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Jakob T, Nordmann AJ, Schandelmaier S, Ferreira-González I, Briel M

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[Intervention Review]

Fibrates for primary prevention of cardiovascular disease events

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ABSTRACT

Background

Fibrates are effective for modifying atherogenic dyslipidaemia, and particularly for lowering serum triglycerides. However, evidence that fibrates reduce mortality and morbidity associated with cardiovascular disease (CVD), or overall mortality and morbidity, in the primary prevention of CVD is lacking.

Objectives

This Cochrane Review and meta-analysis aimed to evaluate the clinical benefits and harms of fibrates versus placebo or usual care or fibrates plus other lipid-modifying drugs versus other lipid-modifying drugs alone for the primary prevention of cardiovascular disease (CVD) morbidity and mortality.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), and Web of Science (all from inception to 19 May 2016). We searched four clinical trial registers (last searched on 3 August 2016) with the help of an experienced professional librarian. We searched the databases to identify randomised controlled trials (RCTs) evaluating the clinical effects of fibrate therapy in the primary prevention of CVD events. We did not impose any language restrictions.

Selection criteria

We aimed to include all RCTs comparing the effects of fibrate monotherapy versus placebo or usual care, or fibrates plus other lipid-modifying drugs versus other lipid-modifying drugs alone. Included studies had a follow-up of at least six months for the primary prevention of CVD events. We excluded trials with clofibrate, because it was withdrawn from the market in 2002.

Data collection and analysis

Two review authors independently screened titles and abstracts for potential study inclusion. Two review authors independently retrieved the full-text papers and extracted data. Disagreements were resolved by consensus. We calculated risk ratios (RRs) and accompanying 95% confidence intervals (CIs) for aggregate data on primary and secondary outcomes. We tested for heterogeneity with the Cochrane Q-test and used the I^2 statistic to measure inconsistency of treatment effects across studies. Using the GRADE approach, we assessed the quality of the evidence and used the GRADE profiler software (GRADEpro GDT) to import data from Review Manager 5 to create 'Summary of findings' tables.

Main results

We identified six eligible trials including 16,135 individuals. The mean age of trial populations varied across trials; between 47.3 and 62.3 years. Four trials included individuals with diabetes mellitus type 2 only. The mean treatment duration and follow-up of participants across

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trials was 4.8 years. We judged the risks of selection and performance bias to be low; risks of detection bias, attrition bias, and reporting bias were unclear. Reporting of adverse effects by included trials was very limited; that is why we used discontinuation of therapy due to adverse effects as a proxy for adverse effects. Patients treated with fibrates had a reduced risk for the combined primary outcome of CVD death, non-fatal myocardial infarction, or non-fatal stroke compared to patients on placebo (risk ratio (RR) 0.84, 95% confidence interval (CI) 0.74 to 0.96; participants = 16,135; studies = 6; moderate-quality of evidence). For secondary outcomes we found RRs for fibrate therapy compared with placebo of 0.79 for combined coronary heart disease death or non-fatal myocardial infarction (95% CI 0.68 to 0.92; participants = 16,135; studies = 6; moderate-quality of evidence); 1.01 for overall mortality (95% CI 0.81 to 1.26; participants = 8471; studies = 5; low-quality of evidence); 1.01 for non-CVD mortality (95% CI 0.76 to 1.35; participants = 8471; studies = 5; low-quality of evidence); and 1.38 for discontinuation of therapy due to adverse effects (95% CI 0.71 to 2.68; participants = 4805; studies = 3; $I^2 = 74\%$; very low-quality of evidence). Data on quality of life were not available from any trial. Trials that evaluated fibrates in the background of statins (2 studies) showed no benefits in preventing cardiovascular events.

Authors' conclusions

Moderate-quality evidence suggests that fibrates lower the risk for cardiovascular and coronary events in primary prevention, but the absolute treatment effects in the primary prevention setting are modest (absolute risk reductions < 1%). There is low-quality evidence that fibrates have no effect on overall or non-CVD mortality. Very low-quality evidence suggests that fibrates are not associated with increased risk for adverse effects.

PLAIN LANGUAGE SUMMARY

Fibrates for patients without established cardiovascular disease

Review question

What are the benefits and harms of using fibrate treatment compared to placebo or usual care for preventing cardiovascular disease in people at increased risk of developing cardiovascular disease?

Background

Cardiovascular disease is the most common cause of death, illness, disability, and reduced quality of life in industrialised countries. One of the major risk factors for cardiovascular disease is elevated low-density lipoprotein cholesterol (LDL-C, 'bad' cholesterol). In addition, persons with elevated serum triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C, 'good' cholesterol) are also at increased risk for cardiovascular disease events such as heart attacks or strokes. Fibrates lower serum triglycerides, modestly raise HDL-C, and modestly lower LDL-C. Therefore, long-term therapy with fibrates may help prevent cardiovascular disease events, in particular in combination with statins, for which it has been shown that they substantially lower LDL-C and reduce the risk of heart attack, stroke, and overall mortality.

Study characteristics

The evidence is current to May 2016. We identified six eligible primary prevention trials including 16,135 individuals without established cardiovascular disease that compared fibrate therapy with placebo or usual care. The mean age of the trial populations varied between 47.3 and 62.3 years; the majority of included individuals had diabetes mellitus type 2. The mean treatment duration and follow-up of participants across trials was 4.8 years.

Key results and quality of the evidence

Moderate-quality evidence suggests a risk reduction of 16% with fibrate therapy for the combined outcome of death due to cardiovascular disease, heart attack, or stroke. In absolute terms, the risk for this combined outcome in patients with cardiovascular risk factors but without established cardiovascular disease was on average reduced from 5.0% to 4.3% over five years. Moderate-quality evidence also suggests a risk reduction for fatal and non-fatal heart attacks with fibrates, but there is low-quality evidence for no risk reduction for overall mortality or death from non-CVD with fibrates. Very-low quality evidence suggests that there is no increased risk for adverse effects with fibrate treatment. The reporting of adverse effects by identified trials was very limited. Data on quality of life were not available from any included study. Trials that evaluated fibrates in the background of statin treatment showed no benefits in preventing cardiovascular events.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table

Fibrates compared to placebo for patients in primary prevention of cardiovascular disease events

Patient or population: patients in primary prevention of cardiovascular disease events

Settings: outpatients

Intervention: fibrates

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Fibrates				
Combined CVD death, non-fatal MI, or non-fatal stroke Follow-up: 2 years to 5 years	62 per 1000	52 per 1000 (49 to 59)	RR 0.84 (0.74 to 0.96)	16,135 (6 studies)	⊕⊕⊕⊖ moderate ¹	
Combined coronary heart disease death or non-fatal MI Follow-up: 2 years to 5 years	46 per 1000	36 per 1000 (31 to 42)	RR 0.79 (0.68 to 0.92)	16,135 (6 studies)	⊕⊕⊕⊖ moderate ¹	
Overall mortality Follow-up: 1 year to 5 years	36 per 1000	36 per 1000 (30 to 45)	RR 1.01 (0.81 to 1.26)	8471 (5 studies)	⊕⊕⊖⊖ low ^{1, 2}	
Non-CVD mortality Follow-up: 1 year to 5 years	22 per 1000	22 per 1000 (16 to 29)	RR 1.01 (0.76 to 1.35)	8471 (5 studies)	⊕⊕⊖⊖ low ^{1, 2}	
Discontinuation of therapy due to adverse effects Follow-up: 2 years to 5 years	261 per 1000	360 per 1000 (185 to 699)	RR 1.38 (0.71 to 2.68)	4805 (3 studies)	⊕⊖⊖⊖ very low ^{1, 3, 4}	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

CI: confidence interval; **CVD:** cardiovascular death; **MI:** myocardial infarction; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ High risk of bias for incomplete outcome data in [FIRST 2014](#) and [SENDAP 1998](#) (attrition bias).
- ² The estimate is imprecise because the 95% CI includes clinically-relevant harm as well as clinically-relevant benefit; in addition there is some evidence for publication bias.
- ³ There is considerable inconsistency across studies (I^2 of 74%) without plausible explanation.
- ⁴ The estimate is imprecise, because the 95% CI includes clinically-important benefit as well as clinically-important harm.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is the most common cause of death, illness, disability, and reduced quality of life in industrialised countries (Thom 2006; WHO 2014). With the increasing incidence of obesity, metabolic syndrome, and type 2 diabetes mellitus, the disease burden of CVD may escalate further in the years to come (Shaw 2010; WHO 2015). One of the major risk factors for CVD is elevated low-density lipoprotein cholesterol (LDL-C). In individuals with elevated LDL-C, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are considered to be the first choice of pharmacological therapy, since they reduce CVD events and total mortality independently of baseline LDL-C levels in primary and secondary prevention of CVD (4S 1994; Baigent 2005; Graham 2007; Heart Protection Study 2002; Hooper 2001; Lestra 2005; Mills 2010). The finding of elevated serum triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C) can identify persons who are at increased risk for CVD, and who might benefit from further lipid-modifying therapy (Graham 2007; Khoury 2011). Several causes underlie elevated triglycerides and low levels of HDL-C in the general population: being overweight and obese, physical inactivity, cigarette smoking, excess alcohol intake, very high-carbohydrate diets (> 60% of total energy), type 2 diabetes, chronic renal failure, nephrotic syndrome, certain drugs (corticosteroids, protease inhibitors for HIV, beta-adrenergic blocking agents, estrogens), and genetic factors (Chait 1990; Stone 1994). When triglyceride levels are ≥ 200 mg/dL, the presence of increased quantities of atherogenic remnant lipoproteins can increase coronary heart disease risk substantially beyond that predicted by LDL-C alone (Steiner 1987). In patients with type 2 diabetes mellitus, the United Kingdom Prospective Diabetes Study (UKPDS) identified low levels of HDL-C (< 40 mg/dL in men, < 45 mg/dL in women) as the second most important coronary risk factor after LDL-C (Turner 1998). However, it remains unclear if therapeutic interventions to raise levels of HDL-C indeed translate into CVD risk reduction (Briel 2009).

Description of the intervention

Currently available fibrates in North America and/or Europe include: gemfibrozil, fenofibrate, fenofibric acid, bezafibrate, etofibrate, and ciprofibrate. Clofibrate is no longer in use due to excess mortality (United Nations 2003; WHO 1978). Fibrates are effective for modifying atherogenic dyslipidaemia; i.e. they prominently lower serum triglyceride levels, modestly raise levels of HDL-C, and modestly lower levels of LDL-cholesterol (Fazio 2004; Abourbih 2009; Jun 2010). Therefore, they appear to be particularly suitable for prevention of CVD events in people with low levels of HDL-C and high triglycerides (Khoury 2011).

Potential side effects or adverse effects from fibrate therapy are increased venous thrombotic events, pancreatitis, reversible rise in creatinine (described with all fibrates except gemfibrozil), rise in homocysteine, and elevations in transaminases, gallbladder disease (since fibrates increase the cholesterol content of bile), and myositis/rhabdomyolysis, in particular for combinations of gemfibrozil with statins (Davidson 2007; Wierzbicki 2010).

How the intervention might work

Improvements in atherogenic dyslipidaemia mainly through reduction of serum triglycerides and modest increase of HDL-

C may result in a reduction of CVD events (Graham 2007; Lee 2011). The underlying mechanisms are probably fibrate induced changes in gene transcriptions controlling parts of lipid metabolism (Staels 1998). Fibrates seem to activate transcription factors, specifically peroxisome proliferator-activated receptors (PPARs). PPAR activation leads to an increased production of major HDL apolipoproteins and lipoprotein lipase. In addition, fibrates enhance the catabolism of triglycerides through stimulation of cellular fatty acid uptake and conversion to acyl-CoA derivatives.

Why it is important to do this review

Evidence from systematic reviews that fibrates reduce overall mortality or CVD mortality is lacking, although fibrates reduced non-fatal coronary events in several previously published meta-analyses (Abourbih 2009; Jun 2010; Keene 2014). In the Jun 2010 meta-analysis that included 18 trials with a total of 45,058 participants, fibrate therapy was associated with a 10% relative risk reduction for major CVD events and a 13% relative risk reduction for coronary events, but was not associated with a risk reduction of stroke. There was no effect of fibrate therapy on the risk of overall mortality or CVD mortality. None of the systematic reviews and meta-analyses reported separate outcomes for the effect of fibrates in primary or secondary prevention.

The main evidence for clinical benefit comes from placebo controlled trials with older fibrates such as gemfibrozil (for which some safety concerns were raised primarily when used in combination with statin therapy) and clofibrate (which is no longer available due to safety concerns) (Graham 2004; Jones 2005; Khoury 2011; Rubins 1999). The large Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial failed to show a reduction in CVD events when patients with type 2 diabetes were treated with fenofibrate plus statins rather than with statins alone (Ginsberg 2010). In the Keene 2014 meta-analysis, fibrate therapy reduced the risk for non-fatal myocardial infarction, but this effect was only statistically significant in the trials without statin treatment and not in those with statin treatment. The difference between these subgroups was, however, not significant. Similarly, the Ip 2015 meta-analysis showed there was not more clinical benefit from statin-fibrate combination therapy compared with statin monotherapy. Therefore, there remains uncertainty as to whether fibrates alone, or as add-on therapy to statins, are effective in reducing CVD events in people at increased risk of developing CVD.

The controversy about the benefit of fibrates is also to some extent reflected in the results of a recent population level, observational cohort study using Intercontinental Marketing Services (IMS) Health data of patients prescribed fibrates in the USA and Canada (Jackevicius 2011). In this study, authors observed an increase in prescriptions for fibrates (particularly fenofibrate) in the USA during the past decade, while prescriptions for fibrates in Canada remained stable.

Limited healthcare resources demand an unbiased appreciation of the available evidence about the benefit and harm of fibrate therapy. In the USA, annual sales of fibrates total more than USD 1 billion (Bloomberg 2011). Since current evidence about the effectiveness of fibrate therapy in the primary prevention of CVD is missing, the results of this Cochrane Review and meta-analysis will serve as a basis for decision-making in health care.

In contrast to another Cochrane Review that focuses on the secondary prevention of CVD and stroke (Wang 2015), and a currently withdrawn Cochrane Review protocol on the combined therapy of statins and fibrates for individuals with dyslipidaemia (Ciapponi 2014), our Cochrane Review and meta-analysis focuses on the effects of fibrates as monotherapy or as add-on therapy to other lipid-modifying drugs for the primary prevention of CVD morbidity and mortality in patients at risk for cardiovascular events.

OBJECTIVES

This Cochrane Review and meta-analysis aims to evaluate the clinical benefits and harms of fibrates versus placebo or usual care or fibrates plus other lipid-modifying drugs versus other lipid-modifying drugs alone for the primary prevention of cardiovascular disease (CVD) morbidity and mortality.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished randomised controlled trials (RCTs) that documented relevant clinical outcome data and had a length of treatment of at least six months. In order to be included as a primary prevention trial, fewer than 10% of participants were required to have established cardiovascular disease (CVD).

Types of participants

Adults (i.e. individuals older than 18 years of age) at increased risk of CVD events (e.g. individuals with type 2 diabetes mellitus, or dyslipidaemia, or both) but not established CVD.

