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[Intervention Review]

Fibrates for secondary prevention of cardiovascular disease and stroke

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ABSTRACT

Background

Fibrates are a class of drugs characterised by mainly lowering high triglyceride, raising high-density lipoprotein (HDL) cholesterol, and lowering the small dense fraction of low-density lipoprotein (LDL) cholesterol. Their efficacy for secondary prevention of serious vascular events is unclear, and to date no systematic review focusing on secondary prevention has been undertaken.

Objectives

To assess the efficacy and safety of fibrates for the prevention of serious vascular events in people with previous cardiovascular disease (CVD), including coronary heart disease and stroke.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 9, 2014) on the Cochrane Library, MEDLINE (OVID, 1946 to October week 1 2014), EMBASE (OVID, 1980 to 2014 week 41), the China Biological Medicine Database (CBM) (1978 to 2014), the Chinese National Knowledge Infrastructure (CNKI) (1979 to 2014), Chinese Science and Technique Journals Database (VIP) (1989 to 2014). We also searched other resources, such as ongoing trials registers and databases of conference abstracts, to identify further published, unpublished, and ongoing studies.

Selection criteria

We included randomised controlled trials (RCTs) in which a fibrate (for example gemfibrozil, fenofibrate) was compared with placebo or no treatment. We excluded RCTs with only laboratory outcomes. We also excluded trials comparing two different fibrates without a placebo or no-treatment control.

Data collection and analysis

Two review authors independently selected trials for inclusion, assessed risk of bias, and extracted the data. We contacted authors of trials for missing data.

Main results

We included 13 trials involving a total of 16,112 participants. Eleven trials recruited participants with history of coronary heart disease, two trials recruited participants with history of stroke, and one trial recruited participants with a mix of people with CVD. We judged overall risk of bias to be moderate. The meta-analysis (including all fibrate trials) showed evidence for a protective effect of fibrates primarily compared to placebo for the primary composite outcome of non-fatal stroke, non-fatal myocardial infarction (MI), and vascular death (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.83 to 0.94; participants = 16,064; studies = 12; I^2 = 45%, fixed effect). Fibrates were moderately effective for preventing MI occurrence (RR 0.86, 95% CI 0.80 to 0.93; participants = 13,942; studies = 10; I^2 = 24%, fixed effect). Fibrates were

not effective against all-cause mortality (RR 0.98, 95% CI 0.91 to 1.06; participants = 13,653; studies = 10; $I^2 = 23\%$), death from vascular causes (RR 0.95, 95% CI 0.86 to 1.05; participants = 13,653; studies = 10; $I^2 = 11\%$, fixed effect), and stroke events (RR 1.03, 95% CI 0.91 to 1.16; participants = 11,719; studies = 6; $I^2 = 11\%$, fixed effect). Excluding clofibrate trials, as the use of clofibrate was discontinued in 2002 due to safety concerns, the remaining class of fibrates were no longer effective in preventing the primary composite outcome (RR 0.90, 95% CI 0.79 to 1.03; participants = 10,320; studies = 7; $I^2 = 50\%$, random effects). However, without clofibrate data, fibrates remained effective in preventing MI (RR 0.85, 95% CI 0.76 to 0.94; participants = 8304; studies = 6; $I^2 = 47\%$, fixed effect). There was no increase in adverse events with fibrates compared to control. Subgroup analyses showed the benefit of fibrates on the primary composite outcome to be consistent irrespective of age, gender, and diabetes mellitus.

Authors' conclusions

Moderate evidence showed that the fibrate class can be effective in the secondary prevention of composite outcome of non-fatal stroke, non-fatal MI, and vascular death. However, this beneficial effect relies on the inclusion of clofibrate data, a drug that was discontinued in 2002 due to its unacceptably large adverse effects. Further trials of the use of fibrates in populations with previous stroke and also against a background treatment with statins (standard of care) are required.

PLAIN LANGUAGE SUMMARY

Fibrates for secondary prevention of cardiovascular disease and stroke

Review question

The aim of this study was to assess the effect of fibrates for the prevention of major events including heart attacks, strokes, and circulatory disease death in people with existing circulatory disease.

