Management & prevention of type 2 diabetes

Fibrates to prevent CVD in diabetes: More trial evidence but still no ACCORD?

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The question of the best lipid-lowering agent to prevent cardiovascular (CV) disease in people with diabetes has long been the subject of debate. Prior to the statin trials, many considered fibrates to be the obvious choice for people with type 2 diabetes given their characteristic dyslipidaemia – higher triglyceride and lower HDL-cholesterol concentrations. Yet, statin trials led the way with overwhelming evidence of their CV benefit in diabetes (Heart Protection Study Collaborative Group, 2002; Colhoun et al, 2004). By contrast, well conducted fibrate trials in diabetes took longer to materialise, but remain important since, despite reaching LDL-cholesterol targets with statins, triglyceride and HDL-cholesterol commonly remain suboptimal in many people with type 2 diabetes, a pattern that continues to concern clinicians.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) lipid study (ACCORD Study Group et al, 2010; summarised alongside) randomised 5518 people with type 2 diabetes at elevated CV risk who were receiving open-label simvastatin to fenofibrate or placebo with follow-up for a mean of 4.7 years. Overall, the authors correctly concluded that their results do not support routine use of combination fenofibrate and simvastatin therapy in high-risk people with type 2 diabetes, thereby extending the conclusions from the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study (Keech et al, 2005).

So does ACCORD signal the end of fenofibrate use in diabetes? If not, should we take note of subgroup analyses and other potential microvascular benefits alluded to previously in the FIELD study? These are difficult questions to answer, in part because current data are by no means conclusive and there also remains a lingering concern about a potential adverse effect of fibrates to increase non-CV mortality. Indeed, a recent meta-analysis (Jun et al, 2010) on fibrates published just after ACCORD (and incorporating its data) showed a trend towards increased non-CV mortality with fibrate use at 10% (95% confidence interval [CI], –0.5 to 21; *P*=0.063). Interestingly, these latter data were given far less prominence than the determination of an overall 10% relative risk reduction (95% CI, 0–18) for major CV events (*P*=0.048) with fibrates, although the astute reader would note near identical confidence intervals for both endpoints and no overall benefit on all-cause mortality (0%; *P*=0.92) with fibrates.

The one area of fibrate benefit that does seem to deserve more study is their potential to lessen risk of some microvascular endpoints. In the FIELD study, fenofibrate therapy appeared to significantly lessen the need for laser treatment for retinopathy, whereas there was a reduction in both microalbuminuria and macroalbuminura in ACCORD.

In the meta-analysis by Jun et al (2010), which included data from these and a few other trials, overall fibrates were associated with a lowering of retinopathy and albuminura risk by 37% and 14%, respectively. These results look impressive but it is important to note the modest heterogeneity of data in the studies that generated these summary results, which suggests a need for further careful study (and more robust ascertainment of microvascular endpoints) before definitive conclusions are drawn.

In the meantime, most physicians will likely use fenofibrate only in a minority of people with diabetes with ongoing high triglyceride levels (for example, >10 mmol/L) despite statin therapy. Statins will continue to be the major lipid-lowering agent in people with diabetes, but the results of ongoing trials are eagerly awaited – including on agents that primarily raise HDL-cholesterol, for example the HPS2–THRIVE (Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events) study.

Colhoun HM, Betteridge DJ, Durrington PN et al (2004) *Lancet* **364**: 685–96

Heart Protection Study Collaborative Group (2002) *Lancet* **360**: 7–22

Jun M, Foote C, Lv J et al (2010) *Lancet* **375**: 1875–84

Keech A, Simes RJ, Barter P et al (2005) *Lancet* **366**: 1849–61

NEJM

Fenofibrate did not reduce rate of fatal CV events

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This article reports the outcomes of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) lipid study.

2 The authors investigated whether combined therapy with a statin plus fibrate would reduce cardiovascular risk more than statin therapy alone.

3 A total of 5518 people with T2D who were already receiving treatment with simvastatin were randomised to treatment with either fenofibrate or placebo.

4 The first occurrence of a major cardiovascular event, such as nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes was the primary outcome.

5 The primary outcome had an annual rate of 2.2% in the fenofibrate group and 2.4% in the placebo group (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.79–1.08; *P*=0.32).

6 The annual rate of death was 1.5% in the fenofibrate group and 1.6% in the placebo group (HR, 0.91; 95% CI, 0.75–1.10; *P*=0.33).

7 A possible benefit for men and possible harm for women (*P*=0.01 for interaction) was identified through prespecified subgroup analyses.

8 Subgroup analyses also revealed a possible benefit for people with both a high baseline triglyceride level and a low baseline level of HDL-cholesterol (*P*=0.057).

9 Treatment with fenofibrate and simvastatin combined did not reduce the rate of fatal cardiovascular events compared with simvastatin monotherapy.