Types of interventions

- Fibrate therapy versus placebo or usual care (combination therapy of a fibrate plus statins versus statins alone was considered in a sensitivity analysis).
- We excluded clofibrate as an intervention, because it is no longer in use. In 1979, clofibrate was withdrawn in some countries and its approval indications were severely restricted in many others due to adverse effects (United Nations 2003; WHO 1978).

Types of outcome measures

Outcome measures were patient-relevant clinical outcomes and adverse effects of fibrate therapy.

Primary outcomes

- Combined outcome of major CVD events (CVD death, non-fatal myocardial infarction, or non-fatal stroke).

Secondary outcomes

- Overall mortality.
- Combined coronary heart disease death (mortality) or non-fatal myocardial infarction as a composite endpoint.
- Non-CVD mortality.
- Diabetic retinopathy (progression of pre-existing diabetic retinopathy, development of new diabetic retinopathy according to individual trial definitions).

- Incidence of albuminuria (incidence of macroalbuminuria, incidence of micro- or macroalbuminuria).
- Patient perceived quality of life.

In addition, we investigated adverse effects of fibrate therapy (especially increases in serum creatinine or liver values (transaminases), myositis/rhabdomyolysis, pancreatitis, venous thrombotic events, gallbladder diseases, and the number of individuals discontinuing therapy due to adverse effects). Because adverse effects were often not specified as outcomes in included trials, we used discontinuation of therapy due to adverse effects as a proxy. We defined the presence or absence of increases in serum creatinine and liver values according to individual trial definitions.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2) in the Cochrane Library, MEDLINE (Ovid, 1946 to May week 2, 2016), Embase Classic and Embase (Ovid, 1947 to 2016 May 18), CINAHL (EBSCO, 1937 to 19 May 2016), Conference Proceedings Citation Index-Science (CPCI-S), and Science Citation Index Expanded (SCI-EXPANDED) on Web of Science (Thomson Reuters, 1990/1900 to 19 May 2016) on 19 May 2016.

We used the Cochrane sensitivity-maximising RCT filter for MEDLINE and terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* for Embase (Lefebvre 2011). We did not impose any language restrictions. The search strategy that was developed to search MEDLINE (Ovid), together with the Cochrane Heart Group, was adapted where necessary to search the other databases listed. The search strategies can be found in Appendix 1.

We searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)) (www.apps.who.int/trialsearch) and individual trial registers for protocols of ongoing trials on 3 August 2016 (www.clinicaltrials.gov; www.controlled-trials.com; www.isrctn.org). For any potentially relevant ongoing trials that were identified, we contacted authors by email or fax to get more precise information on trial methods, recruitment status, and outcome data in case of unpublished trial protocols.

Searching other resources

We searched for reference lists of identified articles, editorials, and reviews on the topic for further eligible studies.

Data collection and analysis

Selection of studies

TJ, AJN, IFG, and MB, working in teams of two, independently reviewed potentially eligible titles and abstracts. If either review author believed the study could have been eligible, we obtained the full report. After obtaining full reports of the studies (either in full peer-reviewed publication or press article), TJ and AJN independently assessed eligibility from full-text papers. Discrepancies were resolved by reviewers' consensus or, if needed, by third party arbitration (MB). Primary prevention trials were defined as trials including fewer than 10% patients with already established cardiovascular disease (CVD).

Data extraction and management

Working in teams of two, TJ, AJN, and SS used pre-piloted forms to independently extract all relevant data on baseline characteristics of trials, patient populations, outcomes, and additional data provided by original trial investigators. Any disagreements between review authors were resolved by discussion and consensus.

For the [ACCORD 2010](#) trial, we obtained the full dataset from the National Institutes of Health, USA. In a first step, we reproduced the reported results; in a second step, we stratified the analyses by primary and secondary prevention and included the results for primary prevention in the meta-analysis. We recalculated the following outcomes using complete cases only: combined outcome of CVD death, non-fatal myocardial infarction, or non-fatal stroke; combined outcome of fatal myocardial infarction (or coronary heart disease death) or non-fatal myocardial infarction; overall mortality; non-CVD mortality; micro- and macroalbuminuria; and elevated serum creatinine.

Assessment of risk of bias in included studies

Working in teams of two, TJ, AJN, and MB independently assessed the risk of bias of each included trial with respect to concealment of treatment allocation, random sequence generation, blinding of patients, blinding of caregivers, blinding of assessors of clinical outcomes, completeness of follow-up, and selective reporting of outcomes ([Higgins 2011](#)). Any disagreements were resolved by discussion and consensus or by third party arbitration, if needed. We explored the influence of individual 'Risk of bias' criteria on summary estimates in sensitivity analyses.

Measures of treatment effect

We used risk ratios (RRs) and accompanying 95% confidence intervals (CIs).

Unit of analysis issues

Except for the [ACCORD 2010](#) trial we used aggregated data for analysis.

Dealing with missing data

In case of unpublished or incomplete data, or published data that could not be directly integrated into our analysis, we contacted the investigators of the original trials and asked for the relevant information.

Assessment of heterogeneity

We tested for heterogeneity using the Cochrane Q-test and used the I^2 statistic to measure inconsistency of treatment effects across different lipid-lowering interventions ([Higgins 2002](#); [Higgins 2003](#); [Higgins 2011](#)).

Assessment of reporting biases

We checked for outcome reporting bias by comparing reported outcomes to outcomes mentioned in corresponding trial protocols, outcomes mentioned in trial registries, or outcomes mentioned in the Methods section of publications. We investigated the presence of publication bias by means of funnel plots ([Sterne 2001](#)).

Data synthesis

We pooled treatment effects across studies and calculated a weighted average RR for all outcomes in the treatment and control groups by using a fixed-effect model (default) if there was no heterogeneity among pooled studies. In cases where we detected heterogeneity, we applied a random-effects model, as described in Section 9.5.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). The random-effects model and the fixed-effect model typically give identical results when there is no heterogeneity among pooled studies. All analyses were conducted using Review Manager 5.3 ([RevMan5 2014](#)).

We created a 'Summary of findings' table using the following outcomes: combined CVD death, non-fatal myocardial infarction, or non-fatal stroke; combined coronary heart disease death or non-fatal myocardial infarction; overall mortality; non-CVD mortality; and discontinuation of therapy due to adverse effects. We used the five Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes ([GRADE Handbook 2013](#)). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), using GRADEpro software ([GRADEpro 2015](#)). We justified all decisions to down- or upgrade the quality of studies using footnotes and we made comments to aid reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

Due to the small number of included trials we did not conduct any subgroup analyses.

Sensitivity analysis

We examined treatment effects according to risk of bias (reported concealed treatment allocation versus no reported concealed treatment allocation, reported blinding of patients and caregivers versus no reported blinding of patients and caregivers, and reported blinded outcome assessment versus no reported blinded outcome assessment). In addition, we conducted sensitivity analyses with respect to fibrate monotherapy versus trials evaluating fibrates in addition to other lipid-modifying drugs (e.g. statins), and prompted by editors of the Heart Group, we conducted sensitivity analyses with respect to follow-up duration (4 years and more versus less than 4 years).

RESULTS

Description of studies

Results of the search

Our literature search for articles, editorials, and reviews on the topic yielded 7735 deduplicated hits ([Figure 1](#)). After exclusion of articles based on titles and abstracts, we reviewed 50 publications in full-text. We identified a total of eight primary prevention trials which fulfilled our inclusion criteria, but excluded two trials that used clofibrate, which is no longer in use ([DIS 1991](#); [WHO 1978](#)). Thus, we were able to analyse data from six primary prevention trials in total ([ACCORD 2010](#); [Emmerich 2009](#); [FIELD 2005](#); [FIRST 2014](#); [Frick 1987](#); [SEND CAP 1998](#)). We were able to obtain separate

primary prevention data from three of these trials that included patients with established cardiovascular disease (CVD) ([ACCORD 2010](#); [Emmerich 2009](#); [FIRST 2014](#)). For [FIELD 2005](#), we could only retrieve primary prevention data for our combined primary outcome (CVD death, non-fatal myocardial infarction, or non-fatal stroke). For [ACCORD 2010](#) we were able to obtain the complete

dataset from the National Institutes of Health, USA, which enabled us to separate primary prevention from secondary prevention participants in the analysis for all outcomes except for adverse effects. Primary prevention trials included a total of 16,135 patients (8087 in the intervention group and 8048 in the control group).

Figure 1. Study flow diagram.

Figure 1. (Continued)

synthesis
(meta-analysis)

Included studies

Design

All included trials were randomised controlled multicentre trials (undertaken in the USA, Canada, Germany, Finland, France, Sweden, Australia, New Zealand, UK). Individual follow-up-periods of included patients varied from two to five years (Table 1). Five of the six trials compared outcomes by intention-to-treat-analysis (ACCORD 2010; Emmerich 2009; FIELD 2005; Frick 1987; SENDCAP 1998), while FIRST 2014 did not report the method of outcome analysis (Characteristics of included studies).

Sample sizes and description of participants

The number of included participants in individual trials varied from 164 to 7664 (Table 1; Characteristics of included studies). Three trials included mostly men (FIELD 2005; Frick 1987; SENDCAP 1998). The mean ages of study participants varied in primary prevention trials between 47.3 and 62.3 years. Four trials included individuals with type 2 diabetes only (ACCORD 2010; Emmerich 2009; FIELD 2005; SENDCAP 1998); of the patients included in FIRST 2014, 47.5% had diabetes type 2 and in Frick 1987, 2.6%. Further information on included trials are summarised in the section Characteristics of included studies.

Interventions

Three trials investigated the effect of fenofibrate (ACCORD 2010, 160 mg/d; FIELD 2005, 200 mg/d; FIRST 2014, 135 mg/d). One trial evaluated the effects of etofibrate (Emmerich 2009, 1000 mg/d), one the effects of bezafibrate (SENDCAP 1998, 400 mg/d), and another the effect of gemfibrozil (Frick 1987, 1200 mg/d). Two trials used fibrate therapy on top of a statin therapy (FIRST 2014, atorvastatin 10 mg/d to 40 mg/d in both study groups; ACCORD 2010, simvastatin 20 mg/d in both study groups), whereby participants in the intervention groups additionally received fibrates while participants in the control group additionally received placebo in these two trials. In FIRST 2014, study investigators had the option of adding ezetimibe 10 mg to the treatment regimen in both study groups, if low-density lipoprotein cholesterol (LDL-C) was still ≥ 3.34 mmol/l (130 mg/dl) despite application of the maximum atorvastatin dose (40 mg). All other trials used fibrates in the intervention groups as monotherapy and placebo in the control groups. Frick 1987 recommended a cholesterol-lowering diet, increase in physical activity, and a reduction in smoking to all patients (both study groups). Further information on included trials are summarised in Characteristics of included studies.

Outcomes

The primary outcome of FIRST 2014 was the rate of change of the left and right mean posterior wall (carotid intima-media thickness) measured by ultrasound. ACCORD 2010 defined as a primary outcome the composite endpoint until the first occurrence of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes, while the primary outcome of the ACCORD eye substudy was the rate of progression of diabetic retinopathy by

at least three steps on the Early Treatment of Diabetic Retinopathy Study (ETDRS) severity scale or development of proliferative diabetic retinopathy necessitating photocoagulation therapy or vitrectomy. Emmerich 2009 defined the improvement or worsening of vision assessed by Consensus Clinical Global Impression of Change (CCGI-C) as a primary outcome (comparison of fundus results at study entry and after one year of treatment). The primary outcomes of FIELD 2005 were coronary events (coronary heart disease death or non-fatal myocardial infarction), while the FIELD 2007 eye substudy investigated primarily the progression of diabetic retinopathy of at least two-steps in the ETDRS-severity scale. The primary endpoint of SENDCAP 1998 was the change in the carotid artery intima-media thickness. The primary outcomes of Frick 1987 were fatal and non-fatal myocardial infarctions and cardiac death. Further information on included trials are summarised in Characteristics of included studies.

Overview of data availability for our primary and secondary outcomes

Concerning our combined primary outcome of CVD death, non-fatal myocardial infarction, or non-fatal stroke, and for the combined outcome of coronary heart disease mortality or non-fatal myocardial infarction we were able to pool data from all six trials. For the secondary outcomes of overall mortality and non-CVD mortality we were able to pool data from all trials with the exception of FIELD 2005. For the outcome of new diabetic retinopathy or the progression of pre-existing diabetic retinopathy, we were not able to obtain data from primary prevention populations: ACCORD 2010 (Accord eye substudy), FIELD 2005 (Field eye substudy), and Emmerich 2009 reported only on patients with and without established CVD (mixed prevention). ACCORD 2010 was the only trial providing data on progression to albuminuria. None of the included trials reported on patient perceived quality of life.

Overview of data availability for adverse effects

Two of six trials reported increases in serum creatinine and transaminases levels (Emmerich 2009; FIRST 2014). None of the six trials reported the occurrence of myositis/rhabdomyolysis. FIRST 2014 reported the occurrence of pancreatitis and FIRST 2014 and Emmerich 2009 reported venous thrombotic events. Three trials reported gallbladder diseases and individuals discontinuing therapy due to adverse effects (Emmerich 2009; FIRST 2014; Frick 1987). Primary prevention data on adverse effects in ACCORD 2010 were not available.

Excluded studies

Reasons for exclusion are presented in the Characteristics of excluded studies table and in Figure 1. We excluded two trials with clofibrate because the drug is no longer in use (DIS 1991; WHO 1978). We excluded 18 trials because more than 10% of trial participants had established CVD at baseline (Acheson 1972; BECAIT 1996; Begg 1971; Benderly 2009; BIP 2000; CDP fibrates 1975; Cullen 1974; DAIS 2001; Frick 1993; Haim 2007; Harrold 1969; LEADER 2002; Liamina 2011; LOCAT 1997; Newcastle 1971; SSP 1971; VA Cooperative 1973; VAHIT 1999). Eleven trials did not report

relevant outcome data to be included in this meta-analysis and review (Chew 2008; Domagala 2013; Farnier 2012; Kawano 2013; Pioneer 2013; Pruski 2009; Rajamani 2011; Rosenson 2007; Scott 2010; Tkacheva 2010; Valensi 2010). We excluded five trials because of the lack of a placebo/usual care group (Bays 2008, fibrate + statin versus fibrate only; Derosa 2009, fibrate only versus statin only versus fibrate and statin in combination; Dohmen 2013, fenofibrate versus bezafibrate; Lee 2012, fibrate and statin versus statin only); Yang 2013, multiple interventions). Two trials were retrospective

trial designs and not RCTs (Klempfner 2014; Webb 2009). In six trials the follow-up time was too short (< 6 months) to be included (Aguilar-Salinas 2001; Betteridge 1994; Chen 2013; Khan 2014; Krysiak 2010; Massin 2014).

Risk of bias in included studies

For details see [Characteristics of included studies](#), [Summary of findings for the main comparison](#), [Figure 2](#), and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ACCORD 2010	+	+	+	+	+	+	+
Emmerich 2009	?	?	+	?	+	?	-
FIELD 2005	+	+	+	+	+	+	+
FIRST 2014	+	+	+	?	-	+	-
Frick 1987	?	+	+	+	+	?	+
SENDCAP 1998	+	+	+	+	-	?	+

Allocation

Two trials did not report the method of random sequence generation (Emmerich 2009; Frick 1987), while four trials did (ACCORD 2010; FIELD 2005; FIRST 2014; SENDCAP 1998); therefore we judged the risk of bias in this domain to be low. All but one trial reported concealment of treatment allocation (Emmerich 2009), and therefore we rated the risk of bias for this domain as low too.