Background

Fibrates have been used for many years as a treatment to prevent further heart attacks and strokes in people who already have disease of their circulatory system. Fibrates are a class of drugs that work by positively influencing fats in the blood, that is lowering triglyceride, raising high-density lipoprotein ('good') cholesterol and lowering the small dense fraction of low-density lipoprotein ('bad') cholesterol. The drug class includes clofibrate, gemfibrozil, fenofibrate, bezafibrate, and ciprofibrate. Successful adjustment of the blood fats in people with disease of their circulatory system could mean these individuals are less likely to have heart attacks, stroke, and die from their circulatory disease. There is currently no clear evidence for benefit of fibrates in such people.

Study characteristics

The duration of fibrates ranged from 12 months to 8 years.

Key results

We included 13 trials in this review with a total of 16,112 participants with a history of coronary heart disease or stroke. This review includes evidence identified up to October 2014.

Our analysis showed that when compared primarily to placebo, fibrates can be effective for prevention of composite outcome of non-fatal stroke, non-fatal heart attack (myocardial infarction), and death due to circulatory disease. However, this beneficial effect relies on the inclusion on data from clofibrates, a drug that was discontinued in 2002 because of safety concerns. In other words, there is no good evidence to support the use of currently available fibrates in the prevention of future heart attacks, strokes, and circulatory disease death in people with existing circulatory disease.

Quality of the evidence

In combination with clofibrate data, quality of evidence was moderate for the composite (non-fatal stroke, non-fatal myocardial infarction (MI), and vascular death) and MI (non-fatal or fatal) outcomes and low for stroke (ischaemic or haemorrhagic, non-fatal or fatal) and death from vascular or any cause during the treatment and scheduled follow-up period. The quality of evidence without clofibrate data was moderate for MI (non-fatal or fatal) outcome and low for the composite (non-fatal stroke, non-fatal MI, and vascular death), stroke (ischaemic or haemorrhagic, non-fatal or fatal), and death from vascular or any cause outcomes during the treatment and scheduled follow-up period.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Fibrates compared with control for secondary prevention of cardiovascular disease and stroke

Fibrates compared with control for secondary prevention of cardiovascular disease and stroke

Patient or population: People with previous clinical manifestations of cardiovascular disease, transient ischaemic attack, or stroke

Settings: Secondary prevention

Intervention: Fibrates

Comparison: Without fibrates

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Fibrates				
Composite outcome of non-fatal stroke, non-fatal myocardial infarction, and vascular death	Study population		RR 0.88 (0.83 to 0.94)	16,064 (12 RCTs)	⊕⊕⊕⊖ moderate ¹	
	233 per 1000	205 per 1000 (194 to 219)				
	Moderate-risk population					
	261 per 1000	230 per 1000 (217 to 246)				
Death from any cause during the treatment and scheduled follow-up period	Study population		RR 0.98 (0.91 to 1.06)	13,653 (10 RCTs)	⊕⊕⊖⊖ low ^{1,2}	
	185 per 1000	182 per 1000 (169 to 196)				
	Moderate-risk population					
	219 per 1000	215 per 1000 (199 to 232)				
Death from vascular causes during the treatment and scheduled follow-up period	Study population		RR 0.95 (0.86 to 1.05)	13,653 (10 RCTs)	⊕⊕⊖⊖ low ^{1,2}	
	132 per 1000	126 per 1000 (114 to 139)				
	Moderate-risk population					

	142 per 1000	135 per 1000 (122 to 149)			
Myocardial infarction (non-fatal or fatal) during the treatment and scheduled follow-up period	Study population		RR 0.86 (0.80 to 0.93)	13,942 (10 RCTs)	⊕⊕⊕⊖ moderate ¹
	190 per 1000	163 per 1000 (152 to 177)			
	Moderate-risk population				
	227 per 1000	195 per 1000 (182 to 211)			
Stroke (ischaemic or haemorrhagic, non-fatal or fatal) during the treatment and scheduled follow-up period	Study population		RR 1.03 (0.91 to 1.16)	11,719 (6 RCTs)	⊕⊕⊖⊖ low ^{1,2}
	83 per 1000	86 per 1000 (76 to 96)			
	Moderate-risk population				
	61 per 1000	63 per 1000 (56 to 71)			

*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; 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.

¹More than 75% of included studies did not report the details of randomisation, and four trials withdrawn or loss to follow-up less than 20%.

²Confidence interval overlaps no effect.

