Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis


CRD summary
This well-conducted review concluded that fibrates can reduce the risk of major cardiovascular events, predominantly through a reduction in coronary events, and may have a role in people at high risk of cardiovascular events and those with combined dyslipidaemia. This conclusion is likely to be reliable.

Authors' objectives
To investigate the effect of fibrates on major cardiovascular outcomes.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched without language restrictions from 1950 to March 2010. Search terms were reported. References of identified studies and reviews were checked. ClinicalTrials.gov was searched.

Study selection
Randomised controlled trials (RCTs) with at least 100 patient years of follow-up and that compared a fibrate with placebo were eligible for inclusion. Trials were required to report one of the following outcomes: major cardiovascular events (including myocardial infarction and stroke); coronary events (myocardial infarction and coronary death); coronary revascularisation; stroke; heart failure; cardiovascular death; non-vascular death; all-cause death; sudden death; new onset albuminuria; and drug-related adverse events. Trials that used fibrates in combination with other drug classes were excluded from the review.

All included studies were multicentre and were conducted in USA, Canada and countries in Europe, Central America and Oceania. Fibrates assessed were clofibrate, bezafibrate, fenofibrate, gemfibrozil and etofibrate. Mean age of participants in trials ranged from 46 to 68 years. Some studies enrolled only men, only patients with diabetes or only patients meeting specific lipid profile criteria. Most studies had the goal of secondary prevention, a smaller number were for primary prevention and the remainder enrolled a mixed population in respect of cardiovascular disease history.

Two reviewers independently assessed the studies for inclusion in the review.

Assessment of study quality
Two reviewers independently assessed validity of studies using the criteria of randomisation, allocation concealment, baseline comparability of groups, reporting of inclusion criteria, completeness of follow-up and use of an intention-to-treat analysis. Studies were scored using the five-point Jadad scale. Differences were resolved through adjudication by a third reviewer.

Data extraction
Two reviewers independently extracted data on event numbers to permit calculation of relative risks (RR) with 95% confidence intervals (CI). Intention-to-treat data were used in each case. Discrepancies were resolved through adjudication by a third reviewer.

Methods of synthesis
Random-effects meta-analyses were used to calculate a pooled relative risk with 95% CI for each outcome. Statistical heterogeneity between studies was assessed using the I² study. Publication bias was assessed using the Egger test and use of Begg funnel plots with trim-and-fill adjustments where this was apparent. Univariate meta-regression was used to explore potential sources of heterogeneity between studies. Cumulative meta-analysis was performed to identify trends in the effect of fibrates over time. A sensitivity analysis was used to examine the impact of an outlier on the pooled estimate.
Results of the review
Eighteen RCTs (n=45,058) were included in the review. Totals of 2,870 major cardiovascular events, 4,552 coronary events and 3,880 deaths were reported. Sample sizes ranged from 81 to 10,627. Trial quality was variable and poor reporting of criteria was widespread; this was particularly the case for randomisation, allocation concealment and use of intention-to-treat analysis. Completion rates ranged from 19% to 100%. Eight trials had a Jadad score of 4, five scored 2 points, four scored 1 and one trial scored 0.

There was a statistically significant reduction in risk of cardiovascular events (RR 0.90, 95% CI 0.82 to 1.00; five RCTs), coronary events (RR 0.87, 95% CI 0.81 to 0.93; 16 RCTs), non-fatal coronary events (RR 0.81, 95% CI 0.75 to 0.89; 10 RCTs) and coronary revascularisation (RR 0.88, 95% CI 0.78 to 0.98; four RCTs) in groups treated with fibrates with no significant statistical heterogeneity. There were also benefits in reduced progression of albuminuria (RR 0.86, 95% CI 0.75 to 0.98; three RCTs) and retinopathy (RR 0.63, 95% CI 0.49 to 0.81; two RCTs).

No statistically significant differences between groups were found for the following outcomes: stroke; all-cause mortality; cardiovascular death; sudden death; non-vascular death; and serious drug-related adverse events. There were statistically significant increases in serum creatinine concentrations in fibrate groups (RR 1.99, 95% CI 1.46 to 2.70), but no other statistically significant differences in adverse events were found.

Results of subgroup and sensitivity analyses were reported. These included the finding that there was a stronger effect of therapy (p=0.03) in trials with a higher mean baseline triglyceride concentration. There was some evidence of publication bias for the outcome of coronary events, but not for major cardiovascular outcomes.

Authors’ conclusions
Fibrates can reduce the risk of major cardiovascular events, predominantly through a reduction in coronary events, and may have a role in people at high risk of cardiovascular events and in those with combined dyslipidaemia.

CRD commentary
The review question and the inclusion criteria were clear. The authors searched three relevant databases and additional sources; the lack of language or publication status restrictions reduced the chance of relevant studies being omitted and bias being introduced. Publication bias was assessed and some evidence of it was seen. The authors reported using methods designed to reduce reviewer bias and error in all stages of the review process. Appropriate criteria were used to assess study validity. The decision to use meta-analyses was appropriate. Reasonable measures were used to assess and explore heterogeneity between studies. The authors’ conclusions reflected the results of the review and appear likely to be reliable, although the poor quality of many of the included studies should be borne in mind.

Implications of the review for practice and research
**Practice**: The authors stated that a therapeutic approach that involved assessment of baseline absolute risk before treatment would produce net benefits in reduced cardiovascular events.

**Research**: The authors stated that there remained a need for a meta-analysis of fibrate use for prevention of cardiovascular outcomes using individual patient data. They also stated that the relative benefits of a broad based approach to treatment compared with a targeted approach should be a priority for research.

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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.