Long-term fenofibrate therapy did not reduce major coronary events but may reduce total CVD events in type 2 diabetes mellitus

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.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Cardiology ★★★★★★☆ Endocrinology ★★★★★☆☆

QUESTION

In patients with type 2 diabetes mellitus, what is the effect of long-term fenofibrate therapy on coronary heart disease (CHD) events?

METHODS

Design: Randomized placebo-controlled trial (Fenofibrate Intervention and Event Lowering in Diabetes [FIELD]).
Allocation: Concealed.*
Blinding: Blinded (clinicians, patients, and outcome assessors).*
Follow-up period: Median 5 years.
Setting: 63 centers in Australia, New Zealand, and Finland.
Patients: 9795 patients 50 to 75 years of age (mean age 62 y, 63% men) who had a World Health Organization diagnosis of type 2 diabetes, total cholesterol level 3 to 6.5 mmol/L, and a total cholesterol/high-density lipoprotein (HDL) cholesterol ratio ≥ 4 or a triglyceride level of 1 to 5 mmol/L, with no clear indication for lipid-modifying therapy. Exclusion criteria were renal impairment, chronic liver disease, symptomatic gallbladder disease, or occurrence of a cardiovascular disease (CVD) event within 3 months before study entry.
Intervention: Micronized fenofibrate, 200 mg/d (n = 4895), or matching placebo (n = 4900).
Outcomes: A composite endpoint of nonfatal myocardial infarction (MI) or CHD mortality. Secondary outcomes included a composite endpoint of major CVD events (CHD events, CVD death, and stroke), total CVD events (major CVD events, and revascularization), individual events of the composite endpoint, and all-cause mortality. The study had 80% power to detect a 22% reduction in the primary outcome.
Patient follow-up: 99% (intention-to-treat analysis).

MAIN RESULTS

Groups did not differ for the primary outcome of nonfatal MI or CHD mortality (Table). Patients who received fenofibrate had a lower incidence of total CVD events than did patients who received placebo, mainly because of a reduction in nonfatal MI and revascularization (Table). The groups did not differ for CHD death or other secondary outcomes.

CONCLUSION

In patients with type 2 diabetes mellitus, long-term fenofibrate therapy did not reduce major coronary events but may reduce total cardiovascular disease events.

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*See Glossary.

Fenofibrate vs placebo in patients with type 2 diabetes at median 5 years†

Outcomes	Fenofibrate	Placebo	RRR (95% CI)	NNT (CI)
Nonfatal MI or CHD mortality	5.0%	6.0%	11% (–5 to 24)	Not significant
CVD events	13%	14%	10% (1 to 19)	70 (36 to 1056)
Nonfatal MI	3.0%	4.0%	24% (6 to 38)	101 (58 to 404)
Revascularization	8.0%	10%	19% (8 to 29)	55 (34 to 136)

†MI = myocardial infarction; CHD = coronary heart disease; CVD = cardiovascular disease. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

In the FIELD study by Keech and colleagues, it is disappointing that fenofibrate did not reduce fatal MI or CHD mortality in patients with type 2 diabetes mellitus. Such patients have greater numbers of small, dense, atherogenic particles than patients without diabetes, even with similar low-density lipoprotein (LDL) cholesterol levels. They also tend to have lower HDL cholesterol and higher triglyceride levels, 3- to 4-fold higher rates of CHD, and higher mortality associated with acute MI. Fibrates have shown beneficial effects on this pattern of lipid abnormalities. Weak evidence from post hoc analyses in the Helsinki Heart Study (1), Veterans Affairs HDL intervention trial (2), and the Bezafibrate Infarction Prevention trial (3) showed reductions in coronary events in patients receiving fibrates. The FIELD study is the first large clinical-endpoint trial of fibrate therapy in patients with diabetes.

Fenofibrate-group patients had reductions in LDL cholesterol, triglyceride, and HDL cholesterol levels. Beneficial secondary outcomes were a 25% relative risk reduction in nonfatal MI, 21% relative reduction in coronary revascularization, reduced rate of progression to albuminuria, and fewer laser treatments for retinopathy. Treatment effects appeared to be greater in patients with no previous CVD (the primary prevention group) and in those < 65 years of age, although chance variation could explain these subgroup findings.

In 2003, a systematic review summarized the benefits of statins in patients with diabetes (4). In the increasing, worldwide challenge to reduce morbidity and mortality from diabetes, the FIELD study shows that fenofibrate may have beneficial effects on microvascular disease and reduce risk for macrovascular events while improving lipid profiles. The study safety data showed no rhabdomyolysis in patients who were also taking a statin and supports the careful use of combined statin and fenofibrate therapy with ongoing safety monitoring. We must wait until 2010 for the results of their combined use in the Action to Control Cardiovascular Risk in Diabetes trial (5).

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