Summary of findings 2. Fibrates compared with control for secondary prevention of cardiovascular disease and stroke - without clofibrate data

Fibrates compared with control for secondary prevention of cardiovascular disease and stroke - without clofibrate data

Patient or population: People with previous clinical manifestations of cardiovascular disease, transient ischaemic attack, or stroke

Settings: Secondary prevention

Intervention: Fibrates
Comparison: Without fibrates

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control in cardiovascular disease and stroke	Fibrates				
Composite outcome of non-fatal stroke, non-fatal myocardial infarction, and vascular death without clofibrate	Study population		RR 0.9 (0.79 to 1.03)	10,320 (7 studies)	⊕⊕⊖⊖ low ^{1,2}	
	204 per 1000	183 per 1000 (161 to 210)				
	Moderate-risk population					
	204 per 1000	184 per 1000 (161 to 210)				
Death from any cause during the treatment and scheduled follow-up period without clofibrate	Study population		RR 1.01 (0.91 to 1.12)	7909 (5 studies)	⊕⊕⊖⊖ low ^{1,2}	
	146 per 1000	148 per 1000 (133 to 164)				
	Moderate-risk population					
	99 per 1000	100 per 1000 (90 to 111)				
Death from vascular causes during the treatment and scheduled follow-up period without clofibrate	Study population		RR 0.98 (0.84 to 1.15)	7909 (5 studies)	⊕⊕⊖⊖ low ^{1,2}	
	73 per 1000	71 per 1000 (61 to 84)				
	Moderate-risk population					
	74 per 1000	73 per 1000 (62 to 85)				
Myocardial infarction (non-fatal or fatal) during the treatment and scheduled follow-up period without clofibrate	Study population		RR 0.85 (0.76 to 0.94)	8304 (6 studies)	⊕⊕⊕⊖ moderate ¹	
	149 per 1000	126 per 1000				

	(113 to 140)				
	Moderate-risk population				
	132 per 1000	112 per 1000 (100 to 124)			
Stroke (ischaemic or haemorrhagic, non-fatal or fatal) during the treatment and scheduled follow-up period without clofibrate	Study population		RR 0.94 (0.78 to 1.14)	7189 (3 studies)	⊕⊕⊕⊕ low ^{1,2}
	56 per 1000	53 per 1000 (44 to 64)			
	Moderate-risk population				
	60 per 1000	56 per 1000 (47 to 68)			

*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; **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.

¹Studies did not report the details of randomisation.

²Confidence interval overlaps no effect.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels, including hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, and rheumatic heart disease (WHO 2010). CVD remains the leading cause of death in the world, claiming an estimated 17.5 million lives a year in 2012, representing 31% of all global deaths (WHO 2014). Although mortality from CVD has shown a downward trend in high-income countries, the overall burden continues to increase in high-, middle-, and low-income countries (Roger 2011). In recent decades, over three-quarters of CVD deaths have taken place in low- and middle-income countries (WHO 2015). Out of the total of 17.5 million CVD deaths, about 7.4 million deaths are attributed to coronary heart disease, and 6.7 million deaths are attributed to stroke (WHO 2014). CVD is a major public health challenge worldwide. Effective strategies for the prevention of CVD are imperative.

Description of the intervention

Fibrates have been available for clinical use for many years (Brown 2007). They include clofibrate, gemfibrozil, fenofibrate, bezafibrate, and ciprofibrate. Clofibrate is not commercially available due to little benefit and excess in total mortality (Khouri 2011). Fibrates are a class of drugs characterised by mainly lowering high triglyceride (TG), raising high-density lipoprotein (HDL) cholesterol, and lowering the small dense fraction of low-density lipoprotein (LDL) cholesterol (Fazio 2004). Generally, their most prominent effect is lowering TG (Fazio 2004). Except for lowering the small dense fraction of LDL, their effects on LDL cholesterol vary, depending largely on the patient's degree of hypertriglyceridaemia (Caslake 1993; de Graaf 1993; Tikkanen 1998). Epidemiological studies and meta-analyses have shown that low HDL cholesterol and high TG are significantly associated with increased risk of CVD (Castelli 1986; Castelli 1992; Gordon 1977; Hokanson 1996; Miller 1977; Stampfer 1991). In addition, CVD risk remains considerable in spite of statin therapy (Khouri 2011). Statins tend to have less effects on TG and HDL cholesterol. Therefore, fibrates seem to be effective for prevention of CVD, especially for people with low HDL cholesterol and high TG.

