Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials


CRD summary
The review concluded that statin therapy was associated with a slightly increased risk of development of diabetes, but the risk was low both in absolute terms and in relation to the reduction in coronary events. The authors' conclusions are likely to be reliable.

Authors' objectives
To establish whether any relation exists between statin use and the development of diabetes mellitus.

Searching
MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies published in English from 1994 to 2009; search terms were reported.

Study selection
Randomised placebo (or standard care) controlled statin trials in adults, with a mean follow-up of at least one year, which assessed cardiovascular outcomes, were eligible for inclusion.

Patients with diabetes, organ transplants, or those receiving haemodialysis were excluded. Trials of less than 1000 participants, or that used surrogate markers of cardiovascular disease, or compared different types or dose of statin, were also excluded. Included trials had to use identical follow-up methods for both treatment groups.

Atorvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin were studied, using various doses. Mean ages ranged from 55 to 76 years, and mean body mass index (BMI) ranged from 24 to 29 kg/m². Most included participants were at risk of, or had a history of, cardiovascular disease, although three trials were of participants without cardiovascular disease. A large majority of trials used placebo as a control. Diabetes diagnostic criteria varied.

Two reviewers independently selected studies for inclusion, with disagreements resolved by a third reviewer.

Assessment of study quality
The authors did not formally assess study quality.

Data extraction
Data were extracted by two reviewers independently, in order to calculate odds ratios (OR) and 95% confidence intervals (CI). Investigators were contacted to request unpublished data relating to incidence of diabetes. The authors reported details of the standard diabetes diagnostic criteria used.

Methods of synthesis
Meta-analysis of pooled odds ratios was performed using a random-effects model. Heterogeneity was assessed using the I² statistic and investigated using meta-regression (using pre-specified factors). Sensitivity analyses were used to investigate the effect of statin type, fasting glucose concentration, type of control, and the removal of individual trials. Publication bias was assessed using a funnel plot and Egger's test.

Results of the review
Thirteen trials (n=91,140 participants) were included in the review. Ten trials were double-blinded and three were open trials. Mean follow-up was around four years.

Statin therapy was associated with a slightly increased risk of development of diabetes (OR 1.09, 95% CI 1.02 to 1.17;
I²=11%). This translated as one additional case of diabetes per 255 patients taking a statin for four years. Funnel plots showed no indication of publication bias.

The association remained at a similar magnitude when the analysis was restricted to just the placebo-controlled trials. There was no evidence of a difference between individual statins, or group type (lipophilic versus hydrophilic statins) for risk of developing diabetes. The association between statin therapy and diabetes was stronger in trials with older participants (p=0.019), but baseline BMI, and percentage change in low-density lipoprotein-cholesterol concentration did not appear to be important factors.

Authors’ conclusions
Statin therapy was associated with a slightly increased risk of development of diabetes, but the risk was low both in absolute terms and in relation to the reduction in coronary events.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify relevant studies were undertaken by searching electronic databases, but the restriction to including only studies published in English raised the possibility that relevant studies may have been missed. However, the reviewers obtained much unpublished data by contacting authors. Suitable methods were employed to reduce the risks of reviewer error and bias for the processes of study selection and data extraction, but the authors did not assess trial quality (although most trials were large, and double-blinded). Sufficient trial details were provided. Appropriate meta-analytic techniques were used to pool the data.

The authors’ conclusions reflected the evidence presented, and appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change. They added that surveillance for dysglycaemia might be useful for older people receiving statin therapy, and that the potentially raised diabetes risk should be taken into account if statin therapy is considered for patients at low cardiovascular risk, or patient groups in which cardiovascular benefit has not been proven.

Research: The authors recommended that development of diabetes is specified as a secondary endpoint in future large endpoint statin trials, and suggested that, when possible, reports of long-term follow-up in existing trials should also include incident diabetes.

Funding
None.

Bibliographic details

PubMedID
20167359

DOI
10.1016/S0140-6736(09)61965-6

Original Paper URL
Database of Abstracts of Reviews of Effects (DARE)
Produced by the Centre for Reviews and Dissemination
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Other publications of related interest
Bhatia L, Byrne CD. There is a slight increase in incident diabetes risk with the use of statins, but benefits likely outweigh any adverse effects in those with moderate-to-high cardiovascular risk. Evid Based Med 2010; 15(3): 84-85

Indexing Status
Subject indexing assigned by NLM

MeSH
Age Distribution; Age Factors; Aged; Anticholesteremic Agents /adverse effects; Cardiovascular Diseases /drug therapy; Diabetes Mellitus, Type 2 /chemically induced /epidemiology; Female; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /adverse effects; Male; Middle Aged; Randomized Controlled Trials as Topic; Risk Factors; Treatment Outcome

AccessionNumber
12010001084

Date bibliographic record published
24/02/2010

Date abstract record published
03/03/2010

Record Status
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.