Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials

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CRD summary
This review aimed to determine the efficacy of lipid-lowering drug treatment in patients with and without diabetes mellitus, for primary and secondary prevention. The authors concluded that lipid-lowering treatment, especially statins, reduces cardiovascular risk in diabetic and non-diabetic patients in both primary and secondary prevention. This was a reasonably well-conducted review and the authors' conclusion is likely to be reliable.

Authors' objectives
To determine the efficacy of lipid-lowering drug treatment in patients with and without diabetes mellitus, for primary and secondary prevention.

Searching
MEDLINE (1966 to April 2004), EMBASE (1980 to April 2004) and the Cochrane CENTRAL Register (Issue 2, 2004) were searched for English language publications; the search terms were reported. The references of relevant articles and reviews were also checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. At least 500 patients per treatment arm and a minimum 3-year follow-up period were required.

Specific interventions included in the review
Studies that compared lipid-lowering or cholesterol treatment with placebo were eligible for inclusion. The included studies used a statin (lovastatin, pravastatin, atorvastatin or simvastatin) or gemfibrozil.

Participants included in the review
Individuals with type 2 diabetes and non-diabetic patients were eligible for inclusion, regardless of whether they had a history of coronary artery disease (CAD). In the included studies, the mean age of the participants ranged from 47 to 75 years, the proportion with diabetes ranged from 2 to 35%, and the proportion of women ranged from 0 to 52%.

Outcomes assessed in the review
The included studies were required to report objective cardiovascular events, either as primary or secondary end points. The outcomes had to be available for diabetic and non-diabetic subgroups. The primary outcome included a composite of major coronary events: CAD death, nonfatal myocardial infarction (MI), or revascularisation procedures. The secondary outcomes included CAD death or nonfatal MI, CAD death, nonfatal MI, revascularisation procedures, stroke and changes in blood lipid concentrations (total cholesterol, low- and high-density lipoprotein cholesterol, and triglycerides).

How were decisions on the relevance of primary studies made?
Two reviewers independently selected articles for inclusion in the review. Any disagreements were resolved by consensus.

Assessment of study quality
The inclusion criteria considered aspects of methodological quality: studies were required to have adequate concealment of random allocation and to be double-blinded (including clinical outcomes). In addition, studies were
rated for quality using the Jadad scale. Two reviewers independently assessed methodological quality. Any disagreements were resolved by consensus.

**Data extraction**
Two reviewers independently extracted the data from the primary studies. Any disagreements were resolved by consensus.

**Methods of synthesis**
How were the studies combined?
The studies were combined in a meta-analysis, using the Mantel-Hansel fixed-effect model if no significant heterogeneity was found, or the DerSimonian and Laird random-effects model if significant heterogeneity was shown. Pooled relative risk reductions, and their associated 95% confidence intervals (CIs), were calculated for all outcomes. The number-needed-to-treat and 95% CI were also calculated from meta-analysis estimates (adjusted odds ratio). Calculations took into account the baseline risk, which was defined as the percentage of patients with events in the control arm.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic and chi-squared test. Separate analyses were conducted for primary and secondary prevention, for diabetic and non-diabetic patients, and for statins and fibrates.

**Results of the review**
Twelve RCTs (n=80,862) were included. Six trials reported data on primary CAD prevention, while 8 trials reported data on secondary prevention.

Event rate.
Diabetic patients demonstrated a significantly higher risk of major coronary events compared with non-diabetic patients in both placebo and treatment groups in primary and secondary prevention trials.

Clinical outcomes.
In primary prevention trials, the relative risk reduction for a major coronary event was 21% in diabetic patients (relative risk, RR 0.79, 95% CI: 0.70, 0.89, P<0.0001) and 23% in non-diabetic patients (RR 0.77, 95% CI: 0.67, 0.88, P=0.0003) treated with either statins or gemfibrozil. Significant heterogeneity was shown in the primary prevention of a major coronary event for non-diabetic patients.

In secondary prevention trials, the relative risk reduction for a major coronary event was 21% in diabetic patients (RR 0.79, 95% CI: 0.69, 0.90, P=0.0005) and 23% in non-diabetic patients (RR 0.77, 95% CI: 0.74, 0.81, P<0.00001) treated with either statins or gemfibrozil. For other outcomes, the relative risk reduction in diabetic and non-diabetic patients was 22% versus 26% for CAD death or nonfatal MI, 30% versus 21% for CAD death, 39% versus 29% for nonfatal MI, 30% versus 23% for revascularisation processes, and 36% versus 22% for stroke. All outcomes showed a significant benefit of treatment over placebo in both groups. Significant heterogeneity was found in the secondary prevention of major coronary events and nonfatal MI in diabetic patients, and in the secondary prevention of CAD death and nonfatal MI in non-diabetic patients.

When the results were adjusted to account for baseline risk, diabetic patients were shown to benefit significantly more than non-diabetic patients in the secondary prevention of CAD death, nonfatal MI, revascularisation and stroke. No statistically significant difference was shown between the diabetic and non-diabetic groups for the primary prevention of major coronary events after adjusting for baseline risk.

Lipids. The change in blood lipids was similar in diabetic and non-diabetic groups, with most trials showing a 15 to 20% decrease in total cholesterol and increases of 5 to 7.5% in high-density lipoprotein cholesterol in treated groups compared with placebo.
**Authors' conclusions**
Lipid-lowering treatment, especially statins, significantly reduces cardiovascular risk in diabetic and non-diabetic patients. However, the results suggest that the greatest benefit is shown for diabetic patients in both primary and secondary prevention.

**CRD commentary**
The review addressed a clear research question and contained explicit inclusion criteria for the participants, intervention, outcomes and study design. Several electronic databases were searched, although studies were limited to those published in English and no efforts were made to identify unpublished studies. Publication bias was not explored and, therefore, cannot be ruled out. Appropriate review methodology was employed to minimise reviewer error or bias. The methodological quality of the primary studies was formally assessed and the inclusion criteria required that studies demonstrated adequate concealment of randomisation and blinding.

Heterogeneity was explored, and the method of study synthesis appeared appropriate. Further differences between the studies were also examined using subgroup analysis. The authors acknowledged several limitations to their study, including the use of composite scores for coronary events and stroke in 3 trials and the use of one trial without a true placebo comparison arm. Despite these limitations, the authors' conclusions appear to be an accurate reflection of the evidence presented.

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

**Practice:** The authors stated that the results of the review support the use of statins for primary and secondary prevention in patients with diabetes mellitus.

**Research:** The authors stated that future research should define the threshold for treatment of diabetic patients and target lipid concentrations, especially in primary prevention.

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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.