How the intervention might work

Fibrates have been recognised to influence plasma lipids and lipoproteins by regulating the expression of several genes involved in lipoprotein metabolism (Staels 1992). They act via a member of a family of nuclear hormone receptors called the peroxisome proliferator-activated receptors (PPARs). Three PPAR genes have been described (α , δ , and γ) (Pineda Torra 1999). PPAR α is predominantly expressed in tissues that metabolise fatty acids, such as liver, kidney, and muscle (Staels 1998). It transmits signals from lipid-soluble factors, such as fatty acids, hormones, and vitamins, to genes in the nucleus by binding to DNA within specific response elements. The molecules of fibrates structurally resemble short-chain fatty acids, and so they are ligands for PPAR α . Once fibrates bind to PPAR α , they will form a complex binding to specific DNA sites and then lead to gene expression (Fazio 2004; Staels 1998). In this way, fibrates reduce serum TG and raise HDL cholesterol levels. The usage of fibrates were usually oral in clinical trials and clinical practice, and their dosage varied (Acheson

1962; Derosa 2004). Regarding potential side effects, previous trial evidence indicates that fibrates may be associated with myopathy, decreased creatinine clearance and estimated glomerular filtration rate, increased serum creatinine and homocysteine (EASCP 2011).

Why it is important to do this review

Although fibrates have been used for decades, evidence demonstrating their efficacy for prevention of serious vascular events is unclear (AHA/ASA 2010; Nissen 2011). Recently, a meta-analysis found that fibrates can reduce the risk of major CVD events predominantly by prevention of coronary events (Jun 2010). Despite this, there is still much uncertainty about their separate role in the primary and secondary prevention of CVD. A systematic review on fibrates for primary prevention of CVD is currently being conducted, and the protocol has been published in Cochrane Library (Nordmann 2012). As for secondary prevention, several trials undertaken in such countries as the United States, Sweden, Israel, Australia, New Zealand, and Finland show inconsistent results. Results from the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) study showed that bezafibrate could reduce coronary events in young survivors of myocardial infarction (MI) and slow the progression of focal coronary atherosclerosis (Ericsson 1996). However, the Bezafibrate Infarction Prevention (BIP) study did not find a statistically significant reduction in coronary heart disease (defined as fatal or non-fatal coronary events) (Anonymous 2000). In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) study gemfibrozil showed a 22% relative risk reduction of the combined endpoint of non-fatal MI or death from coronary causes and no increase in overall or non-CVD mortality (VA-HIT 2001). Furthermore, there was a 25% relative risk reduction in the incidence of new strokes and a 59% reduction in transient ischaemic attacks (TIA) (VA-HIT 2001). In addition, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found that fenofibrate did not reduce coronary heart disease events in the subgroup of participants with previous CVD (FIELD 2005; Scott 2009). Results from individual monotherapy outcomes trials have been variable (EASCP 2011), and to date no attempt to evaluate the overall efficacy of fibrates for secondary prevention using a systematic approach has been made despite many existing reviews (AHA/ASA 2010; Khouri 2011; Nissen 2011). Despite fibrates appearing to be inexpensive, there is little data on economic effectiveness. We therefore sought to perform a systematic review of randomised controlled trials (RCTs) comparing fibrates with control in people with a history of CVD (including coronary heart disease and stroke) to determine whether there is any clear evidence of their benefit in terms of major CVD outcomes.

OBJECTIVES

To assess the efficacy and safety of fibrates for the prevention of serious vascular events in people with previous cardiovascular disease (CVD), including coronary heart disease and stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs in which a fibrate (for example gemfibrozil, fenofibrate) was compared with placebo or no-treatment arm, regardless of the duration of treatment and follow-up. We

considered any RCTs with at least one clinical outcome for this review. We excluded RCTs with only laboratory outcomes. We also excluded trials comparing two different fibrates without a placebo or no-treatment control.

Types of participants

Eligible RCTs included participants at high recurrent risk of CVD events and stroke due to previous clinical manifestations of CVD (that is coronary heart disease or stroke), irrespective of prior lipid levels and prior lipid-modifying treatment or diet. We did not include trials with participants with other conditions such as hypertension or diabetes but without established CVD. We considered both genders and all ages.

