Cardiovascular outcomes trials with non-statin lipid-lowering drugs in diabetes

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Abstract

Statin therapy is proven to reduce cardiovascular morbidity and mortality in people with diabetes, and high-dose statins are recommended for people with established atherosclerotic vascular disease. In two dedicated studies in people with diabetes, fibrates did not significantly reduce cardiovascular events and were associated with serious side effects. A similar lack of benefit was seen in two large studies of niacin. Ezetimibe, when added to statins, may further reduce LDL cholesterol and non-fatal vascular events. The PCSK9 inhibitors are a new class of subcutaneous lipid-lowering drugs which cause profound reductions in LDL cholesterol when added to statins. Evolocumab reduced non-fatal cardiovascular events when added to background statin therapy in a larger group of subjects and the benefits were confirmed in a diabetes subgroup. In another large trial alirocumab reduced major adverse cardiovascular events and total mortality. The clinical use of ezetimibe and PCSK9 inhibitors is currently limited by cost.

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Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality in people with diabetes mellitus. In a previous review we examined the evidence for reductions in cardiovascular outcomes with statins in people with diabetes.[1] This article reviews evidence from randomised controlled cardiovascular outcomes trials on the treatment of dyslipidaemia in diabetes using other lipid-lowering drugs, especially when added to baseline statin therapy. The dyslipidaemia associated with type 2 diabetes mellitus (T2DM) includes raised triglycerides and low high-density lipoprotein cholesterol (HDL cholesterol) concentrations. There are several classes of lipid-lowering drugs which predominantly reduce triglycerides and raise HDL cholesterol (fibrates, niacin), so in theory they could be of particular benefit to people with T2DM, but the results of randomised controlled cardiovascular outcomes trials with these drugs have been disappointing and conflicting. However, there are new lipid-lowering drugs which further reduce low-density lipoprotein (LDL) cholesterol when added to statins and have recently proven cardiovascular benefits, including ezetimibe, the PCSK9 inhibitor evolocumab and the CETP inhibitor anacetrapib. Analyses of diabetes subgroups from these studies are presented.

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Recent cardiovascular outcomes trials with older drugs

Fibrates

Fibrates have multiple effects on lipoprotein metabolism, and some of these effects are mediated through transcription of PPAR-alpha which encodes for proteins that control lipoprotein metabolism. Enhanced catabolism of triglyceride-rich particles and reduced secretion of very low-density lipoprotein (VLDL) contribute to the reduction in triglycerides, whereas the increase in HDL cholesterol concentrations is associated with changes in HDL lipoprotein expression.[2] Fibrates have been suggested as a logical drug treatment in diabetes as their use has been reported to increase concentrations of HDL cholesterol and reduce triglyceride levels. Two major trials have been conducted looking at the use of fibrates in T2DM (Table 1).

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study examined the use of fibrates in 9,795 people with T2DM in 63 centres in Australia, New Zealand and Finland.[3] The majority of patients (78%) had no history of cardiovascular disease and no subject was on lipid-lowering therapy at entry into the study. Fenofibrate therapy did not significantly reduce the primary outcome of coronary events (coronary heart disease death or non-fatal myocardial infarction), but there was a statistically significant 11% reduction in a secondary outcome of the total cardiovascular events (cardiovascular death, myocardial infarction, stroke, coronary or carotid revascularisation) in the fenofibrate group. Of concern, pancreatitis, pulmonary embolism and deep venous thrombosis were increased with fenofibrate.

The investigators offered several explanations for the lack of benefit in the primary outcome, including the observation that the difference in HDL levels between the two groups diminished over time as the study progressed, raising concerns over the long-term efficacy of fibrate treatment. They also noted an increased use of statin therapy in the placebo group (17%) compared with the fenofibrate group (8%). A post-hoc analysis was performed to study the effect of the metabolic syndrome on outcomes.[4] Eighty percent of the participants were defined as having the metabolic syndrome at baseline, and in that subgroup fenofibrate reduced

