



REVIEW ARTICLE

## Analysis of the Cochrane Review: Fibrates for secondary prevention of cardiovascular disease and stroke<sup>☆</sup>



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### KEYWORDS

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Systematic review

**Abstract** The influence of fibrates on cardiovascular risk has been the focus of several clinical trials. This Cochrane Collaboration Systematic Review evaluated the efficacy of fibrates for secondary prevention of cardiovascular events and stroke, analyzing 13 randomized controlled trials, in a total of 16 112 participants with a history of cardiovascular disease. Fibrates showed a protective effect for the composite outcome of non-fatal stroke, non-fatal myocardial infarction (MI) and vascular death, mainly due to reduction in the risk of non-fatal or fatal MI. Nonetheless, these results largely relied on studies including clofibrate, a drug withdrawn from the market in 2002. No statistically significant differences regarding adverse events were found between fibrates and placebo. Although insufficient to support the routine prescription of fibrates in this setting, this evidence should be taken into account when deciding on lipid-modifying therapy in dyslipidemic patients with a history of cardiovascular disease.

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**PALAVRAS-CHAVE**

Fibratos;  
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**Análise da Revisão Cochrane: fibratos na prevenção secundária de doença cardiovascular e acidente vascular cerebral**

**Resumo** A influência dos fibratos no risco cardiovascular tem sido o foco de vários ensaios clínicos. Esta revisão sistemática da *Cochrane Collaboration* avaliou o efeito dos fibratos na prevenção secundária de eventos cardiovasculares e acidente vascular cerebral, incluindo 13 ensaios clínicos aleatorizados, num total de 16 112 participantes com antecedentes de doença cardiovascular. A terapêutica com fibratos demonstrou um efeito protetor no *outcome* composto acidente vascular isquémico não fatal, enfarte agudo do miocárdio não fatal e morte de causa vascular, especialmente devido à redução do risco de enfarte agudo do miocárdio fatal e não fatal. No entanto, estes resultados baseiam-se em grande parte em estudos que incluem o clofibrato, fármaco retirado do mercado em 2002. Não foram encontradas diferenças estatisticamente significativas relativamente a efeitos adversos entre fibratos e placebo. Embora insuficientes para sustentar uma prescrição rotineira de fibratos neste contexto, estes dados devem ser tidos em conta aquando da decisão terapêutica em doentes dislipidémicos com antecedentes de doença cardiovascular.

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**Clinical question**

What is the efficacy of fibrates for secondary prevention of cardiovascular events and stroke?

**Objectives**

To assess the efficacy of fibrates for the prevention of serious vascular events including myocardial infarction (MI), stroke, and vascular death in individuals with previous cardiovascular disease (CVD).<sup>1</sup>

**Methods**

A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted, in which the incidence of cardiovascular events in patients at high recurrent risk for cardiovascular events and stroke (due to previous history of CVD) was compared in individuals treated with a fibrate, and controls (placebo or no treatment).

The bibliographic search (last search in October 2014) was performed on six electronic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE, registries of ongoing trials and databases of conference abstracts.

The authors included RCTs comparing fibrate therapy with placebo or no treatment, regardless of the duration of treatment and follow-up. The primary outcome was a composite outcome of non-fatal stroke, non-fatal MI and vascular death. Secondary outcomes included the separate outcomes of stroke, MI, vascular death and death from all causes, and adverse events. Risk ratios (RR) with 95% confidence intervals (CI) were the measure of effect used. The analysis was performed on an intention-to-treat basis; meta-analysis was performed with fixed and random effect models depending on heterogeneity ( $I^2$  cut-off of 50%), and

subgroup analyses were conducted for age, gender and type of fibrate used. Additionally, a sensitivity analysis was performed based on the trials' risk of bias and concomitant use of statins.

**Results**

Thirteen trials met the inclusion criteria, with a total of 16 112 participants. Six trials included only male participants. Two recruited patients with a history of cerebrovascular disease, one recruited patients with cardiovascular disease (coronary heart disease or stroke), nine recruited patients with coronary heart disease and one recruited patients with lower peripheral arterial disease and controlled angina. Clofibrate was used in five trials, bezafibrate in three, fenofibrate in two and gemfibrozil in three. Two trials used statins in both the intervention and the control group. Only one of the trials included a no-treatment arm, the others using placebo as the comparator. The minimum treatment duration was 12 months and the maximum was eight years. Risk of bias was classified as 'low' in trials with appropriate sequence generation and blinded outcome assessment classified as low risk, and as 'high' in trials in which the same parameters were classified as high or unclear risk. Six trials were classified as 'low risk of bias' and seven as 'high risk'.