Blinding

Study participants and personnel were blinded to treatment groups in all six trials; therefore we judged the risk of performance bias as low.

Blinding of outcome assessment (data collectors and data adjudicators) was reported in three trials (ACCORD 2010; FIELD 2005; Frick 1987). SENDCAP 1998 did not report whether data collectors were blinded, but reported that data adjudicators were blinded. In two trials, blinding of outcome assessment was not

reported (Emmerich 2009; FIRST 2014). Therefore, we rated the risk for detection bias as unclear for all outcomes other than mortality.

Incomplete outcome data

We judged two trials to be at high risk of attrition bias. FIRST 2014 had a loss to follow-up of 31% of patients without reporting the reasons, but numbers of patients lost to follow-up between the intervention and control groups were similar. SENDCAP 1998 lost 22% of patients to follow-up without reporting reasons. The remaining trials had negligible losses to follow-up. Therefore, we rated the risk for attrition bias in these remaining trials as low.

Selective reporting

We searched for study protocols on PubMed (www.pubmed), ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (www.apps.who.int/trialsearch). We found study protocols for three trials (ACCORD 2010; FIELD 2005; FIRST 2014). All reports on randomisation procedures, blinding of patients and caregivers,

blinding of outcome assessment, inclusion and exclusion criteria, and primary and secondary endpoints in trial protocols were in congruence with the corresponding information reported in these individual trials. These trials reported all clinical outcomes and all adverse effects. For the remaining three trials, we did not find study protocols (Emmerich 2009; Frick 1987; SENDCAP 1998). SENDCAP 1998 did not report any adverse effects. Emmerich 2009 did not report the number of patients discontinuing therapy due to adverse effects.

Publication bias

The visual inspection of the funnel plot for the combined primary outcome of CVD death, non-fatal myocardial infarction, or non-fatal stroke did not provide compelling evidence for a potential publication bias (Figure 4). However, the funnel plots for overall mortality (Figure 5), and non-CVD mortality (Figure 6), showed an asymmetry in a way that the risk for harm from fibrate therapy could be underestimated.

Figure 4. Funnel plot of comparison: 1 Outcomes/adverse effects, outcome: 1.1 Combined CVD death, non-fatal MI, or non-fatal stroke.

Figure 5. Funnel plot of comparison: 1 Outcomes/adverse effects primary prevention trials, outcome: 1.3 Overall mortality.

Figure 6. Funnel plot of comparison: 1 Outcomes/adverse effects primary prevention trials, outcome: 1.4 Non-CVD mortality.

Other potential sources of bias

Another potential source of bias is the involvement of pharmaceutical companies in the conduct, analysis, or publication of clinical trials. Design, study conduct, analysis, and financial support of [FIRST 2014](#) were provided by the pharmaceutical company, AbbVie. AbbVie participated in the interpretation of data, review, and approval of the article. The trial by [Emmerich 2009](#) was sponsored and conducted by Merz-Pharmaceuticals. [SENDAP 1998](#) was supported by grants from Boehringer Mannheim, but this company seemed to have had no influence on the performance and data analysis of the trial. In [ACCORD 2010](#) some of the investigators received fees from different pharmaceutical companies, but the study was co-ordinated independently. The two remaining trials did not seem to have conflicted interests ([FIELD 2005](#); [Frick 1987](#)).

Effects of interventions

See: [Summary of findings for the main comparison Summary of findings table](#)

Primary outcome

Combined outcome of major cardiovascular disease (CVD) events

Six trials with a total of 16,135 participants reported data for the combined outcome of CVD death, non-fatal myocardial infarction, or non-fatal stroke ([ACCORD 2010](#); [Emmerich 2009](#); [FIELD 2005](#); [FIRST 2014](#); [Frick 1987](#); [SENDAP 1998](#)). Patients in fibrate groups

had a reduced risk for the primary combined outcome (risk ratio (RR) 0.84, 95% confidence interval (CI) 0.74 to 0.96; $I^2 = 0\%$; moderate quality of evidence) compared with placebo ([Analysis 1.1.1](#)).

Secondary outcomes

Overall mortality

We found no effect of fibrate treatment on overall mortality (RR 1.01, 95% CI 0.81 to 1.26; participants = 8471; studies = 5; $I^2 = 0\%$; low-quality evidence; [Analysis 1.2.1](#)).

Combined coronary heart disease death (mortality) or non-fatal myocardial infarction as a composite endpoint

We found a decreased risk for coronary heart disease death or non-fatal myocardial infarction with fibrate therapy compared to placebo (RR 0.79, 95% CI 0.68 to 0.92; participants = 16,135; studies = 6; $I^2 = 0\%$; moderate-quality evidence; [Analysis 1.3](#)).

Non-CVD mortality

We found no effect of fibrate treatment on non-CVD mortality (RR 1.00, 95% CI 0.76 to 1.33; participants = 8471; studies = 5; $I^2 = 0\%$; low-quality evidence; [Analysis 1.4](#)).

Diabetic retinopathy (progression of pre-existing diabetic retinopathy, development of new diabetic retinopathy according to individual trial definitions)

No primary prevention trial reported data on diabetic retinopathy (development of new diabetic retinopathy or progression of pre-existing diabetic retinopathy). However, using data from mixed prevention populations (patients with and without established CVD) of three trials ([ACCORD 2010](#); [Emmerich 2009](#); [FIELD 2005](#)), the risk for progression of pre-existing diabetic retinopathy was decreased in the fibrate group compared to the placebo group (RR 0.67, 95% CI 0.56 to 0.81; participants = 2901; studies = 3; $I^2 = 0\%$; [Analysis 1.5](#)). Using data from two trials reporting results on the development of new diabetic retinopathy ([Emmerich 2009](#); [FIELD 2005](#)), we found a RR of 0.60 (95% CI 0.17 to 2.09; participants = 1308; studies = 2; $I^2 = 73\%$; [Analysis 1.6](#)).

Incidence of albuminuria (incidence of macroalbuminuria, incidence of micro- or macroalbuminuria)

The incidence of albuminuria was only reported in one trial ([ACCORD 2010](#)). For the incidence of macroalbuminuria (≥ 300 ratio mg albumine / g creatinine) we found a RR of 0.85 (95% CI 0.67 to 1.09; participants = 3246) for fibrate treatment compared with placebo ([Analysis 1.7](#)). For the incidence of micro- or macroalbuminuria (≥ 30 ratio mg albumine / g creatinine) we found a RR of 0.92 (95% CI 0.83 to 1.01; participants = 3246) for fibrate treatment compared with placebo ([Analysis 1.8](#)).

Patient perceived quality of life

No trial reported on patient perceived quality of life.

Adverse effects

We found an increased risk for raised serum creatinine levels with fibrate treatment compared with placebo (RR 1.88, 95% CI 1.65 to 2.15; participants = 4173; studies = 3; $I^2 = 0\%$; [Analysis 1.9](#)). There were only five patients with raised serum transaminase levels (4 in fibrate groups versus 1 in placebo groups) in two trials ([Emmerich 2009](#); [FIRST 2014](#)), resulting in imprecise evidence (RR 2.94, 95% CI 0.47 to 18.21; participants = 724; $I^2 = 0\%$; [Analysis 1.10](#)). No primary prevention trial reported on the risk for myositis/rhabdomyolysis. There was only one patient with pancreatitis (fibrate group) in one trial reporting on pancreatitis ([FIRST 2014](#); RR 2.74, 95% CI 0.11 to 66.88; participants = 480; [Analysis 1.11](#)). There were only few venous thrombotic events (3 in fibrate groups, 2 in placebo groups) resulting in imprecise evidence (RR 1.46, 95% CI 0.24 to 8.78; participants = 724; studies = 2; $I^2 = 0\%$; [Analysis 1.12](#)). Three trials reported on the incidence of gallbladder disease ([Emmerich 2009](#); [FIRST 2014](#); [Frick 1987](#)), with a summary RR of 1.33 (95% CI 0.68 to 2.62; participants = 4805; studies = 3; $I^2 = 0\%$; [Analysis 1.13](#)). Because adverse effects were mostly not specified as an outcome in included trials, we used discontinuation of therapy due to adverse or side effects as a proxy; there were 712 patients (29.4%) who discontinued therapy due to adverse or side effects out of 2420 patients in fibrate groups compared with 622 (26.1%) out of 2385 patients in placebo groups (RR 1.38, 95% CI 0.71 to 2.68; participants = 4805; studies = 3; $I^2 = 74\%$; very low-quality evidence; [Analysis 1.14](#)).

Sensitivity analyses

We performed sensitivity analyses for the primary outcome of combined CVD death, non-fatal myocardial infarction, or non-fatal stroke, and for overall mortality with respect to reported allocation concealment, reported blinding of patients and caregivers, reported blinded outcome assessment, trials using fibrate monotherapy versus trials using fibrates in addition to statins, and trials with at least four years of follow-up).

Concealed treatment allocation versus unclear concealed treatment allocation

There were four trials that reported concealed treatment allocation ([ACCORD 2010](#); [FIELD 2005](#); [FIRST 2014](#); [SEND CAP 1998](#)), with a RR for the combined primary outcome (CVD death, non-fatal myocardial infarction, or non-fatal stroke) of 0.88 (95% CI 0.76 to 1.01; participants = 11810; studies = 4; $I^2 = 0\%$; Analyses 1.1.1 and 1.1.2). The sensitivity analysis on overall mortality focusing on trials that reported concealed allocation yielded a RR of 1.00 (95% CI 0.77 to 1.30; participants = 4146; studies = 3; $I^2 = 0\%$) between patients treated with fibrates compared to patients on placebo (Analyses 1.2.1 and 1.2.2).

Blinding of patients and caregivers versus unclear blinding of patients and caregivers

All six included trials reported blinding of patients and caregivers, making this sensitivity analysis obsolete for the combined primary outcome and overall mortality (Analyses 1.1.3, 1.1.4, 1.2.3, and 1.2.4).

Blinded outcome assessment versus unclear blinded outcome assessment

There were four trials that reported blinding of outcome assessors ([ACCORD 2010](#); [FIELD 2005](#); [Frick 1987](#); [SEND CAP 1998](#)), with a RR for the combined primary outcome (CVD death, non-fatal myocardial infarction, or non-fatal stroke) of 0.85 (95% CI 0.72 to 0.99; participants = 15,411; $I^2 = 0\%$) when comparing fibrate groups with placebo groups (Analyses 1.1.5 and 1.1.6). The sensitivity analysis on overall mortality focusing on trials which reported blinded outcome assessment yielded a RR of 1.02 (95% CI 0.82 to 1.27; participants = 7747; studies = 3; $I^2 = 0\%$; [Analysis 1.2.5](#) and 1.2.6).

Trials using fibrate monotherapy versus trials using fibrates in addition to statins

Four included trials used fibrates as monotherapy ([Emmerich 2009](#); [FIELD 2005](#); [Frick 1987](#); [SEND CAP 1998](#)), with a RR for the combined primary outcome (CVD death, non-fatal myocardial infarction, or non-fatal stroke) of 0.79 (95% CI 0.68 to 0.92; participants = 12,153; studies = 4; $I^2 = 0\%$; [Analysis 1.1.7](#)). Two trials used fibrates in addition to statins ([ACCORD 2010](#); [FIRST 2014](#)), with a RR for the combined primary outcome of 0.99 (95% CI 0.78 to 1.26; participants = 3982; studies = 2; $I^2 = 0\%$; [Analysis 1.1.8](#)). The corresponding analyses for overall mortality yielded a RR of 1.02 (95% CI 0.68 to 1.52; participants = 4489; studies = 3; $I^2 = 0\%$ for trials using fibrate monotherapy ([Analysis 1.2.7](#)), and a RR of 1.01 (95% CI 0.78 to 1.31; participants = 3982; studies = 2; $I^2 = 0\%$) in trials using fibrates in addition to statins ([Analysis 1.2.8](#)). There was some evidence for a difference in treatment effects for the primary combined outcome between groups of trials with fibrate monotherapy and groups of trials using fibrates in addition to

statins (I^2 between groups of 61%), suggesting no relevant risk reduction with fibrates when using them together with statins.

Trials with at least four years of follow-up versus trials with less than four years of follow-up

There were three trials with at least four years of follow-up ([ACCORD 2010](#); [FIELD 2005](#); [Frick 1987](#)), with a RR for the combined primary outcome (CVD death, non-fatal myocardial infarction, or non-fatal stroke) of 0.85 (95% CI 0.72 to 1.00; participants = 15,237; studies = 3; $I^2 = 36\%$; Analyses 1.1.9 and 1.1.10). There were two trials with at least four years of follow-up that reported on overall mortality among primary prevention patients with a RR of 1.03 (95% CI 0.82 to 1.28; participants = 7583; studies = 2; $I^2 = 0\%$) between patients treated with fibrates compared to patients on placebo (Analyses 1.2.9 and 1.2.10).

DISCUSSION

Summary of main results

In trials of primary prevention of cardiovascular disease (CVD) that compared fibrate therapy to placebo or usual care, this Cochrane Review and meta-analysis found moderate-quality evidence for a reduced risk for CVD events (CVD death, non-fatal myocardial infarction, or non-fatal strokes) of 16%, and for coronary events (coronary heart disease death or non-fatal myocardial infarction) of 21%. These effects are modest ($\leq 1\%$) on an absolute scale, taking into account a low baseline risk of 5% or lower over five years for CVD events. In terms of numbers needed to treat (NNTs), we calculated that, assuming a baseline risk of 6%, 112 individuals have to be treated over five years to prevent one CVD event. Furthermore, assuming a baseline risk of 4%, we calculated that 125 individuals have to be treated for five years to prevent one coronary event (coronary heart disease death or non-fatal myocardial infarction). When fibrates were applied in addition to a statin (2 primary prevention trials) compared with statin therapy alone, the treatment effect tended towards no effect. Low-quality evidence suggests that fibrates have no effect on overall mortality or non-CVD mortality. There was very low-quality evidence for no difference between fibrate treated patients and patients receiving placebo or usual care, with respect to discontinuation of therapy due to adverse effects.

Overall completeness and applicability of evidence

This Cochrane Review included all primary prevention trials of fibrate therapy. No primary prevention trial reported results on diabetic retinopathy or quality of life, and only one trial provided data on the development of albuminuria ([ACCORD 2010](#)). The mean age of trial participants ranged from 47.3 to 62.3 years. Thus, the results of this meta-analysis cannot necessarily be generalised to the elderly population. The applicability of our results to female individuals is limited since a large majority of trial participants were male. In addition, the results of our study may not easily be generalisable to individuals without type 2 diabetes mellitus since the number of non-diabetic participants was too small to conduct separate subgroup analyses. Finally, data in this review were primarily from trials without background statin therapy, which is now considered usual care. Only two more recent trials evaluated the effect of combined statin and fibrate therapy ([ACCORD 2010](#); [FIRST 2014](#)), and did not find a reduction in the primary outcome of combined CVD death, non-fatal myocardial infarction, or non-fatal stroke compared to statin therapy alone (Analysis 2.4).