Table 1 Diabetes results from key fenofibrate and niacin studies

Study (year of primary publication)	Comparison	No of subjects	Subjects with diabetes (%)	Diabetes results
FIELD (2005)	Fenofibrate 200 mg vs. placebo	9,795	9,795 (100%)	No significant reduction in primary endpoint
ACCORD Lipid (2010)	Fenofibrate 160 mg vs. placebo	5,518	5,518 (100%)	No significant reduction in primary endpoint
AIM-HIGH (2011)	Extended-release niacin 1600–2000 mg vs. placebo	3,414	1,158 (34%)	No significant reduction in primary endpoint
HPS-THRIVE (2014)	Extended-release niacin 2000 mg plus laropiprant 40 mg vs. placebo	25,673	8,299 (32%)	No significant reduction in primary endpoint

cardiovascular disease events by 11%. By the time the FIELD study was published, the evidence for statins in people with diabetes was overwhelming and the FIELD investigators predicted that the main use of fenofibrate would be as an adjunct to statins, this being addressed by the ACCORD LIPID trial.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was designed to test the effect of intensive treatment of blood glucose on cardiovascular outcomes in 10,251 subjects with T2DM,[5] and had other sub-studies examining the effects of intensive blood pressure lowering[6] or combination lipid lowering.[7] A total of 5,518 people were enrolled in the ACCORD Lipid study and designated to receive open-label simvastatin and either fenofibrate or placebo. About 60% of subjects were taking a statin before enrolment in the study, and the average dose of simvastatin on follow-up was 22 mg.[7]

The annual rate of the primary outcome did not differ between groups, and there was also no difference in secondary outcomes. No additional cardiovascular benefit was demonstrated from the addition of fenofibrate to statin therapy. As was seen in the FIELD study, the effects of fenofibrate on lipids were less than anticipated, with only a very minor increase in HDL cholesterol but greater reductions in triglycerides comparing fenofibrate and placebo.

Niacin (nicotinic acid)

Niacin (nicotinic acid) has multiple hypothesised mechanisms of action which raise HDL cholesterol, reduce LDL cholesterol and reduce triglycerides, and are thought to be complementary to the mechanisms of actions of statins and fibrates. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides Impact on Global Health Outcomes (AIM-HIGH) trial investigated the effects of extended-release niacin in 3,414 people with established cardiovascular disease who had well controlled LDL cholesterol levels on statin therapy or a combination of statin and ezetimibe.[8] Of the study participants, 1,158 (34%) had diabetes at baseline. The trial was terminated early after three years because the boundary for lack of efficacy had been crossed and an unexpected high rate of ischaemic stroke had been observed among patients who were being treated with niacin. Despite niacin increasing HDL cholesterol and decreasing triglyceride levels, no benefit was found in reducing the primary outcome either in the entire cohort or in the subgroup analysis of people with diabetes. Niacin was previously known to worsen fasting glucose and HbA_{1c},[9] and more subjects in the niacin group discontinued medication because of increased blood glucose levels, but the effects on HbA_{1c} were not reported.

The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial was an international trial involving 25,673 subjects with prior vascular disease.[10] At baseline 8,299 subjects (32%) were reported to have diabetes. The study looked at the effects of extended-release niacin plus laropiprant (used to reduce the side effect of flushing commonly seen with niacin) in addition to intensive lipid-lowering treatment (statin alone or statin plus ezetimibe) and found no significant difference in major vascular events compared with placebo. Subgroup analysis of those with diabetes showed no significant difference in absolute lipid level changes or cardiovascular outcomes compared with subjects without diabetes. Niacin-laropiprant was associated with an increased incidence of disturbances in diabetes control that were considered to be serious, and an increase in the new diagnosis of diabetes.

Thus, there is a lack of convincing evidence for fibrates and niacin use providing additional benefit to statin therapy in people with diabetes (Table 1). Fibrates are probably neutral with regard to the development of new onset diabetes, whereas niacin – like statins[11] – is associated with an increased risk of developing diabetes.

Cardiovascular outcomes trials with newer lipid-lowering drugs

Ezetimibe

Ezetimibe is a non-statin therapy which targets the Niemann-Pick C1-like 1 (NPC1L1) protein to reduce intestinal absorption of cholesterol. Working in a complementary way to statins, ezetimibe can reduce LDL cholesterol levels even further in patients already on statin therapy.

