

Fenofibrate and Cardiovascular Events in Patients with Type 2 Diabetes

Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–61.

Study Overview

Objective. To assess the effect of fenofibrate on cardiovascular events in patients with type 2 diabetes.

Design. Randomized, double-blind, placebo-controlled trial with intention-to-treat analysis.

Setting and participants. 9795 patients with type 2 diabetes aged 50 to 75 years from 63 centers in Australia, Finland, and New Zealand who were not taking statins at study entry were randomized to micronized fenofibrate 200 mg daily or placebo for a median of 5 years. Mean baseline lipid values were total cholesterol, 194 mg/dL; low-density lipoprotein (LDL) cholesterol, 119 mg/dL; high-density lipoprotein (HDL) cholesterol, 43 mg/dL; and triglycerides, 154 mg/dL. 22% of patients had prior cardiovascular disease.

Main outcome measures. The primary endpoint was major coronary heart disease (CHD) events (the composite of CHD death and nonfatal myocardial infarction [MI]). Secondary outcomes included major cardiovascular events (composite of CHD death, nonfatal MI, stroke, and other cardiovascular death), total cardiovascular events (major events plus coronary or carotid revascularization), CHD death, any cardiovascular death, hemorrhagic and nonhemorrhagic stroke, coronary and peripheral revascularization procedures, cause-specific non-CHD mortality, and total mortality.

Main results. Major CHD events occurred in 5.9% of placebo-treated and 5.2% of fenofibrate-treated patients (hazard ratio [HR], 0.89 [95% confidence interval {CI}, 0.75–1.05]; $P = 0.16$). Nonfatal MI was reduced in the fenofibrate group (HR, 0.76 [95% CI, 0.62–0.94]), but there was a nonsignificant trend towards greater CHD mortality with fenofibrate (HR, 1.19 [95% CI, 0.90–1.57]). Total cardiovascular events occurred in 13.9% of placebo-treated patients and 12.5% of fenofibrate-treated patients (HR, 0.89 [95% CI, 0.80–0.99]; $P = 0.035$) with the difference largely due to fewer nonfatal MIs and revascularization procedures in the fenofibrate group. Cardiovascular mortality (HR, 1.11 [95% CI, 0.87–1.41]) and total mortality (HR, 1.11 [95% CI, 0.95–1.29]) did

not significantly differ, although they tended to be higher in the fenofibrate group. Possible serious adverse events were rare in both groups (0.5% for placebo versus 0.8% for fenofibrate), but there was a slight increase in pancreatitis and pulmonary embolism in the fenofibrate group. More patients in the placebo group initiated other lipid-lowering medication (ie, statins) (17% versus 8%).

Conclusion. Fenofibrate did not significantly reduce the incidence of CHD events, cardiovascular mortality, or total mortality in type 2 diabetes patients treated for 5 years. Total cardiovascular events, mainly nonfatal MI and revascularization procedures, were reduced. The unequal initiation of statins may have influenced the study's findings.

Commentary

Type 2 diabetes mellitus carries a high lifetime cardiovascular risk and is frequently accompanied by low levels of HDL cholesterol and elevated triglycerides. There is great interest in determining whether drugs that primarily modify these lipid abnormalities will reduce cardiovascular risk in patients with type 2 diabetes. However, clinical trial data directly addressing this question are limited. The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) assessed the impact of treating men with CHD with gemfibrozil (another fibrate) [1]. A quarter of the 2531 patients in the VA-HIT had diabetes, and the 24% relative risk reduction observed in the outcome of coronary death, nonfatal MI, and stroke was similar in both diabetic and nondiabetic subgroups [1]. A post hoc subgroup analysis that included diagnosed and undiagnosed diabetes suggested that gemfibrozil was especially beneficial for patients with diabetes [2]. The Diabetes Atherosclerosis Intervention Study showed more favorable angiographic changes in patients with diabetes treated with fenofibrate compared with placebo over 3 years and showed a trend toward fewer cardiovascular events, but this study was not designed to test for differences in clinical outcomes [3]. Data from these and other studies along with epidemiologic data linking low HDL cholesterol and elevated triglyceride levels to increased cardiovascular risk led the National

Cholesterol Education Program to recommend that when LDL cholesterol is at or near goal, drugs that favorably modify triglyceride and HDL levels (eg, fibrates, niacin) may be considered in patients with these lipid abnormalities, particularly in combination with LDL cholesterol-lowering drugs (eg, statins) [4]. However, gemfibrozil can impair statin metabolism, and this combination has been implicated in rare occurrences of rhabdomyolysis [5]. Fenofibrate does not cause this interaction with statins and could potentially be safer for combination therapy.

The study by Keech et al showed that monotherapy with fenofibrate did not yield the same cardiovascular benefits observed with statins, which have clearly been proven to lower cardiovascular risk in patients with and without diabetes across a range of initial LDL, HDL, and triglyceride levels [6], or with gemfibrozil. Due to the study size, fairly low CHD event rate, and the unequal initiation of statins, this study could have failed to detect a sizable beneficial effect, similar to what was observed in VA-HIT, and it would be premature to completely discard fenofibrate as a potential therapeutic option in this setting. However, examination of the individual components of the study endpoints raises an important question. Nonfatal MI and revascularization procedures were significantly reduced in fenofibrate-treated patients, but there was a trend toward increased cardiovascular mortality with fenofibrate (a pattern that was not observed in VA-HIT). Could fenofibrate reduce plaque burden but predispose patients to death via a proarrhythmic or some other adverse effect? This question remains unanswered.

Applications for Clinical Practice

Fenofibrate should not replace statin therapy as the initial lipid-modifying treatment for adults with diabetes even when patients have moderately elevated triglyceride, below-average

HDL cholesterol, and near-target LDL cholesterol levels. Additional research, such as data from the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, is needed to clarify the role of combination therapy with a statin and a fibrate.

—Review by Stephen D. Persell, MD, MPH

References

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