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Add a fibrate to a statin?

For most patients with diabetes and dyslipidemia, adding a fibrate does not improve cardiovascular outcomes.

PRACTICE CHANGER

Do not routinely add a fibrate to a statin for patients with type 2 diabetes who are at high risk for cardiovascular events.¹

STRENGTH OF RECOMMENDATION

B: Based on a good-quality randomized controlled trial.

The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med.* 2010;362:1563-1574.

ILLUSTRATIVE CASE

A 60-year-old man with cardiovascular disease and diabetes comes to your clinic for a routine check of his dyslipidemia, for which he is on statin therapy. His fasting lipid panel shows a low-density lipoprotein (LDL) of 70 mg/dL, triglycerides of 200 mg/dL, and a high-density lipoprotein (HDL) of 30 mg/dL. Should you recommend adding fenofibrate?

Patients with type 2 diabetes are at increased risk for cardiovascular events. National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines recommend treatment of dyslipidemia for all patients with high risk of cardiovascular events to an LDL goal of <100 mg/dL (optional <70 mg/dL), HDL goal of >40 mg/dL, and triglyceride goal of <150 mg/dL. These recommendations include the use of combination therapy with a statin and fenofibrate for patients who have elevated triglycerides and low HDL cholesterol despite being on statin therapy alone.²

Survival benefit of combo therapy remains unproven

We know that fibrate therapy alone in patients

with type 2 diabetes reduces major cardiovascular events.^{3,4} We also know that adding a fibrate to statin therapy can help patients reach their HDL and triglyceride targets. However, the survival benefit of the fibrate-statin combination over that of a statin alone has not been proven. In addition, there have been concerns about the increased risk of adverse effects with the combination. In fact, the overall benefits (and risks) of combining fibrates and statins for patients with diabetes and dyslipidemia were not addressed in a large randomized trial until the study we report on here.

STUDY SUMMARY

Statin + fibrate = minimal benefit for most patients

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study is among the largest trials conducted in adults with type 2 diabetes at high risk of cardiovascular events.⁵ The study examined 3 approaches to lowering the risk of major cardiovascular events: intensive lowering of blood sugar levels compared with standard blood sugar treatment; intensive lowering of blood pressure (BP) compared with standard BP treatment; and treatment of lipids with 2 drugs—a fibrate plus a statin—compared with a statin alone. This summary focuses on the lipid arm of the ACCORD study.¹

All patients in the study had type 2 diabetes and a hemoglobin A1c $\geq 7.5\%$. The study included patients ages 40 to 79 years with clinical evidence of cardiovascular disease and patients ages 55 to 79 years with either subclinical cardiovascular disease or ≥ 2 cardiovascular risk factors in addition to diabetes.

The lipid arm enrolled patients who had an LDL cholesterol of 60 to 180 mg/dL, an HDL cholesterol <55 mg/dL for women and blacks and <50 mg/dL for all other groups, and a triglyceride level <750 mg/dL for those not receiving lipid therapy and <400 mg/dL for those on lipid therapy. Enrollees (N=5518) were started on open-label simvastatin 20 mg, titrated up as needed to reach the LDL goal, then randomized to receive either fenofibrate or placebo 1 month later. The mean duration of follow-up was 4.7 years.

■ **The primary outcome** was the first occurrence of a major cardiovascular event—nonfatal myocardial infarction (MI), nonfatal stroke, or death from a cardiovascular cause. The annual rate of the primary outcome was 2.2% (n=291) in the fenofibrate-statin group and 2.4% (n=310) in the placebo group, a non-significant difference ($P=.32$).

The results were reported by sex. The primary outcome rate for men during the 4.7-year follow-up was 11.2% in the fenofibrate-statin group vs 13.3% in the placebo group; for women, the outcome rates were 9.1% in the treatment group and 6.6% in the placebo group ($P=.01$). These rates suggest a small benefit for men, and harm for women.

■ **Subgroup analysis showed additional benefit** from fenofibrate in patients with a combination of a high baseline triglyceride level (≥ 204 mg/dL) and very low baseline HDL cholesterol (≤ 34 mg/dL), representing about 16% of the study participants. The primary outcome rate for patients in this subgroup was 12.4% in the fenofibrate-statin group and 17.3% in the placebo group ($P=.057$); number needed to treat (NNT)=20 patients for 4.7 years to prevent 1 major cardiovascular event.

■ **Harm was similar in both groups.** A small number of patients had elevations of alanine aminotransferase of >3 times the upper limit of normal (1.9% in the fenofibrate-statin group and 1.5% in the statin group). The study drug was discontinued in 66 patients (2.4%) in the fenofibrate-statin group (and the placebo was discontinued in 30 patients [1.1%] in the statin group). The fenofibrate *or* statin dose was reduced in 440 patients (15.9%) in the fenofibrate-statin group and in 194 patients (7%) in the statin group due to a decrease in estimated glomerular filtration rate. There

was no significant difference in the incidence of hemodialysis and end-stage renal disease (75 patients in the fenofibrate-statin group vs 77 patients in the statin group).

WHAT'S NEW

We have evidence that combo therapy doesn't further reduce risk

This study examined a previously unaddressed question, the role of combination fibrate-statin therapy in high-risk patients with type 2 diabetes. The findings do not support the routine use of combination therapy compared with a statin alone for most patients with diabetes. Overall, combination therapy with simvastatin and fenofibrate did not lower the risk of MI, stroke, or death from cardiovascular disease more than simvastatin alone.

This trial showed that women with diabetes and hyperlipidemia should not be treated with both a statin and a fibrate. Men appeared to have a very small benefit from combination therapy (NNT=50). Patients with a baseline HDL ≤ 34 mg/dL and baseline triglyceride ≥ 204 mg/dL appeared to benefit from the combination, but this group constituted only 16% of the patients in this trial and the difference had borderline statistical significance. Nonetheless, it may be reasonable to treat such patients with combination therapy until a definitive study is done.

CAVEATS

Statin dose did not match standard practice

This study used a low dose of statin. The average daily simvastatin dose was 22.3 mg in the fenofibrate-statin group and 22.4 mg in the placebo group. This constitutes low-dose therapy compared with doses routinely used in practice (ie, 40 or 80 mg). A higher dose of simvastatin may have negated any outcome differences.

CHALLENGES TO IMPLEMENTATION

This "practice changer" conflicts with NCEP guidelines

The current NCEP ATP III guidelines recommend combination fibrate-statin therapy for all patients when statin therapy alone is not

INSTANT POLL QUESTION

Do you prescribe fibrates for patients with type 2 diabetes who fail to reach lipid goals on statin therapy alone?

- Yes, I routinely prescribe combination therapy
- Occasionally; it depends on the patient
- Rarely or never
- Other _____

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adequate to achieve lipid goals. This is a major challenge to our recommendation against using this combination for most patients with diabetes. Some physicians may choose to follow the ATP III guidelines rather than the new evidence because they feel more confident adhering to national guidelines.

Clinical inertia is another challenge, as clinicians may be hesitant to stop therapy in patients already on a fibrate-statin combination. Finally, specialists may continue to use

fibrate-statin combinations in all patients with diabetes who do not achieve lipid goals on a statin, and family physicians may hesitate to contradict their recommendations. **JFP**

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