large international clinical trial.

The angiotensin-receptor blocker valsartan also failed to prevent cardiovascular events in the same trial, but it did induce an unexpected relative reduction of 14% in the incidence of diabetes, according to the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Study Group.

The results were published online in the New England Journal of Medicine, simultaneously with the planned presentation at the annual meeting of the American College of Cardiology in Atlanta.

In an editorial comment accompanying the two reports, Dr. David M. Nathan of Massachusetts General Hospital, Boston, said, "The authors suggest that the prevention of diabetes with valsartan might make it a preferred drug as compared with antihypertensive drugs that potentially worsen glycemia."

Instead, the study findings show that "for now we should steer away from these two drugs" when attempting to forestall diabetes and cardiovascular complications in high-risk patients, Dr. Nathan said (N. Engl. J. Med. 2010 March 14 [doi:10.1056/NEJMe1002322]).

In NAVIGATOR, 9,306 patients who had impaired glucose tolerance and either known cardiovascular disease or cardiovascular risk factors were randomly assigned to take 60 mg oral nateglinide before meals three times daily, a placebo, or in a 2-by-2 factorial design, oral valsartan or a placebo.

Nateglinide was studied to determine whether it would slow progression to diabetes by restoring a more physiologic insulin response to meals. However, during a mean follow-up of about 6 years, progression to diabetes occurred in 36% of the nateglinide group and 34% of the placebo group, a nonsignificant difference, said Dr. Rury R. Holman of Oxford (England) University's Centre for Diabetes, Endocrinology, and Metabolism, and his associates said (N. Engl. J. Med. 2010 March 14 [doi:10.1056/NEJMoa1001122]).

Similarly, a composite cardiovascular outcome event occurred in 14% of the nateglinide group and 15% of the placebo group, a nonsignificant difference. There also were no differences between the two groups in any of the individual components of the composite cardiovascular outcome, including mortality rates.

The valsartan results were reported in a separate article. Unexpectedly, the angiotensin-receptor blocker had no effect on combined cardiovascular outcomes. Also unexpectedly, it reduced the incidence of diabetes by 14% relative to placebo, said Dr. Robert M. Califf of the Duke Translational Medicine Institute in Durham, N.C., and his NAVIGATOR colleagues.

It is possible that valsartan did not improve cardiovascular outcomes as it should have because most risk factors were already well controlled, since study subjects were allowed to take nonstudy medications such as ACE inhibitors, they said (N. Engl. J. Med. 2010 March 14 [doi:10.1056/NEJMoa1001121]).

Also, a "substantial proportion" of study subjects discontinued valsartan during the trial, which may have further mitigated its beneficial effects, they said.

In his editorial comment, Dr. Nathan agreed that "the high rates of loss to follow-up (13%), use of off-study ACE inhibitors or ARBs among participants assigned to placebo (24%), and nonadherence to valsartan (34% by study end) could explain the absence of an effect on cardiovascular disease."

He went on to question the use of valsartan in the study in the first place. "The rationale behind the choice of valsartan to inhibit the renin-angiotensin axis is less clear, other than the fact that both nateglinide and valsartan are manufactured by the pharmaceutical sponsor, which also designed the study," he said. ■

Fenofibrate Adds No Benefit to Diabetes Patients on a Statin

VITALS

Major Finding: In patients with type 2 diabetes and a high risk for cardiovascular disease, 2,765 treated with fenofibrate in addition to standard medical therapy had a 2.24%-per-year rate of major fatal or nonfatal cardiovascular events during an average 4.7 years of follow-up. The 2,753 patients randomized to placebo in addition to standard medical therapy had a 2.41%-per-year incidence rate of the end point. The difference in rates between the two groups was not statistically significant.

Data Source: ACCORD, a randomized, controlled lipid trial conducted at 77 sites in the United States and Canada during January 2001–July 2009.

Disclosures: Dr. Ginsberg has financial relationships with several pharmaceutical companies, including Merck and Abbott, which donated the simvastatin and fenofibrate/placebo but had no involvement in ACCORD. The trial was funded by the National Heart, Lung, and Blood Institute.