Types of interventions

An eligible intervention was a fibrate (any type and dosage) versus placebo or no treatment. We accepted drug treatments and other interventions provided they were given to both fibrate and comparator arms. Adjuvant treatment with one additional drug if a participant developed excessively abnormal lipids during the trial was acceptable. We included trials if statins were given to both arms. We excluded trials comparing fibrates with statins.

Types of outcome measures

We aimed to extract from each trial the number of participants randomly allocated to each intervention group to allow an intention-to-treat analysis. In both groups, we considered the number of participants that had one of the outcomes. We included outcomes if they occurred within the follow-up treatment period, regardless of whether participants were taking their allocated treatment.

Primary outcomes

The primary outcome was the composite outcome of non-fatal stroke (ischaemic or hemorrhagic stroke), non-fatal MI, and vascular death. We included each participant only once in this composite outcome (for example if a participant had a non-fatal event followed by a fatal event, it was counted as a fatal event only).

Secondary outcomes

1. The separate outcomes of stroke (ischaemic or haemorrhagic, non-fatal or fatal), MI (non-fatal or fatal), vascular death, and death from all causes:
 - a. Stroke (ischaemic or haemorrhagic, non-fatal or fatal) during the treatment and scheduled follow-up period. We took the definition of non-fatal stroke from each particular trial (rather than impose a set duration of survival following the stroke).
 - b. MI (non-fatal or fatal) during the treatment and scheduled follow-up period. We took the definition of non-fatal MI from each particular trial (rather than impose a set duration of survival following the MI).
 - c. Death from vascular causes during the treatment and scheduled follow-up period. We defined vascular causes as stroke or any complication of stroke (e.g. pneumonia, pulmonary embolism, etc), coronary heart disease (e.g. MI, congestive cardiac failure, sudden death), peripheral vascular disease, haemorrhage (intracranial or extracranial), and other vascular cause.
 - d. Death from any cause during the treatment and scheduled follow-up period.

2. Change in plasma levels of total cholesterol concentration, TG, HDL-C, and LDL-C.
3. Quality of life.
4. Adverse events considered included: myopathy, worsening of diabetes control, increased serum creatinine, altered liver function tests, and altered estimated glomerular filtration rate. We evaluated the number of participants developing at least one adverse event listed above.
5. Costs.

Search methods for identification of studies

Electronic searches

We searched the following sources in order to identify trials:

- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 9, 2014) on the Cochrane Library on 13 October 2014;
- Database of Abstracts of Reviews of Effects (DARE; Issue 3, 2014) on the Cochrane Library on 13 October 2014;
- MEDLINE (OVID, 1946 to October week 1 2014) on 13 October 2014;
- EMBASE (OVID, 1980 to 2014 week 41) on 13 October 2014;
- Conference Proceedings Citation Index - Science (CPCI-S) on Web of Science Core Collection (Thomson Reuters, 1990 to 10 October 2014) on 13 October 2014;
- The China Biological Medicine Database (CBM) (1978 to 13 October 2014);
- The Chinese National Knowledge Infrastructure (CNKI) (1979 to 13 October 2014);
- Chinese Science and Technique Journals Database (VIP) (1989 to 13 October 2014).

Appendix 1 lists the search strategies used. We applied the Cochrane sensitivity-maximising RCT filter to MEDLINE and adaptations of it to EMBASE and Web of Science (Lefebvre 2011).

Searching other resources

In an effort to identify further published, unpublished, and ongoing studies, we:

1. searched the following ongoing trials registers: WHO International Clinical Trial Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/>), last searched on 13 October 2014), ClinicalTrials.gov (<http://www.clinicaltrial.gov/>), last searched on 13 October 2014), Current Controlled Trials (<http://www.controlled-trials.com>), last searched on 13 October 2014);
2. searched all reference lists from relevant articles and reviews;
3. contacted experts in the field for information on ongoing and unpublished trials and study authors to obtain further data when necessary.

We searched for relevant trials in all languages and arranged translation of trial reports published in languages other than English.

