The evidence base demonstrating that statins reduce major events, including in people with diabetes mellitus, is arguably as robust as for any cardiovascular therapy. However, many individuals still experience end points despite the use of statins (the Figure). This “residual risk,” which is much higher in people with coexistent cardiovascular disease, is probably most appropriately expressed in absolute terms, acknowledging the development of atherosclerosis over decades rather than the duration of trials and its multifactorial causation. However, the residual risk provides the rationale for testing other lipid-modifying therapies in combination with statins.

People with diabetes mellitus have both qualitative and quantitative lipid changes. They include increased levels of triglycerides, small dense low-density lipoprotein (LDL) particles, and apolipoprotein B, as well as a decrease in levels of high-density lipoprotein (HDL) cholesterol. Fibrates, which are peroxisome proliferator receptor-α agonists, not only reduce triglyceride levels and possibly LDL cholesterol and chylomicron remnants and elevate HDL cholesterol but also are anti-inflammatory. The major beneficial effect of statins is to decrease LDL cholesterol. However, lower levels of HDL cholesterol and possibly increasing levels of triglycerides still denote elevated risk in those taking statins, even when LDL cholesterol levels are very low, and particularly in those with diabetes mellitus.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial
The hypothesis tested was whether, on a background of simvastatin 20 to 40 mg, major vascular events were reduced by fenofibrate, dosed according to baseline glomerular filtration rate. Overall, among 5518 subjects (mean age, 62 years; 31% female; 37% with previous cardiovascular event), mean total cholesterol was 175 mg/dL (4.53 mmol/L), LDL cholesterol was 101 mg/dL (2.61 mmol/L), HDL cholesterol was 38 mg/dL (0.98 mmol/L), and median triglyceride level was 162 mg/dL (1.83 mmol/L). The primary study end point was a standard in trials of preventive therapies, a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Over a mean of 4.7 years of follow-up, there were no significant effects of fenofibrate on this end point (hazard ratio, 0.92; 95% confidence interval, 0.79 to 1.08; \( P = 0.32 \)) or on secondary outcomes, namely the individual components of the primary composite, an expanded composite that also included any revascularization and hospitalization for heart failure, and total mortality.

The trial had 10 prespecified subgroup comparisons. Among them, there was a significant interaction for treatment effect by sex (\( P = 0.01 \)) with a reduction in the primary outcome in men and possible harm in women assigned fenofibrate. In addition, not only were event rates higher, but there was a strong trend toward a greater treatment effect of fenofibrate (31% reduction in the primary end point from 17.3% to 12.4%) in those with triglycerides in the highest tertile, \( \geq 204\text{mg/dL} (\geq 2.30\text{mmol/L}) \), and HDL cholesterol in the lowest tertile, \( \leq 34\text{mg/dL} (\leq 0.88\text{mmol/L}) \) (\( P = 0.057 \) for interaction).

Overall, the combination of simvastatin and fenofibrate was safe. There were no major differences in serious adverse events between the 2 treatment groups. Although mean serum creatinine increased as observed with fibrates previously, there was a significant reduction in both microalbuminuria and macroalbuminuria and no difference in end-stage renal disease.

Neutral or Not?

Statistical Power
The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial was designed to have 87% power to detect a 20% relative risk reduction in the primary outcome with fenofibrate, with an average follow-up of 5800 patients of 5.6 years in those not experiencing an event. The expected annual event rate of 2.4% in those taking placebo was replicated in the trial; there was an adherence to assigned treatment in both groups and a similar prevalence of statin therapy. However, slightly fewer patients were enrolled and follow-up was shorter than planned. Importantly, the observed treatment effect, although not significant, is still consistent with the risk reduction (10%; 95% confidence...
interval, 0 to 18) found in a recent meta-analysis of the effects of fibrates on cardiovascular outcomes. It is also possible that the effects may have been greater if fenofibrate had been started earlier than the median of 9 years after diabetes mellitus was diagnosed.

Subgroup Findings

Subgroup findings are frequently misinterpreted. Large-scale trials are powered to reliably test for significant effects in the overall cohort and not subgroups in which it is appropriate to test for heterogeneity of treatment effect.