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study compared Vytorin (simvastatin 40 mg plus ezetimibe 10 mg) with statin (simvastatin 40 mg) therapy in a group of 18,144 people after a recent acute coronary syndrome.[12] The median follow-up was 6 years. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, hospitalisation for unstable angina, coronary revascularisation or stroke, and this was slightly but significantly reduced by 6% in the combined therapy group. There was no effect on car-

Table 2 Diabetes results from key ezetimibe, CETP inhibitor and PCSK9 inhibitor studies

Study (year of primary publication)	Comparison	No of subjects	Subjects with diabetes (%)	Diabetes results
IMPROVE-IT	Ezetimibe 10 mg vs. placebo	18,144	4,933 (27%)	Significant 15% reduction in primary composite endpoint
REVEAL (2017)	Anacetrapib 100 mg vs. placebo	30,449	11,320 (37%)	Significant 10% reduction in first major coronary events
FOURIER (2017)	Evolocumab 140 mg/ 2 weeks or 420 mg monthly vs. placebo	27,564	11,031 (40%)	Significant 17% reduction in primary composite endpoint
ODYSSEY OUTCOMES (2018)	Alirocomab 150–300 mg/ 2 weeks vs. placebo	18,924	5,444 (29%)	Significant 16% reduction in major adverse cardiovascular events

diovascular death or total mortality. This treatment benefit was also found in the 27% of individuals who had diabetes after subgroup analysis (Table 2). Indeed, most of the benefit of the combination appeared to be in subjects with baseline diabetes.[13]

A detailed description of evidence for the reduction of cardiovascular events with lipid-lowering therapy in people with diabetes and chronic kidney disease is beyond the scope of this review. A guideline for the management of lipids in adults with diabetes and/or chronic kidney disease was recently published in the *British Journal of Diabetes* and contains the evidence base for this treatment.[14] However, the SHARP study is the only other cardiovascular outcomes trial with ezetimibe which had positive results.[15]

The Study of Heart and Renal Protection (SHARP) study recruited 9,270 patients with chronic kidney disease (3,023 on dialysis, 6,247 not on dialysis) and randomised them to simvastatin 20 mg plus ezetimibe 10 mg, or placebo. The primary endpoint of major atherosclerotic events was a composite of coronary death, non-fatal myocardial infarction, non-haemorrhagic stroke or any arterial revascularisation procedure. This was significantly reduced by 17%, and the proportional effects were similar in people with diabetes and those with no diabetes, and in people on dialysis and those not on dialysis. Most of the benefit was in reductions in revascularisation procedures, and there was no effect on cardiovascular death or total mortality. As this was a comparison of a combination versus placebo, it is not possible to determine which part of the combination or both was effective. This would have required one of the components to have been used as an active comparator rather than placebo.

CETP inhibitors

Cholesteryl ester transfer protein (CETP) promotes the transfer of cholesteryl esters from HDL to other lipoproteins, and inhibition of this protein increases HDL cholesterol and decreases LDL cholesterol. CETP inhibitors have been studied in cardiovascular outcomes trials for 10 years, with very mixed results. Torcetrapib added to atorvastatin was studied in the ILLUMINATE trial of 15,067 subjects at high cardiovascular risk.[16] The study was terminated early because of an increase in cardiovascular events and total mortality, with an associated increase in blood pressure. This was subsequently shown to be unrelated to CETP inhibition and was an off-target effect of torcetrapib raising aldosterone and blood pressure.[17] A total of 6,661 subjects in the ILLUMINATE trial had diabetes at baseline, and a post hoc analysis showed statistically significant differences in HbA_{1c} concentrations at 6 months in those on torcetrapib (7.06%) compared with placebo (7.29%), with lower plasma glucose concentrations and lower insulin levels.[18]

Dalcterapib did not have the same adverse effect on blood pressure but seemed to be less effective at reducing LDL cholesterol. The dal-OUTCOMES trial was stopped by the data and safety monitoring committee after 31 months due to futility as dalcetrapib had no effect on cardiovascular outcomes,[19] and further development of the drug was discontinued. Similarly, the ACCELERATE study with evacterapib was halted because of a lack of effect on the cardiovascular outcome.[20]

It therefore came as a surprise that the recently published REVEAL trial with anacterapib was positive.[21] Anacetrapib was added to intensive atorvastatin treatment in 30,499 patients with atherosclerotic vascular disease; 11,320 (37%) were recorded as having diabetes at baseline. During a median follow-up of 4.1 years, anacterapib significantly reduced the primary endpoint of coronary death, myocardial infarction or coronary revascularisation by 9%. The benefit seemed to correlate with reductions in LDL cholesterol rather than increases in HDL cholesterol. The relative risk reduction was similar in pre-specified subgroups including diabetes. In the group without diabetes at baseline anacetrapib reduced the onset of new diabetes and HbA_{1c} was 0.03% lower. No difference in HbA_{1c} was seen in the diabetes subgroup. No substantial safety issues were identified. Although these results were positive, the manufacturers have decided not apply to the FDA or EMA for a licence for anacetrapib.