BY MITCHEL L. ZOLER

ATLANTA — The failure to significantly reduce the cardiovascular event rate with fenofibrate treatment in a large trial of high-risk type 2 diabetes patients probably occurred because the study enrolled too many of the wrong types of patients to clearly show a benefit from this drug, several experts said.

Instead of focusing on patients with diabetes and dyslipidemia, an elevated serum level of triglycerides, and depressed HDL cholesterol, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial enrolled a representative sampling of 5,518 patients with diabetes and a range of triglyceride and HDL cholesterol levels, proving that fibrate treatment, on top of the moderate statin dosage, could not further help most of these patients.

The ACCORD investigators decided to enroll a wide spectrum of patients "to see if [fenofibrate] could apply generally. It's important that we found that fenofibrate on top of a statin will not benefit the majority" of patients with diabetes, Dr. Henry N. Ginsberg said at the annual meeting of the American College of Cardiology.

Existing cholesterol-treatment guidelines from the National Heart, Lung, and Blood Institute—the Adult Treatment Panel III—call for adding a fibrate drug to statin treatment when triglyceride levels are high and HDL cholesterol is low. "I think that's the role for this drug, in patients with the most significant dyslipidemia," said Dr. Ginsberg, professor of medicine and director of the Irving Institute for Clinical and Translational Research at Columbia University, New York.

In ACCORD, 17% of enrolled patients fell into the subgroup with a plasma triglyceride level of at least 204 mg/dL and a plasma HDL cholesterol that was 34 mg/dL or less. Within this subgroup, fenofibrate treatment produced an improvement in the study's primary end point, the combination of major fatal or nonfatal cardiovascular events, that just missed statistical significance, Dr. Ginsberg said. Concurrently with his report at the meeting, the results were posted online (N. Engl. J. Med. 2010 Mar 14 [doi:10.1056/NEJMoa1001282]).

"They tested the drug on the wrong patients," said Dr. Prakash C. Deedwania, a cardiologist at the University of California, San Francisco, in Fresno, Calif. The trial results could potentially have been positive if enrollment had been more focused, he said in an interview.

"The message is that the majority of patients with diabetes don't need a fibrate added," said Dr. Roger S. Blumenthal, professor of medicine and director of preventive cardiology at Johns Hopkins University in Baltimore. "There was good reason to think the results might have been positive, but in ACCORD it was added to a statin, and a statin by itself is hard to beat."

In ACCORD, all patients received standard medical therapy for type 2 diabetes and cardiovascular disease risk, including statin therapy with simvastatin. Randomization assigned half the patients to also receive fenofibrate, at a target dosage of 160 mg/day. Although fenofibrate effectively cut triglyceride and HDL cholesterol levels, the incidence of all cardiovascular disease end points examined was similar between the treatment groups: 2.24% per year for the finofibrate group, 2.41% per year for the placebo group.

Dr. Deedwania has been a consultant to or received honoraria from AstraZeneca and Pfizer. Dr. Blumenthal had no relevant disclosures. ■

MY TAKE

Design Worked Against Fenofibrate

I think of fenofibrate as a triglyceride drug, or possibly as an HDL drug. The median triglyceride level in the ACCORD lipid patients was 162 mg/dL, so it's not very surprising that the overall group did not benefit. It is interesting that patients with high triglycerides and low HDL had some suggestion of benefit, with a *P* value of .06. Another limitation of the study was that fenofibrate was used on top of a statin.

I wonder what would have happened if it had been used alone, in statin-intolerant patients. Another issue is whether the average 4.7 years of follow-up in the study was long enough. Because the drug works via relatively weak risk factors like triglycerides and HDL cholesterol, perhaps the follow-up was too brief.

The study results clearly show no benefit from fenofibrate for all high-risk patients with diabetes. The results particularly indicated no benefit in women. Further studies should be done to address these issues.

PAUL D. THOMPSON, M.D., *is director of preventive cardiology at Hartford (Conn.) Hospital. He disclosed relationships with several pharmaceutical companies including Merck and Abbott, and with the American Board of Internal Medicine, the National Lipid Association, and Genomas. He has served on a data and safety monitoring board for Abbott, and has received other financial benefit from General Electric, Stryker, and Zimmer Holdings.*