Cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus, and dyslipidemia is one of the most important modifiable cardiovascular risk factors in these patients. Dyslipidemia, characterized by increased concentration of small, dense low-density lipoproteins (LDL) as well as triglyceride (TG)-rich lipoproteins and accompanied by low levels of high-density lipoproteins (HDL), is common in patients with type 2 diabetes. Over the past two decades, lipid-lowering therapy with statins has revolutionized the management of cardiovascular risk in type 2 diabetes mellitus. Large, randomized placebo-controlled trials have shown that statins can reduce the risk for primary or secondary cardiovascular events by 20–40% in non-diabetic individuals. A similar degree of benefit can be seen when diabetic subjects are treated with statins. This has been confirmed by the results from recent analyses carried out by the Cholesterol Treatment Trialists Collaboration. The meta-analysis included 14 randomized trials of statin therapy with a total of 18,686 patients with diabetes. The analysis has shown that the significant proportionate benefits of statin therapy in reducing all-cause mortality, vascular mortality and cardiovascular events in subjects with diabetes is comparable to those seen in non-diabetic subjects.

Although statin therapy on top of lifestyle modification is the cornerstone of treatment of dyslipidemia in both diabetic and non-diabetic subjects, significant cardiovascular risk remains despite effective LDL cholesterol lowering treatment. Trial evidence has shown that the remaining risk for cardiovascular events can be as high as 60–80% in some statin-treated patients. Intensive lipid lowering with high-dose statin therapy further improves clinical outcomes compared with less intensive statin therapy, but there is still a significant residual risk, particularly in those with low HDL cholesterol and hypertriglyceridemia. Even if LDL cholesterol levels are <1.8 mmol/L, vascular risk remains up to 40% higher in subjects with low HDL cholesterol (<0.9 mmol/L) or elevated TG (TG > 2.3 mmol/L). Therefore, it has been suggested that development of new approaches to cardiovascular risk reduction should also target non-LDL parameters including HDL cholesterol and TG. Several outcome studies have been initiated in recent years to investigate the potential cardiovascular benefits of lowering TG and raising HDL with either fibrate or nicotinic acid (Table 1).

Fibrates are peroxisome proliferator-activated receptor-α agonists and are particularly effective in lowering plasma TG. On the whole, fibrates lower plasma TG by 20–50%, increase HDL cholesterol levels by 10–20% and favorably modify LDL particle size and density. Several randomized outcome trials with fibrates have been carried out. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study is the largest fibrate trial carried out to date, with nearly 10,000 subjects with type 2 diabetes randomized to micronised fenofibrate or placebo. The study failed to show overall treatment benefits. After a follow-up of 5 years, there was a non-significant reduction of the primary end-point of coronary heart disease death/non-fatal myocardial infarction by 11%. Fenofibrate treatment did significantly reduce the risk of total cardiovascular disease events including non-fatal myocardial infarction and coronary revascularizations. In the subgroup of patients with no previous cardiovascular disease, a relative risk reduction in total cardiovascular disease events of 19% was observed. The results of FIELD were partly confounded by non-study use of statins, which was disproportionately higher in the placebo group. A recent post-hoc analysis of the study has shown that the largest effect of fenofibrate to reduce cardiovascular risk was observed in subjects with marked dyslipidemia (TG ≥ 2.3 mmol/L and reduced HDL cholesterol) in whom a significant relative risk reduction of 27% was seen.

Fibrate monotherapy is less effective than statin monotherapy in reducing cardiovascular risk. However, the question remains whether or not the addition of fibrate can reduce the residual risk in statin-treated patients. The hypothesis has been tested in the lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the results have recently been released. A total of 5518 patients with type 2 diabetes at high cardiovascular risk treated with open label simvastatin were randomized to fenofibrate or placebo in a double-blind manner. At the end of the study, there was a mean 8.4% increase in HDL cholesterol and 22.2% reduction in TG in the fenofibrate group compared with a 6.0% increase in HDL cholesterol and 8.7% reduction in TG in the placebo group. Overall, the trial failed to show any significant reduction in the primary outcome and there was a trend towards an increased risk in women as compared with men. In a predefined subgroup analysis of patients with dyslipidemia (defined as TG ≥ 2.3 mmol/L and low HDL cholesterol ≤ 0.88 mmol/L), there was a trend towards benefit in those treated with fenofibrate. Adding fenofibrate to statin in this subgroup of patients resulted in a 31% reduction in events, with an absolute risk reduction of 4.9%. The results in this subgroup of diabetic patients with dyslipidemia are similar to those in post-hoc subgroup analyses from previous fibrate trials including FIELD.

