Fenofibrate Adds No Benefit to Statin in Diabetes

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.

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%/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%/year incidence rate of the end point. The difference 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. Dr. Deedwania has had financial relationships with AstraZeneca and Pfizer. The trial was funded by the National Heart, Lung, and Blood Institute.

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.

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.

Cholesterol-treatment guidelines from the National Heart, Lung, and Blood Institute—the Adult Treatment Panel III—call for adding a fibrate drug to a statin when triglyceride levels are high and HDL cholesterol is low. "I currently use fenofibrate in patients with a serum triglyceride level above 200 mg/dL or with HDL cholesterol in the 30s [mg/dL] or below. That's the group we identified as having potential benefit. A reasonable guess is that fewer than 5% of diabetes patients are on combination treatment with a statin and a fibrate. I think our results suggest that group could be expanded somewhat," said Dr. Ginsberg, professor of medicine and director of the Irving Institute for Clinical and Translational Research at Columbia University, New York.

In the ACCORD lipid study, 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. The suggestion of benefit in this subgroup was also notable because it concurred with results from three prior, large studies that also examined the efficacy of a fibrate in patients with diabetes, Dr. Ginsberg said. Concurrently with his report at the meeting, the results were published online (N. Engl. J. Med. 2010 March 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. The trial results could potentially have been positive if enrollment had been more focused, he said in an interview.

ACCORD randomized patients at 77 sites in the United States and Canada during January 2001–October 2005 and followed them for a mean of 4.7 years. All patients received standard medical therapy for type 2 diabetes and cardiovascular disease risk, including statin therapy with simvastatin. Half the patients were randomized to also receive fenofibrate, at a target dosage of 160 mg/day; the rest received placebo. Their average age was 62 years, 31% were women, and two-thirds were white. Although fenofibrate effectively cut triglyceride and HDL cholesterol levels, during follow-up the incidence of all cardiovascular disease end points examined was 2.24%/year with finofibrate and 2.41%/year with placebo.

The only significant subgroup interaction involved gender, Dr. Ginsberg said. Men were more likely to do better on fenofibrate, and women were more likely to have better outcomes on placebo. ■

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 the subgroup analysis of 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 financial 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.*

Routine Invasive Strategy Best for All NSTE-ACS Patients

BY BRUCE JANCIN

ATLANTA — A routine invasive strategy in patients with non–ST-segment elevation acute coronary syndrome results in significantly fewer cardiovascular deaths and nonfatal MIs over the subsequent 5 years than does a selective, symptom-driven revascularization approach, according to a meta-analysis of all pertinent clinical trials.

"The key result is that 5 years after the randomization there is a net absolute difference of 3.2% and a 19% relative risk reduction in cardiovascular death or MI in the routine invasive group," Dr. Keith A.A. Fox observed in presenting the meta-analysis at the annual meeting of the American College of Cardiology.

The routine invasive strategy, consisting of early angiography with an eye toward revascularization, showed significant benefit in patients with non–ST-elevation acute coronary syndrome (NSTE-ACS). This finding constitutes a compelling argument for a change in the existing ACC/American Heart Association guidelines, which recommend a routine invasive strategy in NSTE-ACS patients with high-risk indicators, but state that in moderate- or low-risk patients the routine invasive or selective invasive approach is appropriate, said Dr. Fox, professor of cardiology at the University of Edinburgh, Scotland.

The meta-analysis, called the FIR Trial Collaboration, was conducted because the individual trials had inconsistent long-term findings. By combining individual patient data from the 5,467 patients who participated in the three trials, conclusive results emerged.

The 5-year cumulative rate of cardiovascular death or MI was 14.7% with a routine invasive strategy, compared with 17.9% with a selective invasive approach in which angiography was done only in patients with refractory angina or rest ischemia despite optimal medical therapy. The nonfatal MI rate was 10.0% with a routine invasive strategy, compared with 12.9% with a selective invasive approach, a statistically significant 23% relative risk reduction.

The absolute benefit of a routine invasive strategy was greatest in the 13% of patients who fell into the highest-risk group at baseline, but the strategy also showed significant advantages in the moderate- and low-risk groups. (See box.) The difference in outcomes between the two strategies increased steadily over time within all subgroups. ■

Cardiovascular Treatment Outcomes by Risk Category

Risk	Routine invasive (n = 2,721)	Selective invasive (n = 2,746)	Absolute risk difference
Low	8.2%	10.2%	2.0%
Moderate	17.3%	21.1%	3.8%
High	33.0%	44.1%	11.1%

Note: Based on a meta-analysis of data from three randomized clinical trials. Percentages represent the 5-year rate of cardiovascular death or MI. All differences are statistically significant.
Source: Dr. Fox

Disclosures: *Meta-analysis funded by the British Heart Association and the host institutions for the three trials. Dr. Fox has been a consultant to Sanofi-Aventis and Bristol-Myers Squibb.*