Is the use of cholesterol-lowering drugs for the prevention of cardiovascular complications in type 2 diabetics evidence-based? A systematic review

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CRD summary
The authors concluded that cholesterol-lowering drugs (statins and fibrates) did not significantly benefit patients with type 2 diabetes in terms of mortality and cardiovascular complications. Potential for bias in the review, a lack of patient details and contradictory findings compared to previous evidence mean the reliability of the conclusions is unclear.

Authors' objectives
To assess the effects of cholesterol-lowering drugs (statins and fibrates) on mortality and cardiovascular complications in patients with type 2 diabetes.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and DARE were searched for publications in English. Search terms were reported. Search dates were not reported. Reference lists of included studies, relevant reviews and published meta-analyses were screened.

Study selection
Eligible studies were prospective double-blind randomised controlled trials (RCTs) that compared a lipid-lowering drug (statin or fibrate) versus placebo in patients with type 2 diabetes. Outcomes of interest included coronary heart disease, non-fatal cardiovascular endpoints and mortality (overall and cardiovascular). Trials that were terminated early were excluded from the main synthesis.

Statin trials assessed atorvastatin (10mg or 20mg) and the fibrate trial assessed fenofibrate (200mg). One trial included patients with end stage renal disease receiving haemodialysis. Some trials reported composite endpoints (combining hard (fatal) events and weak events such as revascularisation).

Two reviewers performed the initial search and three reviewers independently screened studies for inclusion. Discrepancies were resolved through discussion with two other reviewers.

Assessment of study quality
Eligible trials had to be double blind. Two reviewers validated and classified endpoints by assessing for potential outcome reporting bias and clinical consistency of composite primary endpoints. No other details were provided.

Data extraction
Two reviewers extracted primary outcome data to calculate relative risk (RRs) and 95% confidence intervals (CIs). Primary authors were contacted for further details where necessary. Discrepancies were resolved through discussion.

Methods of synthesis
Due to clinical heterogeneity, data were presented as a narrative synthesis and in tables.

Results of the review
Two RCTs that used atorvastatin (3,665 patients) and one RCT that assessed fenofibrate (9,795 patients) were included in the main synthesis. Follow-up was approximately four to five years. A second RCT that assessed atorvastatin (2,838 patients) was discussed but this trial was terminated early and so was excluded from the main synthesis.

Two statin RCTs were reported to have credible validation and classification of the endpoints and a third eligible statin RCT had unclear validity.

The two RCTs that assessed atorvastatin showed no benefit from statins in patients with diabetes. The RCT that assessed atorvastatin in patients with diabetes and end stage renal disease showed a statistically significantly greater risk.
of fatal stroke with atorvastatin compared to placebo (RR 2.03, 95% CI 1.05 to 3.93).

The eligible trial that assessed fibrate also showed no benefit in terms of cardiovascular complications and overall mortality compared to placebo. The terminated trial was discussed in the review.

**Authors’ conclusions**
Cholesterol-lowering drugs (statins and fibrate) did not result in significant benefit on mortality and cardiovascular complications in patients with type 2 diabetes.

**CRD commentary**
The review question was clearly stated and supported by appropriate inclusion criteria. Various sources were searched for papers published in English but search dates were not reported so potentially relevant data may have been missed. Only RCTs were included in the review but their overall quality was unclear. The review process was performed in duplicate which reduced potential for reviewer error and bias.

Few trials were included but these included a large number of patients. Few patient details were reported but evidence of clinical heterogeneity meant the synthesis presented was appropriate.

The authors stated that the greatest limitation of the review was the inability to clarify the discrepancy between results from the RCTs included in their review and results of previous non-randomised studies and meta-analyses which reported benefits of cholesterol-lowering drugs in diabetics. Potential for bias in the review, a lack of patient details and contradictory findings compared to previous evidence mean the reliability of the findings is unclear.

**Implications of the review for practice and research**
**Practice:** The authors stated that health care professionals, especially those in charge of high risk patients, should be aware of the complex issues surrounding statins and take this into account when exercising their clinical judgement. The authors stated that guidelines on the use of cholesterol-lowering drugs in diabetic patients should be urgently revised.

**Research:** The authors stated that meta-analyses evaluating cholesterol-lowering drugs in diabetic patients should be carefully re-examined.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.