Quality of the evidence

We employed the GRADE approach ([GRADE Handbook 2013](#)) to interpret result findings and the GRADE profiler software ([GRADEpro 2015](#)) allowed us to import data from Review Manager 5 to create 'Summary of findings' tables. According to the GRADE approach, the quality of the evidence was moderate for the primary composite outcome of CVD death, non-fatal myocardial infarction, or non-fatal stroke and for the secondary composite outcome of coronary heart disease death or non-fatal myocardial infarction due to an increased risk of attrition bias for [SENDCAP 1998](#) and [FIRST 2014](#) (Summary of findings for the main comparison). For overall mortality and non-CVD mortality we judged the evidence to be of low-quality, because of wide confidence intervals (imprecise estimates) and an increased risk of attrition bias for [SENDCAP 1998](#) and [FIRST 2014](#); in addition we found some evidence for potential publication bias ([Figure 5](#); [Figure 6](#)). For discontinuation of therapy due to adverse effects, we rated the quality of evidence as very low due to substantial heterogeneity of results across trials that we cannot explain in stratified analyses, an increased risk of attrition bias for [FIRST 2014](#), and imprecision (95% confidence interval (CI) of summary effect includes clinically-important benefit as well as clinically-important harm).

Potential biases in the review process

With the aim to identify and include all eligible randomised trials on the topic, we conducted a highly sensitive literature search, including trial registers and contacts with experts in the field for unpublished studies. Still, funnel plots for overall mortality and non-CVD mortality indicate some asymmetry that could be due to publication bias ([Figure 5](#); [Figure 6](#)). The present results may, therefore, underestimate the risk for harm from fibrate therapy.

Agreements and disagreements with other studies or reviews

Previously published systematic reviews did not report separate effects of fibrate therapy for primary prevention ([Abourbih 2009](#); [Jun 2010](#); [Keene 2014](#)), except for an older systematic review of ours ([Studer 2005](#)). Our results are consistent with two previous systematic reviews reporting the effects of fibrate therapy in a combined primary and secondary prevention population. [Jun 2010](#) reported a 10% risk reduction for major CVD events and a 13% risk reduction for coronary events in individuals treated with fibrate therapy, but did not report any effects on overall mortality, CVD mortality, or non-CVD mortality. They reported a decreased risk for the new development of diabetic retinopathy, including two trials in a pooled primary and secondary CVD prevention population (risk ratio (RR) 0.63, 95% CI 0.49 to 0.81; $I^2 = 41.5\%$) ([Emmerich 2009](#); [FIELD 2005](#)). Our analysis, including results from individuals from the [ACCORD 2010](#) trial, confirms these findings.

[Keene 2014](#) reported an odds ratio (OR) of 0.80 (95% CI 0.74 to 0.87) for non-fatal myocardial infarction in individuals treated with fibrates, but no difference in overall mortality, coronary heart disease mortality, nor stroke. More recently, [Wang 2015](#) reported a RR of 0.88 (95% CI 0.83 to 0.94) for a composite outcome of non-fatal stroke, non-fatal myocardial infarction, and vascular death in individuals treated with fibrate therapy for the secondary prevention of CVD based on a meta-analysis of 13 trials, involving 16,112 participants. However, there was no difference in the primary composite outcome after excluding clofibrate trials. There

was no difference in overall mortality, vascular death, strokes, nor adverse effects.

In conclusion, our meta-analysis confirms results of previous meta-analyses in mixed or secondary CVD prevention trials, reporting a moderate reduction in a composite vascular outcome, as well as for the primary prevention of CVD events.

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate-quality evidence that currently used fibrates lower the risk of a combined outcome of cardiovascular (CVD) death, non-fatal myocardial infarction, or non-fatal stroke by 16%, and the risk of a combined outcome of coronary heart disease death or non-fatal myocardial infarction by 21% in the primary prevention of CVD, without increasing or decreasing overall mortality or non-CVD mortality (low-quality evidence). Very low-quality evidence suggested no difference in discontinuation of treatment due to adverse effects in the fibrate groups compared to placebo groups. Our sensitivity analysis stratifying studies by presence/absence of additional therapy with statins suggests that the benefits of fibrate therapy may no longer be relevant in the context of background therapy with statins (Analysis 2.4). Nevertheless, the beneficial effects of fibrates in terms of a decreased risk for major CVD events without background therapy with statins appear modest on an absolute scale ($\leq 1\%$). There was insufficient data to analyse fibrate therapy for the prevention of diabetic retinopathy in primary prevention individuals.

The recent guidelines from the National Institute for Health and Care Excellence (NICE) in the UK did not recommend fibrates for primary nor secondary prevention of CVD (Rabar 2014). However, the International Atherosclerosis Society (IAS) states that if non-high-density lipoprotein cholesterol (non-HDL-C) and triglycerides remain elevated when the low-density lipoprotein cholesterol (LDL-C) goal is achieved, the addition of a fibrate should be considered (IAS Recommendations 2014), although there is no compelling evidence from clinical trials to support this consideration.

Implications for research

Collected outcome data on CVD events should be reported separately for stroke, fatal stroke, fatal myocardial infarction, non-fatal myocardial infarction and revascularisation procedures, such as bypass grafts and angioplasty. Further randomised controlled trials (RCTs) would be needed to better estimate a potential benefit of fibrate therapy for primary prevention of CVD events on top of statin therapy, and better estimate benefits and harms in non-diabetic patients, in women, and in elderly individuals. In future primary prevention trials of fibrates, data on diabetic retinopathy (development of new diabetic retinopathy and progression of pre-existing diabetic retinopathy), and development of albuminuria should be systematically captured, as well as typical known adverse effects of fibrates such as raised serum creatinine, raised serum transaminases, myositis/rhabdomyolysis, pancreatitis, venous thrombotic events, gallbladder diseases, and the number of patients discontinuing therapy due to side effects, to achieve more precise estimates for these outcomes. Special attention should be given to the systematic reporting and analysis on most relevant adverse effects, which were rather limited in this review due to inadequate reporting.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ACCORD 2010

Methods	Design: RCT, 2 x 2 factorial, multicentre, 77 centres in USA and Canada (Simvastatin therapy in open-label design)
	Follow-up period: 4.7 years.

ACCORD 2010 (Continued)

Method of outcome analysis: Intention-to-treat analysis reported

Participants	<p>Patients in whole trial (n): 5518; Patients in primary prevention (n): 3502 (primary prevention trial in our analysis)</p> <p>Patients in intervention group (n): 1757</p> <p>Patients in control group (n): 1745</p> <p>Men (%): 69 (n = 2416)</p> <p>Age (mean): 62.3 years</p> <p>Percentage of diabetic patients at baseline: 100%</p> <p>Inclusion criteria: Type 2 diabetes, HbA1c $\geq$ 7.5%, aged 40 to 79 for patients with clinical cardiovascular disease, aged 55 to 79 years for patients with subclinical cardiovascular disease or at least two additional cardiovascular risk factors, LDL-C between 60 and 80 mg/dl, HDL-C below 55 mg/dl, triglyceride below 750 mg/dl.</p> <p>Exclusion criteria: History of hypoglycaemic event, history of type 1 diabetes, unwilling to do insulin therapy, BMI > 45, elevated serum creatinine, elevated transaminase, medical therapy with known interactions with the glycaemic interventions, cardiovascular event or hospitalisation for unstable angina within past 3 months, heart failure, weight loss > 10% within past 6 months, risk of pregnancy, recurrent phlebotomy or blood transfusion.</p> <p>Additional exclusion criteria for the lipid trial: Hypersensitivity to statins or fibrates; medical therapy with known interaction with statins or fibrates, refusal to stop lipid-lowering drugs, history of pancreatitis, thyroid disease, history of myositis/myopathy, gallbladder disease.</p> <p>Total lost to follow-up (n): 52 (0.9%) no reasons for losses to follow-up provided; data on loss to follow-up refers to the entire trial collective.</p> <p>Lost to follow-up in intervention group (n): 27 (1.0%)</p> <p>Lost to follow-up in control group (n): 25 (0.9%)</p>	
Interventions	Fenofibrate 160 mg/d + simvastatin (20 mg/d) versus placebo + simvastatin (20 mg/d); ("Because of a rise in serum creatinine levels in some patients while receiving this dose of fenofibrate was adjusted according to the estimated glomerular filtration rate (GFR) with the use of the abbreviated Modification of Diet in Renal Disease (MDRD) equation. At the last clinic visit, 440 patients (15.9%) in the fenofibrate group and 194 (7.0%) in the placebo group were receiving a reduced dose of either fibrate or placebo because of a decreased estimated GFR").	
Outcomes	<p>Primary: Composite endpoint of the time until the first occurrence of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes.</p> <p>Secondary: Fatal myocardial infarction, non-fatal myocardial infarction, fatal stroke, non-fatal stroke, death from cardiovascular causes, revascularisation procedures, hospitalisation due to congestive heart failure.</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation with the use of permuted blocks on the trial's website to maintain concealment of study group assignment.
Allocation concealment (selection bias)	Low risk	Central randomisation with the use of permuted blocks on the trial's website to maintain concealment of study group assignment.

ACCORD 2010 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Caregivers and patients were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data collectors and outcome adjudicators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up 0.9%; losses to follow-up balanced between treatment groups (1% versus 0.9%); no reasons for losses to follow-up provided.
Selective reporting (reporting bias)	Low risk	All key outcomes, adverse effects, and reasons for discontinuation of therapy reported; no differences between protocol and trial in methods, outcomes and inclusion/exclusion criteria.
Other bias	Low risk	Some of the authors received fees from different pharmaceutical companies but the study was co-ordinated independently ("the drug manufacturers had no role in the design of the study, in the accrual or analysis of the data, or in the preparation of the manuscript").

Emmerich 2009

Methods	<p>Design: RCT; multicentre trial (German trial conducted in 2 centres in Latvia)</p> <p>Follow-up period: 1 year double-blind phase with following open-label phase of another year</p> <p>Method of outcome analysis: Intention-to-treat analysis reported</p>
Participants	<p>Patients in whole trial (n): 296; Patients in primary prevention (n): 244 (primary prevention trial in our analysis)</p> <p>Patients in intervention group (n): 118</p> <p>Patients in control group (n): 126</p> <p>Men (%): 29 (n=70)</p> <p>Age (mean): 58.6 years</p> <p>Percentage of diabetic patients at baseline: 100%</p> <p>Inclusion criteria: Type 2 diabetes, diabetic retinopathy (non-proliferative or proliferative) with hard exudates $\geq$ 1 eye; aged 18 to 78</p> <p>Exclusion criteria: HbA1c > 10%; triglycerides > 486 mg/dL, total cholesterol > 920.354 mg/dL, vasodilators, Aspirin, ACE-Inhibitors, calcium antagonists, blood pressure-lowering drugs, lipid-modifying drugs within past 6 weeks, liver function disorder, congestive heart failure, myocardial infarction, cancer; massive opacifications of light-breaking mediums, loss of sight due to macula degeneration, recent eye operation.</p> <p>Total lost to follow-up (n): 34 (11%); no reasons for losses to follow-up provided. Data on losses to follow-up refers to the entire trial collective.</p> <p>Lost to follow-up in intervention and control groups (n): not reported.</p>
Interventions	<p>Etofibrate 1g/d (2 x 500 mg/d) versus placebo</p>

Emmerich 2009 (Continued)

Outcomes

Primary: Improvement or worsening of vision assessed by CCGI-C; comparison of fundus results at study entry and after one year of treatment).

Secondary: Fundus results and visual acuity with best possible correction, lipid levels, fibrinogen levels, diabetes parameters, and CCGI-C after 6 months.

Notes

Emmerich 2009 provided unpublished data that allowed for stratification by primary versus secondary prevention patients. We excluded all secondary prevention patients (those with stroke, myocardial infarction, or extremity amputation for peripheral arterial disease).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported, just "randomised".
Allocation concealment (selection bias)	Unclear risk	Not reported whether allocation was concealed or not.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Caregivers and patients were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, if data collectors or outcome adjudicators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	34 (11%) of patients were lost to follow-up; no reasons for losses to follow-up provided; number of patients lost to follow-up in individual study groups not reported.
Selective reporting (reporting bias)	Unclear risk	All key outcomes and adverse effects reported but reasons for discontinuation of therapy not reported; no trial protocol available.
Other bias	High risk	Not reported whether there was funding or not but data analysis was conducted by staff of Merz-Pharmaceuticals.

FIELD 2005

Methods

Design: RCT; multicentre trial (Australia, New Zealand, Finland) at 63 FIELD sites

Follow-up period: 5 years

Method of outcome analysis: Intention-to-treat analysis reported

Participants

Patients in whole trial (n): 9795; **patients in primary prevention (n):** 7664 (primary prevention trial in our analysis)

Patients in intervention group (n): 3829

Patients in control group (n): 3835

Men (%): 61.5 (n = 4690)

Age (mean): 61.5 years

FIELD 2005 (Continued)

Percentage of diabetic patients at baseline: 100%

Inclusion criteria: Aged 50 to 75, type 2 diabetes, considered to be at high risk for coronary heart disease, total cholesterol level between 117 and 253 mg/dL plus either total cholesterol-to-HDL-C ratio ≥ 4 or a blood triglyceride concentration between 89 and 442 mg/dL.

Exclusion criteria: Blood triglyceride concentration > 442 mg/dL, concurrent treatment with any other lipid-lowering agent, serum creatinine > 1.5 mg/dL; liver disease, gall-bladder disease, myocardial infarction or hospital admission for unstable angina pectoris within past 3 months, risk of pregnancy, cyclosporin or risk of transplantation.

Total lost to follow-up (n): 22 (0.2%); no reasons for loss to follow-up provided. Data on loss to follow-up refers to the entire trial collective.

Lost to follow-up in intervention group (n): 12 (0.2%)

Lost to follow-up in control group (n): 10 (0.2%)

Interventions	Fenofibrate 200 mg/d versus placebo
Outcomes	<p>Primary: coronary events (the composite of coronary heart disease death or non-fatal myocardial infarction).</p> <p>Secondary: total cardiovascular events (the composite of cardiovascular death, myocardial infarction, stroke, coronary and carotid revascularisation).</p>
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done by central computer using a dynamic allocation method with stratification for important prognostic factors, including age, sex, previous myocardial infarction, lipid levels, and urinary albumin concentration.
Allocation concealment (selection bias)	Low risk	Randomisation was carried out using a dynamic allocation method with stratification for important prognostic factors, including age, sex, prior myocardial infarction, lipid levels and urinary albumin excretion.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Caregivers and patients were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data collectors were blinded. Not reported, if outcome adjudicators were it, too. The sponsor of the study had no role in data collection or data analysis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	22 (0.2%) patients lost to follow-up; no reasons for loss to follow-up provided, but balanced between intervention and control group.
Selective reporting (reporting bias)	Low risk	All key outcomes and adverse effects reported (except gallbladder disease); reasons for discontinuation of therapy not reported; no differences between protocol and trial in methods, outcomes and inclusion/exclusion criteria.
Other bias	Low risk	The main sponsor of trial and supplier of the fenofibrate and matching placebo medication, is Laboratoires Fournier S.A., Dijon, France but the study is co-

FIELD 2005 (Continued)

ordinated independently of the sponsors by the NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia and overseen by the study Management Committee. The sponsor of the study had no role in data collection or data analysis.

