Meta-analysis of the effects of statin therapy on endothelial function in patients with diabetes mellitus

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CRD summary
The review concluded that statins significantly improved the flow-mediated dilatation only in patients with better endothelial functions. Flow-mediated dilatation in evaluating therapeutic outcomes should be used carefully in populations at high risk. The authors' lack of use of their study quality assessment results makes it difficult to evaluate the reliability of their conclusions.

Authors' objectives
To determine whether statin therapy could improve endothelial dysfunction in patients with diabetes mellitus.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were searched to August 2011; search terms were reported. Reference lists of retrieved studies and relevant articles were scanned.

Study selection
Randomised controlled trials (RCTs) that compared a statin with placebo in patients with diabetes mellitus were eligible for inclusion. Flow-mediated dilatation had to be reported both at baseline and at the end of treatment.

Most of the included studies recruited only patients with type 2 diabetes; some studies recruited only patients with type 1 diabetes. Mean ages ranged from 34 to 60 years. Mean body mass index (BMI) ranged from 25.5 to 31kg/m². Baseline flow-mediated dilatation values ranged from 1.7% to 5.3%. Atorvastatin was used in most trials (doses ranged from 10 to 80mg/day); cerivastatin and simvastatin were also studied. Treatment durations ranged from six to 104 weeks. Flow-mediated dilatation was measured using ultrasound in brachial arteries.

Two reviewers independently selected studies for inclusion. Disagreements were resolved through discussion.

Assessment of study quality
Two reviewers independently evaluated study quality by assessing the criteria for blinding, allocation concealment, quality of randomisation, generation of random numbers and reporting of withdrawals. Studies were awarded a point for each criterion addressed (maximum score of 5). Disagreements between reviewers were resolved through discussion.

Data extraction
Data were extracted in order to calculate change from baseline in flow-mediated dilatation with 95% confidence intervals (CI). Authors were contacted for missing data where necessary.

Two reviewers independently extracted data. Disagreements were resolved through discussion.

Methods of synthesis
Meta-analyses were performed to calculate pooled weighted mean differences using a random-effects model when heterogeneity (assessed using the $I^2$ statistic) was at least 50%. Publication bias was assessed using a funnel plot and Egger's test. Various subgroup and meta-regression analyses were planned (details presented in the paper).

Results of the review
Ten RCTs were included (845 participants, range 16 to 204). Quality scores ranged from 1 to 5 and most studies scored 2 or 3 out of 5. Six trials were described as being at low risk of bias (scoring ≥3 points) and four trials were judged to be at a high risk of bias. Nine studies were described as being double-blind; one study did not use blinding. Two studies were crossover trials.
Statin therapy significantly improved flow-mediated dilatation compared with placebo (WMD 0.94%, 95% CI 0.38% to 1.5%; I²=67%; 10 RCTs). No significant publication bias was detected.

Subgroup analysis showed that patients with a BMI more than 27.6 kg/m² did not benefit from statin therapy (four RCTs). Significant benefit was seen in patients with BMI of 27.6 kg/m² or less (five RCTs); no significant heterogeneity was seen. Further subgroup analysis results were reported.

Meta-regression analyses found that lower BMI, younger age, higher baseline high-density lipoprotein cholesterol and lower baseline systolic and diastolic blood pressure were all significantly associated with improvement in flow-mediated dilatation.

**Authors’ conclusions**

Statins significantly improved the flow-mediated dilatation only in patients with better endothelial functions. The use of flow-mediated dilatation in evaluating therapeutic outcomes should be careful in populations at high risk.

**CRD commentary**

The review addressed a clear question and was supported by reproducible eligibility criteria. Attempts to identify relevant studies were undertaken by searching electronic databases. It was unclear whether there were any language or publication restrictions so it was possible that studies were missed.

Suitable methods were employed to reduce the risks of reviewer error and bias throughout the review. Study quality was assessed but a basic scoring method was used with little detail presented about sources of bias in individual studies. The quality assessment results were not used when interpreting the results of the review.

Comprehensive study details were provided and appropriate methods were used to pool data and to assess and investigate heterogeneity. The authors’ conclusions appeared to be centred around the observation that certain risk factors (such as age and hypertension) were associated with endothelial function. However, it was unclear why the subgroup or meta-regression analyses did not also examine the effect of baseline flow-mediated dilatation (which the authors stated was widely used as a marker of endothelial function). This, coupled with the authors’ lack of use of their study quality assessment results, makes it difficult to evaluate the reliability of their conclusions.

**Implications of the review for practice and research**

**Practice:** The authors stated that their results provided further evidence that obesity, hypertension and dyslipidaemia should be tightly controlled in diabetes mellitus patients and that statin therapy should be started as early as possible before the onset of severe endothelial dysfunction occurs to achieve the greatest possible benefit.

**Research:** The authors did not state any implications for research.

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