Data collection and analysis

Selection of studies

We merged the search results using Endnote X1, and removed duplicate records of the same report. Two review authors (DW and

BL) independently examined each title and abstract to exclude obviously irrelevant reports. A third review author (ML) arbitrated if there were differences in opinion in the screening of titles and abstracts. We retrieved full text of the potentially relevant reports, and two review authors (DW and BL) independently examined the full texts for eligibility. We included duplicate publication just once. If duplicate publication was uncertain, we attempted to contact the authors of the reports. Disagreements about whether a study should be included were resolved by discussion. When the disagreement was due to a difference in interpretation, a third review author (ML) was invited to arbitrate. If we needed additional information to resolve disagreements, we attempted to obtain this information from the study investigators.

Data extraction and management

Two review authors (DW and BL) independently extracted data from each report on electronic data collection forms. We entered data into RevMan 5. We planned to collect data including details of the study, participants, interventions, and outcome results. We resolved any disagreements among the authors by discussion. A third review author (ML) arbitrated if there were differences in opinion. When necessary, we tried to contact study authors for additional information.

Assessment of risk of bias in included studies

We assessed the risk of bias in all included studies using the recommended tool by The Cochrane Collaboration as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We made judgements of 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias for the following seven domains:

1. random sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective outcome reporting (reporting bias);

We reported these judgements in the 'Risk of bias' table and then generated two figures: 'Risk of bias' graph (Figure 1) and 'Risk of bias' summary (Figure 2). Two review authors (DW and BL) independently performed the assessment of risk of bias in included studies. Any disagreements arising at any stage between authors were resolved through discussion or by involving a third review author (ML) when necessary.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2. 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)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
ACCORD 1999	+	+	+	+	+	+	+
Acheson 1962	?	?	+	+	+	?	?
BECAIT 1985	?	?	+	+	+	+	+
BIP 1990	?	?	+	+	+	+	+
CDP 1968	+	+	+	+	+	+	+
Derosa 2004	?	+	+	-	+	+	+
HHS Ancillary Study 1987	?	?	-	+	+	+	+
LEADER 1992	?	+	-	+	+	+	+
LOCAT 1997	?	?	?	+	+	?	?
Newcastle Trial 1964	?	+	+	+	+	?	+
Scottish Trials 1964	?	+	+	+	+	+	+
VACSA 1966	?	?	-	+	+	+	+
VA-HIT 1991	?	+	+	+	+	+	+

Measures of treatment effect

We expressed results for dichotomous outcomes as risk ratios with 95% confidence intervals, and expressed results for continuous outcomes as mean difference (if the same scale for each trial was available) or standardised mean difference (if different scales were used). We used RevMan 5.3 to analyse the data.

Unit of analysis issues

In cases of studies with non-standard designs (for example cross-over trials, cluster-randomised trials), we managed the data according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

If data were missing, we contacted the investigators for additional information. If data remained unavailable, we considered both best-case and worst-case scenarios.

Assessment of heterogeneity

We assessed statistical heterogeneity by using the I^2 statistic (Higgins 2011). If the I^2 was less than 30%, we considered heterogeneity as not important; 30% to 50% moderate; and more than 50% substantial. In cases where there was substantial statistical heterogeneity, we looked for the potential source(s) of the heterogeneity (that is clinical or methodological heterogeneity).

Assessment of reporting biases

We assessed small-study bias and potential publication bias for the primary composite outcome using a funnel plot (Egger 1997).

Data synthesis

We used RevMan 5.3 for all data entry and analysis. If I^2 statistic was less than 50%, we used fixed-effect meta-analysis. If heterogeneity was substantial, that is equal to or greater than 50%, we undertook both fixed-effect and random-effects meta-analysis, and we reported the most conservative result.

Subgroup analysis and investigation of heterogeneity

As clofibrate is no longer commercially available, we compared meta-analysis results including all fibrate trials versus excluding clofibrate trials for all outcomes.

If appropriate data were available, we intended to perform the following subgroup analysis:

- older (≥ 65 years) versus younger (< 65 years)
- male versus female
- with diabetes mellitus versus without diabetes mellitus
- coronary heart disease versus stroke
- placebo versus no treatment
- each fibrate versus placebo or no treatment
- different fibrate dosages (low and high dose)

Sensitivity analysis

We performed sensitivity analyses based on:

1. trials with low risk of bias (well-concealed randomisation and blinded outcome assessment) versus trials with high-risk of bias;
2. trials with follow-up of more than one year versus those with shorter follow-up;
3. older trials (before 1990) versus newer trials (since 1990);
4. trials in which fibrates were given in the presence of statin therapy (i.e. statin therapy was given to both treated and control groups) versus trials where no statin therapy was given;
5. re-analysing the data by including and excluding studies with assumed values to replace missing data.