Concerning the primary composite outcome (of non-fatal stroke, non-fatal MI and vascular death), a protective effect of fibrates was found using a fixed-effect meta-analysis model (risk ratio 0.88, 95% CI 0.83-0.94,  $I^2$  45%) (Table 1). However, a random-effects model when excluding trials on clofibrate (which was withdrawn from the market in 2002 due to safety concerns) failed to show effectiveness in preventing this composite outcome (RR 0.90, 95% CI 0.79-1.03;  $I^2$  50%) (Table 1). Nevertheless, when analyzing the outcome of MI separately, the fixed-effect model showed a significant

**Table 1** Summary of findings for the main comparison and most important secondary outcomes.

Fibrates compared to control for secondary prevention of cardiovascular disease and stroke						
Patient or population: patients with previous cardiovascular disease, transient ischemic attack, or stroke						
Setting: secondary prevention						
Intervention: fibrates						
Comparison: control						
Outcomes	Anticipated absolute effects <sup>a</sup> (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	I <sup>2</sup>
	Risk with control	Risk with fibrates				
Composite outcome of non-fatal stroke, non-fatal MI, and vascular death (primary outcome)	Study population 233 per 1000	205 per 1000 (194-219)	RR 0.88 (0.83-0.94)	16 064 (12 RCTs)	⊕⊕⊕○ Moderate	45%
Composite outcome of non-fatal stroke, non-fatal stroke, non-fatal myocardial infarction, and vascular death without clofibrate	Study population 204 per 1000	183 per 1000 (161-210)	RR 0.90 (0.79-1.03)	10 320 (7 RCTs)	⊕⊕○○ Low	50%
Myocardial infarction (non-fatal or fatal) during the treatment and scheduled follow-up period	Study population 190 per 1000	163 per 1000 (152-177)	RR 0.86 (0.80-0.93)	13 942 (10 RCTs)	⊕⊕⊕○ Moderate	24%
Death from any cause during the treatment and scheduled follow-up period	Study population 185 per 1000	182 per 1000 (169-196)	RR 0.98 (0.91-1.06)	13 653 (10 RCTs)	⊕⊕○○ Low	23%
Stroke (ischemic or hemorrhagic, non-fatal or fatal) during the treatment and scheduled follow-up period	Study population 83 per 1000	86 per 1000 (76-96)	RR 1.03 (0.91-1.16)	11 719 (6 RCTs)	⊕⊕○○ Low	11%

CI: confidence interval; MI: myocardial infarction; RR: risk ratio.

GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Quality of evidence: more than 75% of included studies did not report details of randomization, and four trials withdrawn or lost to follow-up less than 20%.

<sup>a</sup> The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

risk reduction (RR 0.86, 95% CI 0.80-0.93,  $I^2$  24%) (Table 1) that remained even after the exclusion of clofibrate trials (RR 0.85, 95% CI 0.76-0.94;  $I^2$  47%). Regarding adverse events, two studies reported the risk of myopathy and six studies the risk of gastrointestinal (GI) events; when pooling data regarding these adverse events, there were no statistically significant differences between the fibrate and placebo groups (RR for myopathy 0.86, 95% CI 0.31-2.35,  $I^2$  0%; RR for GI events 1.02, 95% CI 1.00-1.04,  $I^2$  42%).

In subgroup analysis, there was no difference in the protective effect of fibrates for the primary outcome based on age (older vs. younger than 65 years) or gender. However, in subgroup analysis for the type of fibrate (clofibrate, bezafibrate and gemfibrozil), only clofibrate had a significant beneficial effect on the primary outcome (RR 0.86, 95% CI 0.74-1.00,  $I^2$  51%).

In sensitivity analysis, only one study compared the addition of fibrate therapy (fenofibrate) to simvastatin and simvastatin therapy alone, and revealed no difference between arms in the primary composite outcome (RR 0.9, 95% CI 0.74-1.09). It is noteworthy that sensitivity analysis including only trials classified as 'low risk' of bias showed evidence of a significant preventive effect of fibrates on the primary outcome (RR 0.85, 95% CI 0.79-0.91,  $I^2$  47%).

## Conclusion

Fibrates may have a protective effect for the composite outcome of non-fatal stroke, non-fatal MI and vascular death in people with a previous history of CVD; however, this protection is mainly due to the reduction in the risk of non-fatal or fatal MI events. Nonetheless, these results largely rely on studies including clofibrate, a drug withdrawn from the market in 2002.

## Comment

Fibrates are a drug class used predominantly in dyslipidemias due to their established effect in lowering triglycerides and increasing HDL cholesterol.<sup>2,3</sup> However, their effect on cardiovascular risk still generates debate, with several clinical trials reporting inconsistent results. A systematic review and meta-analysis from 2010 found a reduction in the risk of major cardiovascular events, mainly by prevention of coronary events.<sup>4</sup> The specific role of fibrates in primary and secondary prevention, however, is still unclear.

The present systematic review and meta-analysis suggests that fibrates may play a role in the secondary prevention of cardiovascular events, mainly MI. These

results, however, must be interpreted with caution. Five of the thirteen included trials employed clofibrate, a drug withdrawn from the market in 2002 due to safety concerns related to increased overall mortality. Of note, excluding these trials from the analysis, the protective effect of fibrates was only maintained for the secondary outcome of MI. Furthermore, the limited number of studies weakens the results and validity of some of the analysis performed, particularly the comparison between different fibrates and the assessment of the value of addition of fibrates to statin therapy. Finally, when interpreting the results, it should be noted that moderate heterogeneity was found in the majority of outcomes.

Nevertheless, certain interesting conclusions can be inferred from this analysis, especially the absence of significant differences in the effect of fibrates between genders and different age groups, and between fibrates and placebo regarding adverse effects.

## Clinical implications

This review suggests that fibrates may play a role in the secondary prevention of cardiovascular events. However, rather than changing indications for initiating fibrates, the review constitutes further evidence to be considered when deciding on lipid-modifying therapy in dyslipidemic patients with a history of CVD.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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