PCSK9 inhibitors

PCSK-9 is a protein that plays a role in lipid metabolism by modulating the density of LDL receptors at the cell surface. It is produced by hepatocytes and secreted into the plasma in an active form. PCSK-9 binds to LDL receptors and increases internalisation of the receptors and lysosomal degradation. This inhibits recycling of the receptor back to the cell surface and reduces LDL receptor activity, which in turn leads to an increase in serum LDL cholesterol levels. PCSK9 inhibitors bind to PCSK-9, preventing interaction with LDL

receptors. This decreases degradation of the receptor, which recycles back to the cell surface, enhancing clearance of LDL cholesterol from the bloodstream and reducing LDL concentrations.

Two PCSK9 inhibitors have been approved for clinical use in Europe (alirocumab and evolocumab) and we now have evidence of benefit following a cardiovascular outcomes trial with evolocumab. The Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) trial was a very large randomised placebo-controlled trial of 27,564 subjects with atherosclerotic vascular disease who were already on statin therapy, and whose baseline LDL cholesterol concentration was greater than 1.8 mmol/L.[22] Subjects were treated with subcutaneous evolocumab 140 mg every two weeks, or 420 mg monthly, or matching placebo. After a median follow-up of 2.2 years the primary endpoint (a composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation) was significantly reduced by 15%. Most of the reduction was due to reductions in non-fatal myocardial infarction and coronary revascularisation, with no reduction in cardiovascular death or total mortality. At baseline, 11,031 subjects had diabetes (40%) and a detailed pre-specified subgroup analysis has been performed.[23] The results were similar to the overall results, with a significant reduction in the primary endpoint that was particularly due to reductions in non-fatal myocardial infarction and coronary revascularisation. In subjects without diabetes at baseline, evolocumab did not increase new-onset diabetes and no changes in HbA_{1c} or fasting plasma glucose were identified.

The Long-term safety and tolerability of alirocumab in high cardiovascular risk patients with hypercholesterolaemia not adequately controlled with their lipid modifying therapy (ODYSSEY LONG TERM) trial randomised people with high LDL cholesterol levels to statin therapy or statin therapy with alirocumab. The addition of alirocumab significantly decreased LDL cholesterol levels, increased HDL cholesterol levels and reduced triglyceride levels.[24] The recently presented ODYSSEY outcomes trial was a dedicated cardiovascular outcomes trial assessing the cardiovascular effects of alirocumab in 18,924 individuals following an acute coronary syndrome.[25] A total of 5,444 subjects (29%) had a history of diabetes at baseline. Alirocumab significantly reduced major adverse cardiovascular events by 15%, and in particular non-fatal myocardial infarction. There was also a nominal 15% reduction in all-cause mortality. There was no difference in new-onset diabetes or worsening of diabetes, and in the subgroup with diabetes at baseline there was a significant 16% reduction in major adverse cardiovascular events.

Conclusions

The role of statins in improving cardiovascular outcome in people with diabetes is well established. Many additional therapies have been postulated as potential adjuncts to statin therapy due to their molecular effects. Long-term outcome trials are important as molecular efficacy may not translate into cardiovascular benefit, as demonstrated by fibrates and niacin. Both ezetimibe and evolocumab have been demonstrated to further reduce non-fatal cardiovascular events when added to baseline statins, furthering the LDL hypothesis.[26] The clinical use of these therapies is likely to be heavily influenced by the cost, as evolocumab and alirocumab are relatively expensive therapies. By contrast, ezetimibe will be available as a generic drug in the near future and so will be more likely to be widely used as an add-on to statins in people with diabetes where targets are not being reached or following an acute coronary syndrome.

Key messages

- Fibrates and nicotinic acid have not demonstrated cardiovascular benefits when added to background statin therapy in people with diabetes
- Ezetimibe significantly reduced non-fatal events when added to simvastatin following an acute coronary syndrome in people with diabetes
- PCSK9 inhibitors evolocumab and alirocumab reduce major cardiovascular events when added to maximum tolerated doses of statins in people with diabetes

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