Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis
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CRD summary
The review concluded that fibrate therapy, directed at markers of atherogenic dyslipidemia, reduced the risk of subsequent vascular events. Given the uncertain study quality and that results were based on data taken from subgroups that were not the basis of the pre-specified trial hypothesis, the authors’ conclusion should be treated with caution.

Authors' objectives
To determine the efficacy of fibrate therapy on vascular risk reduction in individuals with atherogenic dyslipidemia.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, World Health Organisation international trials registry and the Internet Stroke Center stroke trials registry were searched from 1966 to April 2010 without language restriction. Search terms were reported. Key sections of retrieved trials and previous meta-analyses were also checked for relevant studies.

Study selection
Eligible randomised controlled trials (RCTs) compared fibrates with placebo in people with triglyceride levels above 200mg/dl (milligrams per decilitre) and/or high-density lipoprotein cholesterol. Treatment periods were at least a six months. Trials were required to report incidence of cardiovascular disease or coronary heart disease events for the intervention and control groups separately. Trials were excluded if they had cohorts of less than 100, compared fibrates with statin or niacin, or were trials in which one group received an additional treatment.

Included trials assessed the effect of mono-therapies (gemfibrozil, fenofibrate or bezafibrate versus placebo) and a combination therapy (fenofibrate plus simvastatin versus simvastatin). Populations included individuals with pre-existing diabetes mellitus, coronary heart disease, dyslipidemia, high-density lipoprotein and non high-density lipoprotein. Trials of both primary and secondary prevention were included. High-density lipoprotein-cholesterol and triglyceride cut-points varied across trials. Half the trials reported cardiovascular endpoints while the rest reported coronary heart disease risk.

The authors did not state how many reviewers were involved in the selection of trials for inclusion in the review.

Assessment of study quality
The authors did not state if they formally assessed the methodological quality of the included trials.

Data extraction
Two reviewers independently extracted data according to a standard protocol and any disagreements were resolved by a third reviewer. Data were extracted on an intention-to-treat basis to allow for the calculation of relative risk (RR) and 95% confidence intervals (CIs) by atherogenic dyslipidemia group. Publication bias was assessed by visual examination of the funnel plots.

Methods of synthesis
Summary relative risks and 95% confidence intervals were estimated using a random-effects model. Heterogeneity was assessed using X² and I². When cardiovascular disease endpoints were not available, coronary heart disease events were used. Sensitivity analyses were also conducted using a fixed-effect model. The removal of individual trials from the analyses was performed to assess the influence of individual trials on the overall treatment effect. Subgroup analyses were performed according to baseline vascular risk condition, primary versus secondary prevention, treatment regimen, mono- versus combination therapy and analysis endpoint.

Results of the review
Six RCTs were included in the review (25,410 participants, range 395 to 9,795). Study duration ranged from 2.7 to 6.3 years.

Compared with placebo, fibrate therapy reduced the risk of vascular events in patients with high triglycerides (RR 0.75, 95% CI 0.65 to 0.86; I²=24%, five studies), low high-density lipoprotein cholesterol (RR 0.84, 95% CI 0.77 to 0.91; I²=7%, six studies), and high triglycerides and low high-density lipoprotein (RR 0.71, 95% CI 0.62 to 0.82; I²=13%, five studies). No between group difference was found in patients with neither high triglycerides, nor low high-density lipoprotein cholesterol. Results did not significantly differ when using a fixed-effect model or when individual trials were excluded.

Fibrate therapy was found to reduce vascular risk in patients with high serum triglycerides and/or low high-density lipoprotein cholesterol in all subgroups across a range of different conditions. This did not reach statistical significance in all conditions (full details were reported in the paper).

Evidence of some publication bias was observed in the funnel plots for patients with high triglycerides and high triglycerides and low high-density lipoprotein cholesterol.

**Authors’ conclusions**
Fibrate therapy directed at markers of atherogenic dyslipidemia reduced the risk of subsequent vascular events.

**CRD commentary**
The review question was supported by clearly defined inclusion criteria. Several electronic databases were searched unrestricted by language and attempts were made to locate unpublished trials. Evidence of potential publication bias was reported, but assessment may not be reliable due to the small number of trials included in the analysis. Appropriate steps were taken to minimise the risk of error and bias in the selection of trials and the data extraction. The authors did not say how they selected trials and the possibility of bias introduced at this stage could not be ruled out. The quality of the included trials was not formally assessed so the reliability of the pooled estimates was not clear.

Trials were pooled using appropriate methods. Heterogeneity was assessed and pre-specified subgroup analysis performed. The authors highlighted a number of possible limitations such as the data was taken from subgroups in RCTs that were not the basis of the pre-specified trial hypothesis. Overall, the authors’ conclusion should be treated with caution.

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