The ACCORD trial did not simply test fenofibrate in people with dyslipidemia. A particular effect of fibrates in individuals with elevated triglycerides and possibly low HDL cholesterol levels and other features of the metabolic syndrome had been observed in posthoc analyses of other fibrate trials. If multiple subgroup comparisons are made, a more stringent criterion for significance in an individual subgroup should probably be applied (eg, \( P < 0.02 \)). Although this criterion or indeed the conventional boundary for statistical significance (\( P < 0.05 \)) may not have been met in ACCORD, the consistency of these observations, albeit posthoc in previous trials, supports the potential use of fibrates in this scenario. Fenofibrate is safer than gemfibrozil because it has no pharmacodynamic interaction with statins.

Interaction by sex had not been found previously. Because there is also no biologically plausible explanation, it likely represents a chance finding.

Lipid Effects

Compared with simvastatin and placebo, the combination of simvastatin and fenofibrate resulted in a similar reduction in LDL cholesterol (19 versus 21 mg/dL [0.49 versus 0.54 mmol/L]; \( P = 0.16 \)) to a mean of 80 mg/dL (2.1 mmol/L), a numerically small but significant increase in HDL cholesterol (3.2 versus 2.3 mg/dL [0.09 versus 0.06 mmol/L]; \( P = 0.01 \)), and greater reduction in triglycerides (42 versus 16 mg/dL [0.47 versus 0.18 mmol/L]; \( P < 0.001 \)).

Large-scale trials ultimately test the intervention rather than the multiple mechanism(s) that might be targeted. The results do not permit dissection of the relative importance of these and other effects or fenofibrate.

Possible Effects on Microvascular Disease

Fibrates significantly reduce the important microvascular complications of diabetes mellitus, including the progression of albuminuria and need for laser therapy. ACCORD-Eye analyses will provide further data on the effects of fenofibrate on diabetic retinopathy.

Implications for Guidelines and Clinical Practice

In the absence of manifest cardiovascular disease, major guidelines recommend statin therapy in people with diabetes mellitus because they ascribe an equivalent risk to them and to patients with known coronary heart disease or in cases when additional risk factors such as advancing age, longer duration since diagnosis of diabetes mellitus, or microalbuminuria are present.

Lifestyle advice and statins remain the cornerstone of lipid therapy, and ACCORD failed to establish an adjunctive role for fenofibrate in all people with diabetes. The National Cholesterol Education Program Adult Treatment Panel III guidelines suggest that fibrate or nicotinic acid be considered in addition in those with high triglyceride and low HDL cholesterol levels. The subgroup data in ACCORD support use of fenofibrate in this context.
Most guidelines recommend an LDL cholesterol target <100 mg/dL (2.6 mmol/L) in primary prevention and <70 to 80 mg/dL (1.8 to 2.0 mmol/L) in secondary prevention in people with diabetes mellitus. If this is not achieved with a potent statin, ezetimibe or nicotinic acid could be added. A triglyceride target level <150 mg/dL (1.7 mmol/L) is also given in some guidelines, partly because atherogenic small dense LDL particles are the predominant phenotype at higher triglyceride levels. The ACCORD trial will not affect these recommendations.

Concluding Comments on Combination Lipid Therapy

Clinical management is informed by factors other than large-scale trials that establish efficacy of a treatment. The epidemiological data related to HDL cholesterol are very robust. Furthermore, in the ACCORD trial, fenofibrate resulted in only a small increase in HDL cholesterol but had a greater effect on triglycerides. The association between triglyceride levels and risk is less clear. However genetic polymorphisms of the apolipoprotein A5 gene, which increase triglyceride levels over a lifetime and can reduce confounding by other factors such as decreased HDL cholesterol, suggest a causal association with coronary heart disease.

There are diverse approaches to increasing HDL cholesterol levels. Trials are ongoing or planned with the cholesterol ester transfer protein inhibitors anacetrapib and dalcetrapib in combination with statins. Other ongoing trials will also provide further evidence about the potential addition of extended-release formulations of niacin, possibly combined with a prostaglandin D2 receptor blocker to reduce flushing, and other agents such as ezetimibe. Future agents might also target other lipid mechanisms.

Disclosures

None.

References


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