FIRST 2014

Methods	<p>Design: RCT; multicentre trial undertaken at 94 USA sites</p> <p>Follow-up period: 2 years</p> <p>Method of outcome analysis: Intention-to-treat analysis not reported</p>
Participants	<p>Patient in whole trial (n): 682; patients in primary prevention (n): 480 (primary prevention trial in our analysis)</p> <p>Patients in intervention group (n): 251</p> <p>Patients in control group (n): 229</p> <p>Men (%): 68 (n = 326)</p> <p>Age (mean): 61 years</p> <p>Percentage of diabetic patients at baseline: 49.9% (n = 337). Percentage of diabetic patients at baseline primary prevention data: 47.5% (n = 228); (intervention group 49% (n = 123); control group: 45.9% (n = 105))</p> <p>Inclusion criteria: aged ≥ 45, coronary heart disease or risk equivalent, carotid intima-media thickness (cIMT) ≥ 0.7 mm, LDL-C ≤ 100 mg/dL during atorvastatin run-in, triglycerides ≥ 150 mg/dL, HDL-C ≤ 45 (men) and 55 mg/dL (women)</p> <p>Exclusion criteria: systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, type 1 diabetes, ketoacidosis; HbA1c of $> 10.5\%$, history of pancreatitis, liver or renal disorder.</p> <p>Total lost to follow-up (n): 211 (30.9%); no reasons for loss to follow-up provided; data on loss to follow-up refers to the entire trial collective.</p> <p>Lost to follow-up in intervention group (n): 112 (32.9%)</p> <p>Lost to follow-up in control group (n): 99 (28.9%)</p>
Interventions	<p>Fenofibric acid 135 mg/d + atorvastatin 10 mg/d to 40 mg/d versus placebo + atorvastatin 10 mg/d to 40 mg/d; If LDL-C was still ≥ 3.34 mmol/L (130 mg/dL) despite application of the maximum atorvastatin dose (40 mg) study investigators had the option of adding ezetimibe 10 mg to the treatment regimen in both study groups.</p>
Outcomes	<p>Primary: Rate of change from baseline through week 104 of the left and right mean posterior wall cIMT measured by ultrasound.</p> <p>Secondary: Maximal posterior wall cIMT of CCA; mean posterior wall cIMT of CCA, ICA and carotid bifurcation; maximal posterior wall cIMT of CCA, ICA and carotid bifurcation; maximal posterior and anterior wall cIMT of CCA, ICA and carotid bifurcation; rate of change from baseline to week 104 in: 1) mean of the median, 10th percentile, and 90th percentile posterior wall IMT of the left and right CCAs; 2) the occurrence of CV events as a composite of CV mortality, non-fatal myocardial infarction, and non-fatal stroke; 3) the occurrence of CV events as a composite of CV mortality, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, carotid endarterectomy/stenting, hospitalisation for unstable angina, and hospitalisation for congestive heart failure; 4) change from baseline in lipid profile and inflammatory markers (total cholesterol, LDL-C, HDL-C; triglycerides, triglyceride/HDL-C ratio;</p>

FIRST 2014 (Continued)

non-HDL-C; VLDL-C, Apo AI, Apo AII, Apo B, Apo B/Apo all ratio; Apo CIII associated with Apo B-containing lipoprotein particles, hs-CRP.

Notes We received separate unpublished stratified data for primary prevention patients from AbbVie.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation schedule stratified by baseline atorvastatin dose-assigned patient numbers to blinded treatment assignments (fenofibric acid or placebo) in a 1:1 ratio. An additional randomisation schedule assigned study drug bottle numbers to blinded treatment assignments, and a random subset of study drug bottles were then supplied to each site. At visit 1, the patient was assigned a unique screening number through the use of an IVRS. At baseline, the assigned screening number and the current atorvastatin dose was given to the IVRS by the site. The IVRS then assigned a 4-digit patient number and one of the study drug bottle numbers corresponding to the randomised treatment assignment to each patient.
Allocation concealment (selection bias)	Low risk	Randomisation was double-blind and stratified by atorvastatin dose (10, 20, or 40 mg) at baseline.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Caregivers and patients were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported whether data collectors and outcome adjudicators were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	211 (31%) of patients lost to follow-up; no reasons for high loss to follow-up provided; balanced between intervention and control group.
Selective reporting (reporting bias)	Low risk	All key outcomes reported; all adverse effects (except myositis/rhabdomyolysis) reported; reasons for discontinuation of therapy not exactly reported; no differences between protocol and trial in methods, outcomes, and inclusion/exclusion criteria.
Other bias	High risk	The design, study conduct, analysis and financial support of the study were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the article. Intention-to-treat analysis not reported.

Frick 1987

Methods	Design: RCT; multicentre trial at 37 clinics (Finland) Follow-up period: 5 years Method of outcome analysis: Intention-to-treat analysis reported
Participants	Patients total (n): 4081 (primary prevention trial in our analysis) Patients in intervention group (n): 2051 Patients in control group (n): 2030

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Frick 1987 (Continued)

Men (%): 100 (n = 4081)

Age (mean): 47.3 years

Percentage of diabetic patients at baseline: 2.6% (n = 108)

Inclusion criteria: men, aged 40 to 55, employed by one of 8 Finnish companies, free of coronary symptoms, LDL + VLDL $\geq$ 200 mg/dL.

Exclusion criteria: coronary heart disease, congestive heart failure, valvular heart disease, gall bladder disease, liver disease, renal disease, unexplained abnormal leucocyte count, hypertension, type 1 diabetes.

Total lost to follow-up (n): 0 (0%)

Lost to follow-up in intervention group (n): 0 (0%)

Lost to follow-up in control group (n): 0 (0%)

Interventions	Gemfibrozil 1.2 g/d (2 x 600 mg/d) versus placebo (+ cholesterol-lowering diet, increase in physical activity and a reduction in smoking was recommended to all patients).
Outcomes	Primary: Fatal and non-fatal myocardial infarction; cardiac death; sudden death. Secondary: -
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No method described, just "randomised".
Allocation concealment (selection bias)	Low risk	Not reported but probably concealed ("The randomisation procedure was carried out by the drug supplier for each individual clinic (performed by staff who were not involved in any other aspect of the study). During the intervention visit, subjects were randomly allocated either to active drug or to placebo by dispensing the packages in numerical order. A sealed envelope containing the randomisation code for each clinic was held at the Central Office at Helsinki to be opened only in case of emergency").
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and caregivers were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Yes ("all end-point-assessments were made without knowledge of subject's treatment").
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	All key outcomes reported; not all adverse effects reported (increases in serum creatinine and serum transaminases levels, myositis/rhabdomyolysis, pancreatitis and venous-thrombotic events); reasons for discontinuation of therapy not exactly reported; no trial protocol available.

Frick 1987 (Continued)

Other bias	Low risk	No funding by the pharmaceutical industry.
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SENDCAP 1998

Methods	<p>Design: RCT; multicentre trial (UK)</p> <p>Follow-up period: 3 years</p> <p>Method of outcome analysis: Intention-to-treat analysis reported</p>
Participants	<p>Patients total (n): 164 (primary prevention trial in our analysis)</p> <p>Patients intervention group (n): 81</p> <p>Patients control group (n): 83</p> <p>Men (%): 71 (n = 117)</p> <p>Age (mean): 51 years</p> <p>Percentage of diabetic patients at baseline: 100%</p> <p>Inclusion criteria: aged 35 to 65, type 2 diabetes, total blood cholesterol $\geq$ 202 mg/dL, triglycerides $\geq$ 159 mg/dL, HDL-C $\leq$ 43 mg/dL, total cholesterol/HDL-C ratio $\geq$ 4.7</p> <p>Exclusion criteria: history of clinical cardiovascular disease, triglycerides > 708 mg/dL and total cholesterol/HDL-C ratio $\geq$ 7.2, renal disease, clinically detectable retinopathy, neuropathy, liver disease, positive ECG chest wall mapping test, systolic blood pressure $\geq$ 180 mmHg, diastolic blood pressure $\geq$ 110 mmHg, carotid stenosis $\geq$ 50%, alcohol abuse, anticoagulants, lipid-lowering drugs.</p> <p>Total lost to follow-up (n): 36 (22.0%); no reasons for losses to follow-up provided</p> <p>Lost to follow-up in intervention or control group (n): not reported</p>
Interventions	Bezafibrate 400 mg/d (bezalip retard) versus placebo
Outcomes	<p>Primary: Intima-media complex in common carotid artery; maximum intima-media thickness in carotid artery bifurcation; intima-media complex in common femoral artery; maximum intima-media thickness in common femoral artery; arterial ultrasound score all measured by ultrasound.</p> <p>Secondary: Myocardial infarction; blood glucose; HbA1c; fibrinogen; triglycerides; total cholesterol; HDL-C; LDL-C; non-HDL-C; total cholesterol/HDL-C ratio; Apo protein A1; Apo protein B; alkaline phosphatase.</p>
Notes	The study was supported by grants from Boehringer Mannheim but this company seemed to have no influence on the performance and assessment of the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A randomised list was prepared by the statistician in advance so that numbers assigned to each treatment would be approximately equal after every 10 subjects. Subjects satisfying entry criteria were given the next consecutive number in a double-blind fashion".
Allocation concealment (selection bias)	Low risk	"A randomised list was prepared by the statistician in advance so that numbers assigned to each treatment would be approximately equal after every

SENDCAP 1998 (Continued)

		10 subjects. Subjects satisfying entry criteria were given the next consecutive number in a double-blind fashion".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and caregivers were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data adjudicators were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	36 (22%) of patients lost to follow-up; no reasons for loss to follow-up provided; "There was no significant difference in the follow-up rate in the placebo and bezafibrate group".
Selective reporting (reporting bias)	Unclear risk	All key outcomes reported; no adverse effects reported; numbers and reasons of/for discontinuation of therapy not reported); no trial protocol available.
Other bias	Low risk	The study was supported by grants from Boehringer Mannheim but this company seemed to have no influence on the performance and assessment of the trial.

ACE-inhibitor: angiotensin-converting-enzyme inhibitor

BMI: body mass index

CCA: common carotid artery

CCGI-C: Consensus Clinical Global Impression of Change

cIMT: carotid intima-media thickness

CV: cardiovascular

ECG: electrocardiogram

HbA1c: hemoglobin A1c, glycated hemoglobin

HDL-C: high-density lipoprotein cholesterol

hs-CRP: highly sensitive C-reactive protein

ICA: internal carotid artery

IVRS: Interactive Voice Response System

LDL-C: low-density lipoprotein cholesterol

RCT: randomised controlled trial

VLDL-C: very low density lipoprotein cholesterol

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Acheson 1972	> 50% of patients with established CVD at baseline.
Aguilar-Salinas 2001	Follow-up period 8 weeks only.
Bays 2008	Lacking placebo/usual care group.
BECAIT 1996	> 50% of patients with established CVD at baseline.
Begg 1971	> 50% of patients with established CVD at baseline.
Benderly 2009	> 50% of patients with established CVD at baseline.
Bettendorfer 1994	Follow-up period 8 weeks only.

Study	Reason for exclusion
BIP 2000	> 50% of patients with established CVD at baseline.
CDP fibrates 1975	> 50% of patients with established CVD at baseline.
Chen 2013	Follow-up period 12 weeks only.
Chew 2008	No relevant outcome data.
Cullen 1974	> 50% of patients with established CVD at baseline.
DAIS 2001	48% of patients with established CVD at baseline.
Derosa 2009	Lacking placebo/usual care group.
DIS 1991	Intervention with clofibrate which is no longer in use.
Dohmen 2013	Lacking placebo/usual care group (fenofibrate versus bezafibrate).
Domagala 2013	No relevant outcome data.
Farnier 2012	No relevant outcome data.
Frick 1993	> 50% of patients with established CVD at baseline.
Haim 2007	> 50% of patients with established CVD at baseline.
Harrold 1969	41% of patients with established CVD at baseline.
Kawano 2013	No relevant outcome data.
Khan 2014	Follow-up period 6 weeks only.
Klempfner 2014	Not a RCT.
Krysiak 2010	Follow-up period 90 days only.
LEADER 2002	> 50% of patients with established CVD at baseline.
Lee 2012	Lacking placebo/usual care group.
Liamina 2011	> 50% of patients with established CVD at baseline.
LOCAT 1997	> 50% of patients with established CVD at baseline.
Massin 2014	Follow-up period < 6 months (no response from authors following requests to find out if there are results for longer follow-up periods).
Newcastle 1971	> 50% of patients with established CVD at baseline.
Pioneer 2013	No relevant outcome data.
Pruski 2009	No relevant outcome data.
Rajamani 2011	No relevant outcome data.

Study	Reason for exclusion
Rosenson 2007	No relevant outcome data.
Scott 2010	No relevant outcome data.
SSP 1971	> 50% of patients with established CVD at baseline.
Tkacheva 2010	No relevant outcome data.
VA Cooperative 1973	> 50% of patients with established CVD at baseline.
VAHIT 1999	> 50% of patients with established CVD at baseline.
Valensi 2010	No relevant outcome data.
Webb 2009	Not a RCT.
WHO 1978	Intervention with clofibrate which is no longer in use.
Yang 2013	Lacking placebo/usual care group.

CVD: cardiovascular disease

RCT: randomised controlled trial

Characteristics of ongoing studies [ordered by study ID]

[ACTRN12611000394943](#)

Trial name or title	The effect of combination of rosuvastatin and fenofibrate and metoprolol on the coronary atheroma plaque progression detected by multi-detector spiral computed tomography
Methods	Study type: RCT; masking: blinded; intervention assignment: parallel; target sample size: 520; follow-up period: 6 months; type of endpoints: efficacy; phase: phase 4
Participants	<p>Inclusion criteria: aged 18 to 70, mild to moderate coronary atheroma plaque by MDCT; diameter narrowing is less than 50%; LDL-C > 100 mg/dl, triglyceride 150 mg/dl.</p> <p>Exclusion criteria: coronary artery disease, coronary revascularisation (or risk of), lipid-lowering therapy, genetic form of dyslipidaemia, renal disease, liver disease, triglyceride > 500 mg/dl, uncontrolled hypertension, decompensated heart failure, risk of pregnancy, decreased life expectancy, heart rate < 60 beats/min, sick sinus syndrome, atrioventricular block.</p>
Interventions	3 arms: Intervention 1: rosuvastatin 10 mg/day plus fenofibrate 80 mg/day plus metoprolol 50 mg/day for 6 months; Intervention 2: rosuvastatin 10 mg/day plus fenofibrate 80 mg/day for 6 months; Intervention 3: rosuvastatin 10 mg/day plus metoprolol 50 mg/day for 6 months.
Outcomes	<p>Primary outcome: change of atheroma plaque volume is assessed by coronary computed tomography angiography; major cardiovascular events (death, myocardial infarction, coronary revascularisation, rehospitalisation driven by symptom).</p> <p>Secondary outcome: change of PAV assessed by coronary computed tomography angiography; change of coronary artery calcification score assessed by MDCT without contrast enhancement; change of coronary artery remodelling index assessed by coronary computed tomography angiography; the change of coronary artery area stenosis assessed by coronary computed tomography angiography; the change of coronary artery MLA assessed by coronary computed tomography angiography; change of LDL-C measured by standard enzymatic methods; change of HDL-C measured by standard enzymatic methods; change of triglyceride measured by standard enzymatic methods; change of hs-CRP assessed by ELISA method; change of lipoprotein-associated phospholipase</p>

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ACTRN12611000394943 (Continued)

A2 (Lp-PLA2) assessed by ELISA method; change of liver function assessed by blood serum assay; change of creatine kinase assessed by blood serum assay.