ACCORD Study Group, Ginsberg HN, Elam MB et al (2010) Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* **362**: 1563–74

"Treatment with atorvastatin significantly increased fasting insulin and HbA_{1c} levels despite beneficial reductions in LDL-cholesterol and apoliprotein-B."

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Atorvastatin increases HbA_{1c} levels despite reduction in LDL

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 It has been suggested that some statin treatments might increase the risk of diabetes despite reductions in LDL-cholesterol and improvement in endothelial dysfunction.

2 This study investigated whether atorvastatin decreases insulin sensitivity and increases fasting insulin and HbA_{1c} levels in people with hypercholesterolaemia.

3 Participants were given placebo and then 10, 20, 40 and 80 mg daily doses of atorvastatin over the 2-month study period. The sample size for each dose, including placebo, was 44, 42, 44, 43 and 40, respectively.

4 At all doses atorvastatin significantly reduced LDL-cholesterol and apoliprotein-B levels compared with baseline ($P<0.001$).

5 Atorvastatin at 10, 20, 40, and 80 mg increased fasting plasma insulin significantly (mean changes 25%, 42%, 31% and 45%, respectively) and HbA_{1c} levels (2%, 5%, 5% and 5%, respectively) compared with baseline ($P<0.05$) or placebo ($P=0.009$ for insulin; $P=0.008$ for HbA_{1c}).

6 Insulin sensitivity was also decreased by atorvastatin treatment compared with baseline at doses of 10, 20, 40 and 80 mg ($P=0.312$, $P=0.008$, $P<0.001$ and $P=0.008$, respectively) and compared with placebo ($P=0.033$).

7 Treatment with atorvastatin significantly increased fasting insulin and HbA_{1c} levels despite beneficial reductions in LDL-cholesterol and apoliprotein-B.

Koh KK, Quon MJ, Han SH et al (2010) Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. *J Am Coll Cardiol* **55**: 1209–16

DIABETES

Decreased cancer risk associated with insulin use

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 It is unknown whether the use of insulin increases cancer risk, or whether it decreases cancer risk because it lowers blood glucose.

2 Matched cohort T2D pairs from the Hong Kong diabetes registry were analysed by stratified Cox regression to obtain hazard ratios (HRs) of insulin therapy and HbA_{1c} for cancer risk.

3 Out of a total of 973 insulin users, 971 had matched non-insulin users.

4 Non-insulin users had a higher incidence of cancer than insulin users (49.2 vs 10.2 per 1000 person-years; $P<0.0001$).

5 After adjustment for other significant covariates and non-linear associations with cancer, a higher HbA_{1c} was associated with an increased cancer risk (HR per percentage point, 1.26; 95% confidence interval, 1.03–1.5).

6 In Chinese adults with T2D, hyperglycaemia was associated with a higher risk of cancer and insulin use was associated with a lower risk.

Yang X, Ko GT, So WY et al (2010) Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. *Diabetes* **59**: 1254–60

BMJ

Specificity and sensitivity of HbA_{1c} for diagnosis

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The use of HbA_{1c} as a T2D diagnostic tool was assessed in this cross-sectional epidemiological survey of 4886 Chinese adults.

2 The area under the receiver operating characteristics curve for detecting undiagnosed diabetes was 0.856 for HbA_{1c} alone and 0.920 for fasting plasma glucose (FPG) alone.

3 High specificity (96.1%; 95% confidence interval, 95.5–96.7) was achieved at an HbA_{1c} threshold of 6.3% (45 mmol/mol).

4 Sensitivity of HbA_{1c} was 62.8%, which was equivalent to the sensitivity of a FPG threshold of 7.0 mmol/L (57.5%).

5 An HbA_{1c} level of 6.3% (45 mmol/mol) is highly specific for detecting undiagnosed diabetes in Chinese adults.

6 It was concluded that HbA_{1c} may be a suitable diagnostic test when FPG and oral glucose tolerance tests are not available.

Bao Y, Ma X, Li H et al (2010) Glycated haemoglobin A1c for diagnosing diabetes in Chinese population: cross sectional epidemiological survey. *BMJ* **340**:c2249

ANNALS OF INTERNAL MEDICINE

Salsalate for T2D?

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓✓✓

1 This parallel randomised trial compared the efficacy and safety of salsalate (a non-acetylated prodrug of salicylate) in different doses to treat T2D.

2 After a 4-week run-in period participants were randomly assigned to receive placebo or 3.0, 3.5 or 4.0 g salsalate daily for 14 weeks in addition to their current therapy.

3 More people in the three salsalate groups lowered their HbA_{1c} level by 0.5 percentage points from baseline compared with the placebo group ($P=0.009$).

4 Treatment with salsalate lowered HbA_{1c} in people with T2D. Renal and cardiac safety of the drug have yet to be assessed.

Goldfine AB, Fonseca V, Jablonski KA et al (2010) The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomized trial. *Ann Intern Med* **152**: 346–57