RESULTS

Description of studies

Results of the search

We searched 8287 records after initial electronic searches and included 13 RCTs involving a total of 16,112 participants in the review (Acheson 1962; BECAIT 1985; BIP 1990; CDP 1968; Derosa 2004; LOCAT 1997; LEADER 1992; Newcastle Trial 1964; Scottish Trials 1964; VACSA 1966; HHS Ancillary Study 1987; VA-HIT 1991; ACCORD 1999). All included RCTs were of parallel-group design with participant-level allocation to study arms. See [Characteristics of included studies](#). We tried to identify further published, unpublished, and ongoing studies by searching other resources outlined in the [Methods](#) section. However, we identified no additional studies. For details, see [Figure 3](#).

Figure 3. Study flow diagram.

However, we did identify one ongoing study that is investigating the efficacy and safety of the addition of fenofibrate to atorvastatin compared with atorvastatin alone in mixed hypercholesterolaemic and coronary heart disease patients (CKD 2013). The study started in December 2013 and was expected to be completed in February 2015. We will seek to include this study when updating the review (see [Characteristics of ongoing studies](#)).

Included studies

One trial, [BECAIT 1985](#), recruited participants who were all younger than 45 years, and one trial reported insufficient information on age of participants ([Acheson 1962](#)). In the remaining 11 trials, the age of the participants ranged from 18 to 90 years. Six trials included only male participants ([BECAIT 1985](#); [CDP 1968](#); [LOCAT 1997](#); [LEADER 1992](#); [VACSA 1966](#); [VA-HIT 1991](#)), and the others included participants of both sexes.

Two trials recruited participants with history of cerebrovascular diseases ([Acheson 1962](#); [VACSA 1966](#)); one trial recruited participants with cardiovascular disease (CVD) ([ACCORD 1999](#)); nine trials recruited participants with history of coronary heart disease ([BIP 1990](#); [BECAIT 1985](#); [CDP 1968](#); [Derosa 2004](#); [Newcastle Trial 1964](#); [Scottish Trials 1964](#); [HHS Ancillary Study 1987](#); [VA-HIT 1991](#); [LOCAT 1997](#)); and one trial recruited participants with lower extremity arterial disease and controlled angina ([LEADER 1992](#)).

Clofibrate was used as intervention in five trials ([Acheson 1962](#); [CDP 1968](#); [Newcastle Trial 1964](#); [Scottish Trials 1964](#); [VACSA 1966](#)); the dosage of clofibrate was 1800 mg per day in one trial ([CDP 1968](#)), 1000 to 2000 mg per day in three trials ([Acheson 1962](#); [Newcastle Trial 1964](#); [Scottish Trials 1964](#)), and 2000 mg per day in one trial ([VACSA 1966](#)). Bezafibrate was used as intervention in three trials ([BECAIT 1985](#); [BIP 1990](#); [LEADER 1992](#)); the dosage of bezafibrate was 400 mg per day in two trials, [BIP 1990](#) and [LEADER 1992](#), and 600 mg per day in one trial ([BECAIT 1985](#)). Fenofibrate was used as intervention in two trials ([ACCORD 1999](#); [Derosa 2004](#)); the dosage of fenofibrate was 160 mg per day in [ACCORD 1999](#) and 200 mg per day in [Derosa 2004](#). Gemfibrozil was used as intervention in three trials at a dosage of 1200 mg per day ([HHS Ancillary Study 1987](#); [LOCAT 1997](#); [VA-HIT 1991](#)). Two trials used statins in both arms ([ACCORD 1999](#); [Derosa 2004](#)), one trial used no treatment as control ([Derosa 2004](#)), and the other 10 trials used placebo as control.

The included studies differed in duration of treatment. The shortest reported duration was 12 months for the [Derosa 2004](#) study, followed by the [LOCAT 1997](#) study with average duration of 2.5 years, 3 to 8 years for the [LEADER 1992](#) study, 4.5 years for the [VACSA 1966](#) study, 5 years for [BECAIT 1985](#), [Newcastle Trial 1964](#), [HHS Ancillary Study 1987](#), [VA-HIT 1991](#), and [ACCORD 1999](#) studies, 6 years for [BIP 1990](#), [CDP 1968](#), and [Scottish Trials 1964](#) studies, and 8 years for the [Acheson 1962](#) study.