Starting date	Date of registration: 14/4/2011; date of enrolment: 1/5/2011; rate of registration: 24/08/2009; recruitment status: not recruiting.
Contact information	The Cardiology Department, Chinese PLA General Hospital, No.28 Fuxing Road, 100853 Beijing, China. Luyue Gai (Email: luyuegai301@yahoo.com; but email does not work).
Notes	Status: not recruiting (6/18/2015); source of information: www.apps.who.int/trialsearch.

NCT00965315

Trial name or title	A multicenter, randomized, parallel-group study to investigate the efficacy of a combination of rosuvastatin and fenofibrate in the patients with diabetes or atherosclerotic vascular diseases with metabolic syndrome
Methods	Study design: not provided; study type: expanded access; study phase: phase 4; target sample size: no information; follow-up period: 6 months; no further information provided on clinicaltrials.gov.
Participants	Inclusion criteria: aged 20 to 79, diabetes mellitus or atherosclerotic vascular diseases with metabolic syndrome. Exclusion criteria: contraindication to statin or fibrate, liver disease, risk of pregnancy, uncontrolled hypothyroidism; LDL-C > 190 mg/dl, triglyceride > 500 mg/dl, coronary heart disease or revascularisation within 1 month, congestive heart failure, valvular heart disease, gastrointestinal conditions affecting absorption of drugs, renal disease, life-threatening malignancy, immunosuppressive drug, lipid-modifying drug.
Interventions	Intervention: rosuvastatin 5 mg + fenofibrate 160 mg; Control: rosuvastatin 10 mg once daily
Outcomes	Primary outcome: the change of atheroma plaque volume assessed by coronary computed tomography angiography; the change of CT attenuation value assessed by coronary computed tomography angiography; major cardiovascular events (death, myocardial infarction, coronary revascularisation, rehospitalisation driven by symptom). Secondary outcome: the change of PAV assessed by coronary computed tomography angiography; the change of coronary artery calcification score assessed by MDCT without contrast enhancement; the change of coronary artery remodelling index assessed by coronary computed tomography angiography; the change of coronary artery area stenosis assessed by coronary computed tomography angiography; the change of coronary artery MLA assessed by coronary computed tomography angiography; the change of LDL-C measured by standard enzymatic methods; the change of HDL-C measured by standard enzymatic methods; the change of triglyceride measured by standard enzymatic methods; the change of hs-CRP assessed by the ELISA method; the change of lipoprotein-associated phospholipase A2 (Lp-PLA2) assessed by the ELISA method; the change of liver function assessed by blood serum assay; the change of creatine kinase assessed by blood serum assay.
Starting date	Not provided on clinicaltrials.gov; date of registration: 28/8/2009.
Contact information	National Taiwan University Hospital. Chau Chung Wu (Email: chauchungwu@ntu.edu.tw); no response to email.
Notes	Status: not recruiting (6/18/2015); source of information: www.apps.who.int/trialsearch.

ELISA: enzyme-linked immunosorbent assay
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
MDCT: multidetector computed tomography
MLA: minimal lumen area
PAV: per cent atheroma volume
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Fibrates versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Combined CVD death, non-fatal MI, or non-fatal stroke	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Primary analysis	6	16135	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.96]
1.2 Concealed treatment allocation	4	11810	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.76, 1.01]
1.3 Unclear concealed treatment allocation	2	4325	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.51, 0.95]
1.4 Blinding of patients and care-givers	6	16135	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.96]
1.5 Unclear blinding of patients and caregivers	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Blinded outcome assessment	4	15411	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.74, 0.96]
1.7 Unclear blinded outcome assessment	2	724	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.22, 1.95]
1.8 Trials using fibrates monotherapy	4	12153	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.68, 0.92]
1.9 Trials using statins in addition to fibrates	2	3982	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.78, 1.26]
1.10 Trials with at least 4 years of follow-up	3	15237	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.75, 0.96]
1.11 Trials with less than 4 years of follow-up	3	888	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.21, 1.51]
2 Overall mortality	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Primary analysis	5	8471	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Concealed treatment allocation	3	4146	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.77, 1.30]
2.3 Unclear concealed treatment allocation	2	4325	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.69, 1.56]
2.4 Blinding of patients and caregivers	5	8471	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.26]
2.5 Unclear blinding of patients and caregivers	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Blinded outcome assessment	3	7747	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.82, 1.27]
2.7 Unclear blinded outcome assessment	2	724	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.17, 3.39]
2.8 Trials using fibrates as monotherapy	3	4489	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.68, 1.52]
2.9 Trials using statins in addition to fibrates	2	3982	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.31]
2.10 Trials with at least 4 years of follow-up	2	7583	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.28]
2.11 Trials with less than 4 years of follow-up	3	888	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.17, 2.46]
3 Combined coronary heart disease death or non-fatal MI	6	16135	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.68, 0.92]
4 Non-CVD mortality	5	8471	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.76, 1.33]
5 Progression of pre-existing diabetic retinopathy	3	2901	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.56, 0.81]
6 Development of new diabetic retinopathy	2	1308	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.17, 2.09]
7 Incidence of macroalbuminuria (≥ 300 ratio mg albumine/g creatinine)	1	3246	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.67, 1.09]
8 Incidence of micro- or macroalbuminuria (≥ 30 ratio mg albumine/g creatinine)	1	3246	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.01]
9 Raised serum creatinine	3	4173	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.65, 2.15]
10 Raised serum transaminases	2	724	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.47, 18.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Pancreatitis	1	480	Risk Ratio (M-H, Fixed, 95% CI)	2.74 [0.11, 66.88]
12 Venous thrombotic events	2	724	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.24, 8.78]
13 Gallbladder disease	3	4805	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.68, 2.62]
14 Discontinuation of therapy due to side effects	3	4805	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.71, 2.68]

Analysis 1.1. Comparison 1 Fibrates versus placebo, Outcome 1 Combined CVD death, non-fatal MI, or non-fatal stroke.

Analysis 1.2. Comparison 1 Fibrates versus placebo, Outcome 2 Overall mortality.

Analysis 1.3. Comparison 1 Fibrates versus placebo, Outcome 3 Combined coronary heart disease death or non-fatal MI.

Analysis 1.4. Comparison 1 Fibrates versus placebo, Outcome 4 Non-CVD mortality.

Analysis 1.5. Comparison 1 Fibrates versus placebo, Outcome 5 Progression of pre-existing diabetic retinopathy.

Analysis 1.6. Comparison 1 Fibrates versus placebo, Outcome 6 Development of new diabetic retinopathy.

Analysis 1.7. Comparison 1 Fibrates versus placebo, Outcome 7 Incidence of macroalbuminuria (≥ 300 ratio mg albumine/g creatinine).

Analysis 1.8. Comparison 1 Fibrates versus placebo, Outcome 8 Incidence of micro- or macroalbuminuria (≥ 30 ratio mg albumine/g creatinine).

Analysis 1.9. Comparison 1 Fibrates versus placebo, Outcome 9 Raised serum creatinine.

Analysis 1.10. Comparison 1 Fibrates versus placebo, Outcome 10 Raised serum transaminases.

Analysis 1.11. Comparison 1 Fibrates versus placebo, Outcome 11 Pancreatitis.

Analysis 1.12. Comparison 1 Fibrates versus placebo, Outcome 12 Venous thrombotic events.

Analysis 1.13. Comparison 1 Fibrates versus placebo, Outcome 13 Gallbladder disease.

Analysis 1.14. Comparison 1 Fibrates versus placebo, Outcome 14 Discontinuation of therapy due to side effects.

ADDITIONAL TABLES

Table 1. Baseline characteristics of primary prevention trials

Trial name	Patients total, n	Follow-up, years	Average age, years (SD)	Men (%)	Diabetes mellitus type 2 (%)	Arterial hypertension (%)	Smokers (%)	Established cardiovascular disease at baseline (%)
ACCORD 2010	3502	4.7	62.3 (NA)	NA	100	NA	NA	0
Emmerich 2009	244	2	58.6 (NA)	28.7	100	NA	NA	0
FIELD 2005	7664	5	61.5 (6.8)	61.5	100	53.3	8.9	0
FIRST 2014	480	2	NA	NA	47.5	75	NA	0
Frick 1987	4081	5	47.3 (4.6)	100	2.6	14	36	0
SENDCAP 1998	164	3	51 (8)	71	100	16	18	0

SD: standard deviation

NA: not available

APPENDICES

Appendix 1. Search strategies

CENTRAL

- #1 MeSH descriptor Fibric Acids explode all trees
- #2 (fibrate* or fibric acid*)
- #3 MeSH descriptor Clofibric Acid explode all trees
- #4 (gemfibrozil or gemfibrocil)
- #5 MeSH descriptor Gemfibrozil, this term only
- #6 (ciprofibrat*)
- #7 MeSH descriptor Bezafibrate, this term only
- #8 MeSH descriptor Clofibrate, this term only
- #9 (fenofibrate)
- #10 MeSH descriptor Fenofibrate, this term only
- #11 (bezafibrate or clofibrate)
- #12 (bezafibrate or 41859-67-0 or asufibrat or azufibrat or (bm-15075 or bm15075))
- #13 (bezafibrate)
- #14 (befibrat or befizal or beza or bezabeta or bezacur or bezafibratum)
- #15 (bezafisal or bezagen or beza-lande or bezalande or bezalex or bezalip)
- #16 (bezamerck or bezamil or beza-puren or bezapuren or bezastad or bezatol)
- #17 (bionolip or cedur or colser or difaterol or durabezur or eulitop)
- #18 (hadiel or klestran or (lo-44 or lo44) or liparol or lipitrol or lipocin)
- #19 (lipox or norlip or pms-bezafibrate or polyzalip or redalip)
- #20 (reducerol or regadrin b or sklerofibrat or solibay or wayfrato)
- #21 (zafibrat or zimbacol or ciprofibrate or 52214-84-3 or bi-lipanol)
- #22 (hyperlipen or cirpol or lipanol or modalim or oroxadin) or (win-35833 or win35833)
- #23 (clofibrate or 637-07-0 or 882-09-7 or abirate or amotril)
- #24 (anparton or anti-lipide-ratiopharm or apolan or arterioflexin)
- #25 (arteriosan or artevil or ateculon or ateriosan or atheropront)
- #26 (atromidin or atromid-s) or (ay-61123 or ay61123)
- #27 (bioscleran or cartagyl or claripex or clobren or clofibrat)
- #28 (clofibrat or clofibratum or clofirem or clofi or clofibrin or clofibrinic acid or clofinit or clofenapate or methylclofenapate)
- #29 (colebron or col or geromid or hyclorate). or (ici-28257 or ici28257 or ici55695 or ici-55695 or nsc1149 or nsc-1149)
- #30 (liaptene or lipavil or lipavlon or lipilim or lipofacton or lipomid)
- #31 (liprinal or miscleron or misclerone or neo-atromid or athromidin or normet)

- #32 (regulipid or sinteriod or serotinex or sklerepmexe or skleromexe)
- #33 (s trat os or stratos or sklero-tablinene or sklerolip or ticlobran)
- #34 (xyduril or gemfibrozil) or 25812-30-0 or apo-gemfibrozil or ausgem
- #35 (bolutol or (ci-719 or ci719) or decrelip or deopid or dom-gemfibrozil)
- #36 (dropid or elmogan or emfib or fibrocit or fibros or gemcor)
- #37 (gemfibril or gemfibromax or gemhexal or gemizol or gemlipid)
- #38 (gemnpid or gen-gemfibrozil or nugemfibrozil or genlip or genozil or genozil)
- #39 (gozid or hidil or ipolipid or jezil or lipazil or lipidys or lipox gemfi or gemfi 1a pharma or lipidil or lofibra or lipison)
- #40 (litarek or locholes or lopid or lopizid or mariston or med-gemfibrozil)
- #41 (norpid or novo-gemfibrozil or pilder or pms-gemfibrozil or poli-fibrozil)
- #42 (tentroc or tiba or trialmin or fenofibrate or procetofen)
- #43 (49562-28-9 or apofen or ankebin or apo-fenofibrate or apo-feno-micro)
- #44 (catalip or cil or controlip or dom-fenofibrate or durafenat)
- #45 (elasterin or fegenor or fenobeta or fenobrate or fenogal or fenofanton or phenofibrate)
- #46 (fenolip or fenotard or feno-micro-200 or fulcro or gen-fenofibrate)
- #47 (lexemin or (1f-179 or 1f179) or (1f-178 or 1f178) or lipanon or lipanthyl)
- #48 (lipantil or liparison or lipcor or lipidax or lipidil or lipil)
- #49 (lipirex or lipoclar or lipofene or lipofen or lipo red or liposit)
- #50 (lipovas or lipsin or livesan or nolipax or normalip or procetofene)
- #51 (qualecon or scleril or procetoken or protolipan or secalap)
- #52 (supralip or tilene or tricolor or volutine or tocofibrate) or 50465-39-9
- #53 (transferral or theofibrate or etofylline clofibrate) or 54504-70-0
- #54 (duolip or (ml-1024 or ml1024) or theofol)
- #55 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54)
- #56 MeSH descriptor Cardiovascular Diseases explode all trees
- #57 MeSH descriptor Cerebrovascular Disorders explode all trees
- #58 (coronary)
- #59 (heart next (disease* or attack*))
- #60 (coronary next (disease* or event*))
- #61 (cerebrovascular* or cardiovasc*)
- #62 (myocardial next (infarct* or re?vascular* or ischemi*))
- #63 (stroke* or mortal*)
- #64 (morbid near/5 (heart* or cardiovascula* or coronary* or isch?em* or myocard*))
- #65 (cardio* or cardia* or heart* or coronary* or angina* or ventric* or myocard* or pericard* or isch?em*)

#66 (apoplexy or (brain near/2 accident*))

#67 ((brain* or cerebral or lacunar) near/2 infarct*)

#68 MeSH descriptor Hypertension explode all trees

#69 (hypertensi* or (peripheral arter* disease*))

#70 ((high or increased or elevated) near/2 blood pressure)

#71 MeSH descriptor Hyperlipidemias explode all trees

#72 (hyperlipid* or hyperlip?emia* or hypercholesterol* or hypercholester?emia* or hyperlipoprotein?emia* or hypertriglycerid?emia*)

#73 (emboli* or arrhythmi* or thrombo* or atrial fibrillat* or tachycardi* or endocardi* or (sick next sinus))

#74 (#56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73)

#75 (#55 AND #74)

MEDLINE

Cochrane sensitivity-maximising RCT filter applied ([Lefebvre 2011](#))

1 exp Fibric Acids/ or fibrate\$.mp. or fibric acid\$.tw. or exp Clofibrac Acid/

2 gemfibrozil.mp. or Gemfibrozil/ or gemfibrocil.tw.

