Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials

CRD summary
This well-conducted review reliably concluded that fibrate lipid-lowering therapy substantially reduces coronary heart disease events in patients with type 2 diabetes mellitus.

Authors' objectives
To evaluate the cardiovascular effects of lipid-lowering treatment with fibrates in patients with type 2 diabetes mellitus.

Searching
MEDLINE (inception to November 2005) and the Cochrane CENTRAL Register (Issue 3, 2005) were searched; the search terms were not reported. In addition, reference lists, reviews, conference abstracts and specialist journals were searched for further studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing fibrate lipid-lowering therapy with placebo were eligible for inclusion. The included studies assessed clofibrate, gemfibrozil, clofibric acid, bezafibrate and fenofibrate.

Participants included in the review
Studies of patients with type 2 diabetes mellitus were eligible for inclusion. Both patients with known coronary heart disease (CHD; secondary prevention) and no known pre-existing CHD (primary prevention) were included in the review. Where stated, the proportion of females ranged from 0 to 60%, mean age ranged from 46 to 65 years, and the proportion of current smokers ranged from 9 to 34%.

Outcomes assessed in the review
Studies that prospectively recorded cardiovascular events and included a follow-up of at least 2 years were eligible for inclusion. The primary outcome measure was the incidence of CHD events, defined as a combination of nonfatal myocardial infarction (MI) or death due to CHD. The secondary end points included death due to CHD (e.g. fatal MI, congestive heart failure or sudden death), fatal and nonfatal MI, and fatal and non fatal stroke. Outcome data had to be reported separately for patients with type 2 diabetes mellitus. The duration of follow-up ranged from 2 to 6 years.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion. Any discrepancies were resolved through discussion with a third reviewer.

Assessment of study quality
Two reviewers independently assessed the adequacy of allocation concealment, the blinding of care providers and those evaluating outcome data, and the use of intention-to-treat data. Any disagreements were resolved through discussion with a third reviewer.

Data extraction
Two reviewers independently extracted the data. Any discrepancies were resolved through discussion with a third reviewer. Study authors were contacted for additional data on patients with type 2 diabetes mellitus if required. Incidence rate ratios (IRR)s with 95% confidence intervals (CIs) were calculated for each study.
Methods of synthesis
How were the studies combined?
Pooled IRRs with 95% CIs were calculated using a fixed-effect model. Sensitivity analyses were also carried out using a random-effects model. Funnel plots were used to assess publication bias. The number-needed-to-treat was calculated by applying the pooled IRRs to incidence rates typical for placebo groups.

How were differences between studies investigated?
The I-squared statistic was used to assess statistical heterogeneity. Subgroup analyses were performed for primary CHD prevention and secondary CHD prevention. The effects of the following variables were explored using a univariate meta-regression model: mean age at baseline; duration of diabetes; body mass index; proportion of smokers; proportion of women; mean total cholesterol at baseline; mean low-density lipoprotein cholesterol at baseline and study follow-up; mean high-density lipoprotein cholesterol at baseline and study follow-up; mean triglyceride level at baseline and study follow-up; and parameters of methodological quality. Analyses were repeated after the exclusion of trials that included additional lipid-modifying treatments.

Results of the review
Eight RCTs (n=12,249) were included.

All trials were of high methodological quality: all used adequate allocation concealment and all but one used intention-to-treat data.

In comparison with placebo, fibrate treatment was associated with a significant reduction in CHD events (IRR 0.84, 95% CI: 0.74, 0.96; 8 studies). It was also associated with non significant reductions in deaths due to CHD (IRR 0.96, 95% CI: 0.77, 1.20; 7 studies), myocardial infarction (IRR 0.88, 95% CI: 0.69, 1.12; studies) and stroke (IRR 0.87, 95% CI: 0.73, 1.05; 5 studies). There was no evidence of heterogeneity for any of these analyses: I-squared was 0% in three and 23.5% in the other.

Similar results were reported for random-effects analyses and for subgroup analyses according to primary or secondary prevention. Meta-regression analyses suggested a positive association between the lowering of triglyceride levels and the reduction in CHD events (p=0.036). There was no or very little evidence to suggest an association between CHD events and the other variables tested. Larger benefits were reported when the analysis was restricted to trials that were not confounded by unequal provision of additional lipid-lowering therapy (2 trials were excluded).

The funnel plots suggested there was no risk of publication bias.

Authors' conclusions
Fibrate treatment reduced CHD events in patients with type 2 diabetes mellitus, with larger benefits associated with trials not confounded by the unequal provision of additional lipid-lowering therapy.

CRD commentary
This well-conducted review answered a clearly described research question using adequate review methods to prevent publication and language bias and reviewer error and bias. Sources of heterogeneity were investigated and considered in the analysis, as was the quality of the trials. Overall, the conclusions of the review are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies are required to better define the role of fibrate therapy in type 2 diabetes mellitus. They suggested that perhaps an individual patient data analysis of existing trials would be useful in this context.

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