Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: a pooled meta-analysis of randomized placebo-controlled clinical trials

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CRD summary
This review found that the long-term use of fibrates was associated with a significant reduction in the risk of non-fatal myocardial infarction in patients with type II diabetes mellitus but that there was no significant effect on mortality or other adverse cardiovascular outcomes. Some methodological flaws mean that the reliability of the authors’ conclusions is unclear.

Authors’ objectives
To evaluate the effectiveness of fibrates for the prevention of cardiovascular events in patients with type II diabetes mellitus.

Searching
MEDLINE and the Cochrane Library were searched for relevant published studies in English language to December 2007; search terms were reported. Reference lists of the retrieved trials and relevant reviews were checked to identify additional studies.

Study selection
Randomised placebo-controlled trials that evaluated the use of fibrates for the prevention of cardiovascular events in patients with type II diabetes mellitus were eligible for inclusion. Eligible trials had to have more than 50 patients in each trial arm and have a mean duration of at least one year. Additional inclusion criteria were that clinical endpoints were pre-defined and reported for the enrolled patients. Trials that used clofibrate as the study intervention were excluded because of the lack of clinical relevance, the withdrawal of clofibrate from the market, and differences in trial design and patient characteristics.

The populations in the included trials comprised patients both with and without previous histories of cardiovascular disease and myocardial infarction. The mean age of patients in included trials ranged from 47 to 64 years; the proportion of men ranged from 63 to 100% of the enrolled population. The fibrate medications given in the trials were gemfibrozil (1200mg/day), bezafibrate (400mg/day) and fenofibrate (200mg/day). The endpoints evaluated were all-cause mortality, cardiac mortality, fatal and non-fatal myocardial infarction, stroke, unstable angina, requirements for invasive coronary revascularisation, risk of cancer, and cancer-related death.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed using the Delphi list which was used to assess the suitability of the trials for inclusion in the meta-analysis.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted independently by both authors using standardised protocols to calculate relative risks (RR) and 95% confidence intervals (CI) for the outcomes. Corresponding authors were contacted to obtain missing clinical event data. The authors stated that results were all analysed using intention-to-treat analyses. Any disagreements between the reviewers were resolved by discussion.

Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated using a Mantel-Haenszel fixed-effects model. Statistical heterogeneity was assessed using the $\chi^2$ and $I^2$ tests. If heterogeneity was observed across the trials for the outcomes, the results were pooled using a DerSimonian and Laird random-effects model.
Results of the review
Six trials were included in the review (20,079 patients, sample sizes ranged from 164 to 9,795); 11,590 patients had type II diabetes mellitus (range across trials from 138 to 9,795). Three trials enrolled only patients with type II diabetes mellitus; in the remaining three trials, only small numbers of patients had type II diabetes. Follow-up in the trials ranged between three and 6.2 years.

There was a 21% statistically significant reduction in the risk of non-fatal myocardial infarction observed with the use of fibrates (RR 0.79, 95% CI 0.67 to 0.93; four RCTs). There was also a statistically non significant trend observed in decrease in the risk of stroke (RR 0.88, 95% CI 0.73 to 1.05; four RCTs).

The risk of unstable angina was found to be slightly higher for the patients who received fibrates, but the increase in risk was not statistically significant (RR 1.16, 95% CI 0.98 to 1.37; four RCTs).

There were no statistically significant differences observed with the use of fibrates compared with placebo for the risks of all-cause mortality (four RCTs), cardiac mortality (five RCTs), fatal myocardial infarction (three RCTs), cancer (four RCTs) or cancer-related death (three RCTs). There was also no difference observed in the risk of invasive coronary revascularisation (two RCTs).

Moderate heterogeneity was observed across the trials for all-cause mortality ($I^2=55.9\%$), cardiac mortality ($I^2=57.7\%$), fatal myocardial infarction ($I^2=45.3\%$). Significant heterogeneity was found the risk of invasive coronary revascularisation ($I^2=82.6\%$).

All the trials reported reductions in total cholesterol levels (4 to 10%) and triglyceride levels (21 to 36%).

Authors’ conclusions
The long-term use of fibrates in patients with type II diabetes mellitus was associated with significant reductions in the risk of non-fatal myocardial infarction, but there was no significant effect on mortality or other adverse cardiovascular outcomes.

CRD commentary
The review addressed a clear question and the criteria for the inclusion of studies were stipulated. The review was restricted to published studies, so there was some risk of publication bias. The restriction of the review to studies published only in English language meant that there was also a risk of language bias. Steps were taken by the reviewers to minimise errors and bias for data extraction, but were not reported for study selection or methodological quality assessment.

There was no reporting of the quality assessment, apart from the reporting on the use of intention-to-treat analyses. There was no indication of numbers of patients lost to follow-up. The quality assessment was also used to determine the suitability of the trials for inclusion in the meta-analysis. This meant that it was unclear whether the authors’ decision to pool the results of the trials in a meta-analysis was justified.

Although the authors’ conclusions were based on the evidence presented, some methodological flaws, particularly the lack of information about the quality of the included trials, mean that the reliability of the authors’ conclusions is unclear.

Implications of the review for practice and research
**Practice:** The authors stated that, although statins should be considered to be first-line antidyslipidemic agents in patients with diabetes mellitus, fibrates may be useful adjunctive agents for the prevention of non-fatal myocardial infarction in patients with high triglyceride and low HDL-cholesterol levels. Fibrates may also be useful in patients with isolated hypertriglyceridaemia and may be useful in patients with statin resistance who have not achieved target lipid levels or for those who experience adverse events with statins.

**Research:** The authors stated that further trials to evaluate other lipid lowering agents would need to evaluate the efficacy of these agents in patients with type II diabetes mellitus against a background of statin use.

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