3 bezafibrate/ or clofibrate/ or ciprofibrat\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

4 fenofibrate.mp. or Procetofen/

5 (bezafibrate or clofibrate).mp.

6 bezafibrate/ or bezafibrate.mp. or 41859-67-0.rn. or asufibrat.mp. or azufibrat.mp. or (bm-15075 or bm15075).rn,mp.

7 (befibrat or befizal or beza or bezabeta or bezacur or bezafibratum).mp.

8 (bezafisal or bezagen or beza-lande or bezalande or bezalex or bezalip).mp.

9 (bezamerck or bezamil or beza-puren or bezapuren or bezastad or bezatol).mp.

10 (bionolip or cedur or colser or difaterol or durabezur or eulitop).mp.

11 (hadiel or klestran or (lo-44 or lo44) or liparol or lipitrol or lipocin).mp.

12 (lipox or norlip or pms-bezafibrate or polyzalip or redalip).mp.

13 (reducterol or regadrin b or sklerofibrat or solibay or wayfrato).mp.

14 (zafibrat or zimbacol or ciprofibrate or 52214-84-3 or bi-lipanol).mp,rn.

15 (hyperlipen or cirpol or lipanol or modalim or oroxadin).mp. or (win-35833 or win35833).mp,rn.

16 clofibrate.mp. or 637-07-0.rn. or 882-09-7.rn. or abitrate.mp. or amotril.mp.

17 (anparton or anti-lipide-ratiopharm or apolan or arterioflexin).mp.

18 (arteriosan or artevil or ateculon or ateriosan or atheropront).mp.

19 (atromidin or atromid-s).mp. or (ay-61123 or ay61123).mp,rn. or azionly.mp.

20 (bioscleran or cartagyl or claripex or clobren or clofibrat).mp.

21 (clofibrat or clofibratum or clofirem or clofi or clofibrin or clofibrinic acid or clofinit or clofenapate or methylclofenapate).mp.

22 (colebron or col or geromid or hyclorate).mp. or (ici-28257 or ici28257 or ici55695 or ici-55695 or nsc1149 or nsc-1149).mp,rn.

- 23 (liaptene or lipavil or lipavlon or lipilim or lipofacton or lipomid).mp.
- 24 (liprinal or miscleron or misclerone or neo-atromid or athromidin or normet).mp.
- 25 (regulipid or sinteriod or serotinx or sklerepmexe or skleromexe).mp.
- 26 (s trat os or stratos or sklero-tablinene or sklerolip or ticlobran).mp.
- 27 (xyduril or gemfibrozil).mp. or 25812-30-0.rn. or apo-gemfibrozil.mp. or ausgem.mp.
- 28 bolutol.mp. or (ci-719 or ci719).mp,rn. or decrelip.mp. or deopid.mp. or dom-gemfibrozil.mp.
- 29 (dropid or elmogan or emfib or fibrocit or fibros or gemcor).mp.
- 30 (gemfibril or gemfibromax or gemhexal or gemizol or gemlipid).mp.
- 31 (gemnpid or gen-gemfibrozil or nugemfibrozil or genlip or genozil or genozil).mp.
- 32 (gozid or hidil or ipolipid or jezil or lipazil or lipidys or lipox gemfi or gemfi 1a pharma or lipidil or lofibra or lipison).mp.
- 33 (lipofor or lipogen or lipoite or lipozid or lipozil or lipur).mp.
- 34 (litarek or locholes or lipid or lopizid or mariston or med-gemfibrozil).mp.
- 35 (norpid or novo-gemfibrozil or pilder or pms-gemfibrozil or poli-fibrozil).mp.
- 36 (polyxit or recozil or riva-gemfibrozil or synbrozil or taborcil).mp.
- 37 (tentroc or tiba or trialmin or fenofibrate or procetofen).mp.
- 38 49562-28-9.rn. or apofen.mp. or ankebin.mp. or apo-fenofibrate.mp. or apo-feno-micro.mp.
- 39 (catalip or cil or controlip or dom-fenofibrate or durafenat).mp.
- 40 (elasterin or fegenor or fenobeta or fenobrate or fenogal or fenofanton or phenofibrate).mp.
- 41 (fenolip or fenotard or feno-micro-200 or fulcro or gen-fenofibrate).mp.
- 42 lexemin.mp. or (1f-179 or 1fl79).mp,rn. or (1f-178 or 1fl78).mp,rn. or lipanon.mp. or lipanthyl.mp.
- 43 (lipantil or liparison or lipcor or lipidax or lipidil or lipil).mp.
- 44 (lipirex or lipoclar or lipofene or lipofen or lipo red or liposit).mp.
- 45 (lipovas or lipsin or livesan or nolipax or normalip or procetofene).mp.
- 46 (qualecon or scleril or procetoken or protolipan or secalip).mp.
- 47 (supralip or tilene or tricolor or volutine or tocofibrate).mp. or 50465-39-9.rn.
- 48 (transferal or theofibrate or etofylline clofibrate).mp. or 54504-70-0.rn.
- 49 duolip.mp. or (ml-1024 or ml1024).mp,rn. or theofol.mp.
- 50 or/1-49
- 51 exp Cardiovascular Diseases/
- 52 exp Cerebrovascular Disorders/
- 53 coronary.mp.
- 54 (heart adj (disease\$ or attack\$)).mp.
- 55 (coronary adj (disease\$ or event\$)).mp.
- 56 (cerebrovascular\$ or cardiovasc\$).mp.
- 57 (myocardial adj (infarct\$ or re?vascular\$ or ischemi\$)).mp.

58 (stroke\$ or mortal\$).mp.
59 (morbid adj5 (heart\$ or cardiovascula\$ or coronary\$ or isch?em\$ or myocard\$)).mp.
60 (cardio\$ or cardia\$ or heart\$ or coronary\$ or angina\$ or ventric\$ or myocard\$ or pericard\$ or isch?em\$).tw.
61 (apoplexy or (brain adj2 accident\$)).tw.
62 ((brain\$ or cerebral or lacunar) adj2 infarct\$).tw.
63 exp Hypertension/
64 (hypertensi\$ or peripheral arter\$ disease\$).tw.
65 peripheral arter\$ disease\$.tw.
66 ((high or increased or elevated) adj2 blood pressure).tw.
67 exp Hyperlipidemias/
68 (hyperlipid\$ or hyperlip?emia\$ or hypercholesterol\$ or hypercholester?emia\$ or hyperlipoprotein?emia\$ or hypertriglycerid?emia\$).tw.
69 (emboli\$ or arrhythmi\$ or thrombo\$ or atrial fibrillat\$ or tachycardi\$ or endocardi\$ or (sick adj sinus)).tw.
70 or/51-69
71 randomized controlled trial.pt.
72 controlled clinical trial.pt.
73 randomized.ab.
74 placebo.ab.
75 drug therapy.fs.
76 randomly.ab.
77 trial.ab.
78 groups.ab.
79 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78
80 exp animals/ not humans.sh.
81 79 not 80
82 50 and 70 and 81

EMBASE

Cochrane RCT filter applied ([Lefebvre 2011](#))

1 exp Fibric Acids/ or fibrate\$.mp. or fibric acid\$.tw. or exp Clofibrac Acid/
2 gemfibrozil.mp. or Gemfibrozil/ or gemfibrocil.tw.
3 bezafibrate/ or clofibrate/ or ciprofibrat\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4 fenofibrate.mp. or Procetofen/
5 (bezafibrate or clofibrate).mp.
6 bezafibrate/ or bezafibrate.mp. or 41859-67-0.rn. or asufibrat.mp. or azufibrat.mp. or (bm-15075 or bm15075).rn,mp.
7 (befibrat or befizal or beza or bezabeta or bezacur or bezafibratum).mp.

- 8 (bezafisal or bezagen or beza-lande or bezalande or bezalex or bezalip).mp.
- 9 (bezamerck or bezamil or beza-puren or bezapuren or bezastad or bezatol).mp.
- 10 (bionolip or cedur or colser or difaterol or durabezur or eulitop).mp.
- 11 (hadiel or klestran or (lo-44 or lo44) or liparol or lipitrol or lipocin).mp.
- 12 (lipox or norlip or pms-bezafibrate or polyzalip or redalip).mp.
- 13 (reducerol or regadrin b or sklerofibrat or solibay or wayfrato).mp.
- 14 (zafibral or zimbacol or ciprofibrate or 52214-84-3 or bi-lipanor).mp,rn.
- 15 (hyperlipen or cirpol or lipanor or modalim or oroxadin).mp. or (win-35833 or win35833).mp,rn.
- 16 clofibrate.mp. or 637-07-0.rn. or 882-09-7.rn. or abitrate.mp. or amotril.mp.
- 17 (anparton or anti-lipide-ratiopharm or apolan or arterioflexin).mp.
- 18 (arteriosan or artevil or ateculon or ateriosan or atheroprnt).mp.
- 19 (atromidin or atromid-s).mp. or (ay-61123 or ay61123).mp,rn. or azionly.mp.
- 20 (bioscleran or cartagyl or claripex or clobren or clofibril).mp.
- 21 (clofibrat or clofibratum or clofirem or clofi or clofibrin or clofibrinic acid or clofinit or clofenapate or methylclofenapate).mp.
- 22 (colebron or col or geromid or hyclorate).mp. or (ici-28257 or ici28257 or ici55695 or ici-55695 or nsc1149 or nsc-1149).mp,rn.
- 23 (liaptene or lipavil or lipavlon or lipilim or lipofacton or lipomid).mp.
- 24 (liprinal or miscleron or misclerone or neo-atromid or athromidin or normet).mp.
- 25 (regulipid or sinteriod or serotinx or sklerepmexe or sklromexe).mp.
- 26 (s trat os or stratos or sklero-tablinene or sklerolip or ticlobran).mp.
- 27 (xyduril or gemfibrozil).mp. or 25812-30-0.rn. or apo-gemfibrozil.mp. or ausgem.mp.
- 28 bolutol.mp. or (ci-719 or ci719).mp,rn. or decrelip.mp. or deopid.mp. or dom-gemfibrozil.mp.
- 29 (dropid or elmogan or emfib or fibrocit or fibros or gemcor).mp.
- 30 (gemfibril or gemfibromax or gemhexal or gemizol or gemlipid).mp.
- 31 (gemnpid or gen-gemfibrozil or nugemfibrozil or genlip or genozil or genozil).mp.
- 32 (gozid or hidil or ipolipid or jezil or lipazil or lipidys or lipox gemfi or gemfi 1a pharma or lipidil or lofibra or lipison).mp.
- 33 (lipofo or lipogen or lipoite or lipozid or lipozil or lipur).mp.
- 34 (litarek or locholes or lipid or lopizid or mariston or med-gemfibrozil).mp.
- 35 (norpid or novo-gemfibrozil or pilder or pms-gemfibrozil or poli-fibrozil).mp.
- 36 (polyxit or recozil or riva-gemfibrozil or synbrozil or taborcil).mp.
- 37 (tentroc or tiba or trialmin or fenofibrate or procetofen).mp.
- 38 49562-28-9.rn. or apofen.mp. or ankebin.mp. or apo-fenofibrate.mp. or apo-feno-micro.mp.
- 39 (catalip or cil or controlip or dom-fenofibrate or durafenat).mp.
- 40 (elasterin or fegenor or fenobeta or fenobrate or fenogal or fenofanton or phenofibrate).mp.
- 41 (fenolip or fenotard or feno-micro-200 or fulcro or gen-fenofibrate).mp.
- 42 lexemin.mp. or (1f-179 or 1fl79).mp,rn. or (1f-178 or 1fl78).mp,rn. or lipanon.mp. or lipanthyl.mp.

- 43 (lipantil or liparison or lipcor or lipidax or lipidil or lipil).mp.
- 44 (lipirex or lipoclar or lipofene or lipofen or lipo red or liposit).mp.
- 45 (lipovas or lipsin or livesan or nolipax or normalip or procetofene).mp.
- 46 (qualecon or scleril or procetoken or protolipan or secalip).mp.
- 47 (supralip or tilene or tricolor or volutine or tocofibrate).mp. or 50465-39-9.rn.
- 48 (transferal or theofibrate or etofylline clofibrate).mp. or 54504-70-0.rn.
- 49 duolip.mp. or (ml-1024 or ml1024).mp,rn. or theofol.mp.
- 50 or/1-49
- 51 exp Cardiovascular Diseases/
- 52 exp Cerebrovascular Disorders/
- 53 coronary.mp.
- 54 (heart adj (disease\$ or attack\$)).mp.
- 55 (coronary adj (disease\$ or event\$)).mp.
- 56 (cerebrovascular\$ or cardioasc\$).mp.
- 57 (myocardial adj (infarct\$ or re?vascular\$ or ischemi\$)).mp.
- 58 (stroke\$ or mortal\$).mp.
- 59 (morbid adj5 (heart\$ or cardiovascula\$ or coronary\$ or isch?em\$ or myocard\$)).mp.
- 60 (cardio\$ or cardia\$ or heart\$ or coronary\$ or angina\$ or ventric\$ or myocard\$ or pericard\$ isch?em\$).tw.
- 61 (apoplexy or (brain adj2 accident\$)).tw.
- 62 ((brain\$ or cerebral or lacunar) adj2 infarct\$).tw.
- 63 exp Hypertension/
- 64 (hypertensi\$ or peripheral arter\$ disease\$).tw.
- 65 peripheral arter\$ disease\$.tw.
- 66 ((high or increased or elevated) adj2 blood pressure).tw.
- 67 exp Hyperlipidemias/
- 68 (hyperlipid\$ or hyperlip?emia\$ or hypercholesterol\$ or hypercholester?emia\$ or hyperlipoprotein?emia\$ or hypertriglycerid?emia\$).tw.
- 69 (emboli\$ or arrhythmi\$ or thrombo\$ or atrial fibrillat\$ or tachycardi\$ or endocardi\$ or (sick adj sinus)).tw.
- 70 or/51-69
- 71 random\$.tw.
- 72 factorial\$.tw.
- 73 crossover\$.tw.
- 74 cross over\$.tw.
- 75 cross-over\$.tw.
- 76 placebo\$.tw.
- 77 (doubl\$ adj blind\$).tw.

78 (singl\$ adj blind\$).tw.

79 assign\$.tw.

80 allocat\$.tw.

81 volunteer\$.tw.

82 crossover procedure/

83 double blind procedure/

84 randomized controlled trial/

85 single blind procedure/

86 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85

87 (animal/ or nonhuman/) not human/

88 86 not 87

89 50 and 70 and 88

CINAHL

RCT filter adapted from Cochrane RCT filter.