Nicotinic acid is the most effective drug currently available to increase HDL cholesterol. Nicotinic acid increases HDL cholesterol by 15–35%, lowers plasma TG by 25–30% and...
LDL cholesterol by 15–20%. Nicotinic acid can also reduce lipoprotein(a) by up to 30%. Early long-term studies from the ‘pre-statin’ era have shown favorable effects of nicotinic acid on coronary heart disease events. More recent studies have investigated the effect of combination therapy of nicotinic acid with statin, and results from clinical trials studying surrogate end-points, such as carotid intima-media thickness, have become available. The recently published Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 – HDL and LDL Treatment Strategies trial (ARBITER 6 – HALTS) compared the effects of nicotinic acid versus ezetimibe in 363 patients already on statin therapy\(^2\). ARBITER 6 – HALTS used a higher dose of nicotinic acid (2000 mg/day) than the earlier ARBITER 2 trial. Hence, this trial in fact compared the strategy of raising HDL cholesterol and lowering LDL cholesterol with high-dose nicotinic acid versus lowering LDL cholesterol alone using ezetimibe in the background of statin therapy. The primary outcome showed significant regression in the nicotinic acid arm compared with the ezetimibe arm, suggesting that to achieve regression, it might be important to achieve optimal levels of both LDL cholesterol and HDL cholesterol. ARBITER 6 – HALTS has a number of limitations. The sample size was small and the fact that the study was terminated prematurely has raised concern. The final data analyzed were based on only a modest number of 208 patients, as the trial was terminated prematurely within 14 months. The use of a surrogate end-point cannot answer clinical questions regarding the role of nicotinic acid in preventing cardiovascular events in the current statin era. These important questions will hopefully be answered when two ongoing large-scale trials are completed. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) study has randomized 3300 patients to receive simvastatin or simvastatin and extended release nicotinic acid. The Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2 – THRIVE) investigates the addition of the preparation nicotinic acid/laropiprant to statin therapy and will enrol 25,000 patients. One-third of the participants being recruited will be patients with diabetes. Hence, the concern about nicotinic acid worsening glycemic control in patients with diabetes mellitus can also be addressed.

In summary, lowering LDL cholesterol remains the first priority in cardiovascular protection in patients with type 2 diabetes mellitus. The efficacy and safety of statin therapy in this respect has been proven by a large body of evidence, and statins remain the mainstay of lipid-lowering therapy for the treatment of diabetic dyslipidemia and prevention of cardiovascular disease. The ACCORD Lipid study has clearly shown that not all patients with type 2 diabetes benefit from dyslipidemia management beyond LDL cholesterol, and routine use of combination therapy with fenofibrate and statin is not justified. It seems that only patients with persistent atherogenic dyslipidemia characterized by elevated TG and low HDL cholesterol might benefit from combination therapy, and this approach is consistent with the recommendations of current guidelines. What the best second add-on agent is and the degree of benefit that can be derived

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Table 1 | Summary of recent major randomized lipid lowering trials

| Field\(^3\) | ACCORD Lipid\(^4\) | ARBITER 6 – HALTS\(^5\) |
|---|---|---|
| Drugs | Fenofibrate versus placebo | Fenofibrate/simvastatin versus placebo/simvastatin | Extended release nicotinic acid/statin versus ezetimibe/statin |
| Participants | 9795 type 2 diabetic subjects (78.2% without prior CVD, 21.8% with CVD) | 5518 type 2 diabetic subjects at high risk of CVD events | 363 patients with CHD or CHD risk equivalent (40% with diabetes) |
| Mean follow-up | 5 years | 4.7 years | Terminated prematurely after 14 months |
| Primary end-point | First occurrence of non-fatal MI or CHD death | First occurrence of non-fatal MI, non-fatal stroke or death from cardiovascular causes | Between group difference in the change in mean carotid IMT from baseline |
| Key results | No significant difference in primary outcome, hazard ratio 0.89 (95% CI 0.75–1.05) | No significant difference in primary outcome, hazard ratio 0.92 (95% CI 0.79–1.08) | Data based on 208 patients showed significant reduction in mean carotid IMT only in nicotinic acid group |

ACCORD Lipid, Action to Control Cardiovascular Risk in Diabetes Lipid study; ARBITER 6 – HALTS, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 – HDL and LDL Treatment Strategies trial; CHD, coronary heart disease; 95% CI, 95% confidence interval; CVD, cardiovascular disease; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes study; HDL, high density lipoprotein; IMT, intima-media thickness; MI, myocardial infarction; TG, triglyceride.
still needs to be determined. More evidence is expected over the next few years from large outcome studies that are currently in progress.

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