S75 S73 and S74

S74 (random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

S73 S53 and S72

S72 S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71

S71 (emboli* or arrhythmi* or thrombo* or atrial fibrillat* or tachycardi* or endocardi* or (sick next sinus))

S70 (hyperlipid* or hyperlip?emia* or hypercholesterol* or hypercholester?emia* or hyperlipoprotein?emia* or hypertriglycerid?emia*)

S69 (MH "Hyperlipidemia+")

S68 ((high or increased or elevated) N2 blood pressure)

S67 (hypertensi* or (peripheral arter* disease*))

S66 (MH "Hypertension+")

S65 ((brain* or cerebral or lacunar) N2 infarct*)

S64 (apoplexy or (brain N2 accident*))

S63 (cardio* or cardia* or heart* or coronary* or angina* or ventric* or myocard* or pericard* or isch?em*)

S62 (morbidity N5 (heart* or cardiovascula* or coronary* or isch?em* or myocard*))

S61 (stroke* or mortal*)

S60 "myocardial infarct*" or "myocardial re?vascular*" or "myocardial ischemi*"

S59 (cerebrovascular* or cardioasc*)

S58 "coronary disease*" or "coronary event"

S57 "heart disease*" or "heart attack"

S56 (coronary)

S55 (MH "Cerebrovascular Disorders+")

Fibrates for primary prevention of cardiovascular disease events (Review)

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S54 (MH "Cardiovascular Diseases+")

S53 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52

S52 (duolip or (ml-1024 or ml1024) or theofol)

S51 (transferal or theofibrate or etofylline clofibrate) or 54504-70-0

S50 (supralip or tilene or tricolor or volutine or tocofibrate) or 50465-39-9

S49 (qualecon or scleril or procetoken or protolipan or secalap)

S48 (lipovas or lipsin or livesan or nolipax or normalip or procetofene)

S47 (lipirex or lipoclar or lipofene or lipofen or lipo red or liposit)

S46 (lipantil or liparison or lipcor or lipidax or lipidil or lipil)

S45 (lexemin or (1f-179 or 1fl79) or (1f-178 or 1fl78) or lipanon or lipanthyl)

S44 (fenolip or fenotard or feno-micro-200 or fulcro or gen-fenofibrate)

S43 (elasterin or fegenor or fenobeta or fenobrate or fenogal or fenofanton or phenofibrate)

S42 (catalip or cil or controlip or dom-fenofibrate or durafenat)

S41 (49562-28-9 or apofen or ankebin or apo-fenofibrate or apo-feno-micro)

S40 (tentroc or tiba or trialmin or fenofibrate or procetofen)

S39 (norpid or novo-gemfibrozil or pilder or pms-gemfibrozil or poli-fibrozil)

S38 (litarek or locholes or lipid or lopizid or mariston or med-gemfibrozil)

S37 (gozid or hidil or ipolipid or jezil or lipazil or lipidys or lipox gemfi or gemfi 1a pharma or lipidil or lofibra or lipison)

S36 (gemnpid or gen-gemfibrozil or nugemfibrozil or genlip or genozil or genozil)

S35 (gemfibril or gemfibromax or gemhexal or gemizol or gemlipid)

S34 (dropid or elmogan or emfib or fibrocit or fibros or gemcor)

S33 (bolutol or (ci-719 or ci719) or decrelip or deopid or dom-gemfibrozil)

S32 (xyduril or gemfibrozil) or 25812-30-0 or apo-gemfibrozil or ausgem

S31 (s trat os or stratos or sklero-tablinene or sklerolip or ticlobran)

S30 (regulipid or sinteriod or serotoninex or sklerepmexe or skleromexe)

S29 (liprinal or miscleron or misclerone or neo-atromid or athromidin or normet)

S28 (liaptene or lipavil or lipavlon or lipilim or lipofacton or lipomid)

S27 (colebron or col or geromid or hyclorate). or (ici-28257 or ici28257 or ici55695 or ici-55695 or nsc1149 or nsc-1149)

S26 (clofibrat or clofibratum or clofirem or clofi or clofibrin or clofibrinic acid or clofinit or clofenapate or methylclofenapate)

S25 (bioscleran or cartagyl or claripex or clobren or clofibril)

S24 (atromidin or atromid-s) or (ay-61123 or ay61123)

S23 (arteriosan or artevil or ateculon or ateriosan or atheroprnt)

S22 (anparton or anti-lipide-ratiopharm or apolan or arterioflexin)

S21 (clofibrate or 637-07-0 or 882-09-7 or abibrate or amotril)

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S20 (hyperlipen or cirpol or lipanor or modalim or oroxadin) or (win-35833 or win35833)

S19 (zafibral or zimbacol or ciprofibrate or 52214-84-3 or bi-lipanor)

S18 (reducterol or regadrin b or sklerofibrat or solibay or wayfrato)

S17 (lipox or norlip or pms-bezafibrate or polyzalip or redalip)

S16 (hadiel or klestran or (lo-44 or lo44) or liparol or lipitrol or lipocin)

S15 (bionolip or cedur or colser or difaterol or durabezur or eulitop)

S14 (bezamerck or bezamil or beza-puren or bezapuren or bezastad or bezatol)

S13 (bezafisal or bezagen or beza-lande or bezalande or bezalex or bezalip)

S12 (befibrat or befizal or beza or bezabeta or bezacur or bezafibratum)

S11 (41859-67-0 or asufibrat or azufibrat or (bm-15075 or bm15075))

S10 (bezafibrate or clofibrate)

S9 (MH "Fenofibrate")

S8 (fenofibrate)

S7 Clofibrate

S6 Bezafibrate

S5 (ciprofibrat*)

S4 (MH "Gemfibrozil")

S3 (gemfibrozil or gemfibrocil)

S2 (MH "Clofibrilic Acid+")

S1 (fibrate* or fibrilic acid*)

Web of Science (CPCI-S and SCI-Expanded)

RCT filter adapted from Cochrane RCT filter.

31 #30 AND #29

30 TS=((random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*))

29 #28 AND #21

28 #27 OR #26 OR #25 OR #24 OR #23 OR #22

27 TS((((high or increased or elevated) near/2 "blood pressure") or (hyperlipid* or hyperlip?emia* or hypercholesterol* or hypercholester?emia* or hyperlipoprotein?emia* or hypertriglycerid?emia*) or (emboli* or arrhythmi* or thrombo* or atrial fibrillat* or tachycardi* or endocardi* or ("sick sinus"))))

26 TS((((apoplexy or (brain near/2 accident*)) or ((brain* or cerebral or lacunar) near/2 infarct*) or (hypertensi* or (peripheral arter* disease*)))))

25 TS=((cardio* or cardia* or heart* or coronary* or angina* or ventric* or myocard* or pericard* or isch?em*))

24 TS(("myocardial infarct*" or "myocardial re?vascular*" or "myocardial ischemi*" or stroke* or mortal* or (morbid near/5 (heart* or cardiovascula* or coronary* or isch?em* or myocard*))))

23 TS(("myocardial infarct*" or "myocardial re?vascular*" or "myocardial ischemi*"))

22 TS=((coronary) or ("heart disease" or "heart attack") or ("coronary disease*" or "coronary event*") or (cerebrovascular* or cardiovasc*))

21 #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

20 TS=((supralip or tilene or tricar or volutine or tocofibrate) or 50465-39-9 or (transferal or theofibrate or etofylline clofibrate) or 54504-70-0 or (duolip or (ml-1024 or ml1024) or theofol))

19 TS=((lipirex or lipoclar or lipofene or lipofen or lipo red or liposit) or (lipovas or lipsin or livesan or nolipax or normalip or procetofene) or (qualecon or scleril or procetoken or protolipan or secalap))

18 TS=((fenolip or fenotard or feno-micro-200 or fulcro or gen-fenofibrate) or (lexemin or (1f-179 or 1fl79) or (1f-178 or 1fl78) or lipanon or lipanthyl) or (lipantil or liparison or lipcor or lipidax or lipidil or lipil))

17 TS=((49562-28-9 or apofen or ankebin or apo-fenofibrate or apo-feno-micro) or (catalip or cil or controlip or dom-fenofibrate or durafenat) or (elasterin or fegenor or fenobeta or fenobrate or fenogal or fenofanton or phenofibrate))

16 TS=((litarek or locholes or lipid or lopizid or mariston or med-gemfibrozil) or (norpil or novo-gemfibrozil or pilder or pms-gemfibrozil or poli-fibrozil) or (tentroc or tiba or trialmin or fenofibrate or procetofen))

15 TS=((gemfibril or gemfibromax or gemhexal or gemizol or gemlipid) or (gemnpil or gen-gemfibrozil or nugemfibrozil or genlip or genozil or genozil) or (gozid or hidil or ipolipid or jezil or lipazil or lipidys or lipox gemfi or gemfi 1a pharma or lipidil or lofibra or lipison))

14 TS=((bolutol or (ci-719 or ci719) or decrelip or deopid or dom-gemfibrozil) or (xyduril or gemfibrozil) or (25812-30-0 or apo-gemfibrozil or ausgem) or (dropid or elmogan or emfib or fibrocit or fibros or gemcor))

13 TS=((regulipil or sinteriod or serotinex or sklerepmexe or skleromexe) or (s trat os or stratos or sklero-tablinene or sklerolip or ticlobran))

12 TS=((liaptene or lipavil or lipavlon or lipilim or lipofacton or lipomid) or (liprinal or miscleron or misclerone or neo-atromid or athromidin or normet))

11 TS=((colebron or col or geromid or hyclorate) or (ici-28257 or ici28257 or ici55695 or ici-55695 or nsc1149 or nsc-1149))

10 TS=((bioscleran or cartagyl or claripex or clobren or clofibril) or (clofibrat or clofibratum or clofirem or clofi or clofibrin or clofibrinic acid or clofinit or clofenapate or methylclofenapate))

9 TS=((anparton or anti-lipide-ratiopharm or apolan or arterioflexin) or (arteriosan or artevil or ateculon or ateriosan or atheropront) or (atromidin or atromid-s) or (ay-61123 or ay61123))

8 TS=((hyperlipen or cirpol or lipanor or modalim or oroxadin) or (win-35833 or win35833) or (clofibrate or 637-07-0 or 882-09-7 or abitrate or amotril))

7 TS=((reducerol or regadrin b or sklerofibrat or solibay or wayfrato) or (zafibril or zimbacol or ciprofibrate or 52214-84-3 or bi-lipanol))

6 TS=((lipox or norlip or pms-bezafibrate or polyzalip or redalip) or (reducerol or regadrin b or sklerofibrat or solibay or wayfrato))

5 TS=((bionolip or cedur or colser or difaterol or durabezur or eulitop) or (hadiel or klestran or (lo-44 or lo44) or liparol or lipitrol or lipocin))

4 TS=((bionolip or cedur or colser or difaterol or durabezur or eulitop) or (hadiel or klestran or (lo-44 or lo44) or liparol or lipitrol or lipocin))

3 TS=((bezafisal or bezagen or beza-lande or bezalande or bezalex or bezalip) or (bezamerck or bezamil or beza-puren or bezapuren or bezastad or bezatol))

2 TS=((41859-67-0 or asufibrat or azufibrat or (bm-15075 or bm15075)) or (befibrat or befizal or beza or bezabeta or bezacur or bezafibratum))

1 TS=((fibrate* or fibric acid*) or (gemfibrozil or gemfibrocil) or (ciprofibrat*) or (fenofibrate) or (bezafibrate or clofibrate))

WHO International Clinical Trial Registry Platform (ICTRP)

"hyperlipid* OR hypercholester* " in the condition and "fenofibrate OR clofibrate OR gemfibrozil OR bezafibrate OR ciprofibrate" in the intervention

ClinicalTrials.gov

fenofibrate OR clofibrate OR gemfibrozil OR bezafibrate OR ciprofibrate

Current Controlled Trials

fenofibrate as intervention

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clofibrate as intervention
gemfibrozil as intervention
bezafibrate as intervention
ciprofibrate as intervention

ISRCTN.org

Advanced search:

fenofibrate as intervention
clofibrate as intervention
gemfibrozil as intervention
bezafibrate as intervention
ciprofibrate as intervention

WHAT'S NEW

Date	Event	Description
9 March 2017	Amended	Minor adjustments to analyses 1.1 and 1.2 - totals suppressed

CONTRIBUTIONS OF AUTHORS

- TJ screened titles and abstracts and full-texts, extracted data, assessed risk of bias, conducted part of the analysis, interpreted the results, and drafted the manuscript text.
- AJN developed the protocol, screened titles and abstracts and full-texts, extracted data, assessed risk of bias, prepared the 'Summary of findings' table, interpreted the results, and drafted the manuscript text.
- SS extracted data, conducted part of the analysis, and drafted the manuscript text.
- IFG developed the protocol, screened titles and abstracts, and critically reviewed the manuscript.
- MB developed the protocol, screened titles and abstracts, arbitrated full-texts, assessed risk of bias, prepared the 'Summary of findings' table, interpreted the results, drafted the manuscript text, and is guarantor of this Cochrane Review.

All authors approved the final version of the manuscript.

DECLARATIONS OF INTEREST

- TJ has no conflict of interest to declare.
- AJN has no conflict of interest to declare.
- SS has no conflict of interest to declare.
- IFG has no conflict of interest to declare.
- MB has no conflict of interest to declare.

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Internal sources

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External sources

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A competitive grant

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The aim of this Cochrane Review and meta-analysis was to evaluate the benefits and harms of fibrate therapy in the primary prevention of cardiovascular disease (CVD) events. We changed our primary outcome of major CVD events from the protocol (CVD death, non-fatal myocardial infarction, non-fatal stroke, and revascularisation procedures such as bypass grafts and angioplasty); due to scarce reporting of outcome data on bypass grafts and angioplasty, we removed revascularisation procedures from the review.

We excluded clofibrate as an intervention, because it is no longer in use. In 1979, clofibrate was withdrawn in some countries and its approval indications were severely restricted in many others due to adverse effects ([United Nations 2003](#); [WHO 1978](#)).

We extended the definition of the adverse effects of 'progression to albuminuria' to include 'development of albuminuria', the extended definition additionally included 'progression from microalbuminuria to macroalbuminuria'.

We created a 'Summary of findings' table using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence ([GRADE Handbook 2013](#)) following recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Four of the six included trials exclusively included individuals with type 2 diabetes mellitus ([ACCORD 2010](#); [Emmerich 2009](#); [FIELD 2005](#); [SENDCAP 1998](#)); [FIRST 2014](#) included 47.5% of individuals suffering from diabetes type 2 and [Frick 1987](#) included 2% of individuals suffering from diabetes mellitus type 2. We therefore did not conduct an originally planned subgroup analysis of trials with diabetic patients versus trials with patients not suffering from diabetes.

We did not collect data on change of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) or triglycerides at baseline and follow-up, because these changes were inconsistently reported in included trials. In addition, as only six trials were eligible for our meta-analysis, this did not allow for any meaningful meta-regression analyses of changes in lipid levels on clinical outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Primary Prevention [standards]; Atorvastatin [therapeutic use]; Bezafibrate [therapeutic use]; Cardiovascular Diseases [mortality] [*prevention & control]; Clofibric Acid [analogs & derivatives] [therapeutic use]; Fenofibrate [therapeutic use]; Gemfibrozil [therapeutic use]; Hypolipidemic Agents [adverse effects] [*therapeutic use]; Myocardial Infarction [epidemiology] [mortality]; Simvastatin [therapeutic use]; Stroke [epidemiology] [mortality]

MeSH check words

Humans; Middle Aged