Excluded studies

see [Characteristics of excluded studies](#).

We excluded nine studies on the following grounds: four trials were focused on primary prevention of CVD ([Hanefeld 1991](#); [SENDAP 1998](#); [HHS 1987](#); [Rottiers 1975](#)); three trials reported both the primary and secondary prevention of CVD, but the data of secondary prevention was not available even after we sought to obtain detailed data from the authors ([DAIS 2001](#); [FIELD 1998](#); [FIRST 2008](#)); one trial reported only laboratory outcomes without

clinical endpoints ([Tonelli 2004](#)); and one trial did not report clinical endpoints ([Li 2013](#)).

Risk of bias in included studies

See [Figure 1](#) and [Figure 2](#).

Allocation

All of the included trials reported they were randomised, but only two trials reported the details of random sequence generation ([ACCORD 1999](#); [CDP 1968](#)), and seven trials reported the details of allocation concealment ([ACCORD 1999](#); [CDP 1968](#); [Derosa 2004](#); [LEADER 1992](#); [Newcastle Trial 1964](#); [Scottish Trials 1964](#); [VA-HIT 1991](#)). The remaining trials did not report the method of random sequence generation and allocation concealment, hence we graded random sequence generation and allocation concealment for these trials as 'unclear risk'.

Blinding

Twelve trials reported they were double blind, and one trial, [Acheson 1962](#), reported no information on blinding. Of the 12 trials reported as double blind, 10 gave information about who was blinded. In all these cases, we judged both participants and outcome assessors to be blinded ([ACCORD 1999](#); [BECAIT 1985](#); [BIP 1990](#); [CDP 1968](#); [Derosa 2004](#); [HHS Ancillary Study 1987](#); [LEADER 1992](#); [Scottish Trials 1964](#); [VACSA 1966](#); [VA-HIT 1991](#)). For one trial, we judged that outcome assessors were blinded, but we were uncertain whether participants were blinded ([Newcastle Trial 1964](#)). One trial reported as double-blind did not give details of who was blinded ([LOCAT 1997](#)).

Incomplete outcome data

All the included trials reported losses to follow-up or withdrawal. Five trials reported an intention-to-treat analysis ([ACCORD 1999](#); [BIP 1990](#); [HHS Ancillary Study 1987](#); [LEADER 1992](#); [VA-HIT 1991](#)). We categorised one trial as 'unclear risk' for incomplete data due to insufficient information of exclusion and withdrawal ([LOCAT 1997](#)). We categorised nine trials as 'low risk' for incomplete data due to withdrawal or loss to follow-up of less than 20% ([ACCORD 1999](#); [Acheson 1962](#); [BECAIT 1985](#); [BIP 1990](#); [CDP 1968](#); [Derosa 2004](#); [Newcastle Trial 1964](#); [VA-HIT 1991](#); [Scottish Trials 1964](#)). We categorised the remaining three trials as 'high risk' for incomplete data.

Selective reporting

The protocols of seven trials were available and all the prespecified outcomes were reported ([ACCORD 1999](#); [BECAIT 1985](#); [BIP 1990](#); [CDP 1968](#); [LEADER 1992](#); [VA-HIT 1991](#); [LOCAT 1997](#)); the protocols of five trials were not available ([Acheson 1962](#); [HHS Ancillary Study 1987](#); [Newcastle Trial 1964](#); [Scottish Trials 1964](#); [VACSA 1966](#)), but all the published reports included all expected outcomes, so we categorised them as 'low risk' for selective reporting. One or more outcomes of interest in this review was reported incompletely by one trial ([Derosa 2004](#)), so we categorized this trial as 'high risk' for selective reporting.

Other potential sources of bias

The funnel plot for the primary outcome showed some evidence of asymmetry (see [Figure 4](#)), indicating that some level of publication bias may exist.

Figure 4. Funnel plot of comparison: 1 Fibrates vs control in cardiovascular disease and stroke, outcome: 1.1 Composite outcome of non-fatal stroke, non-fatal myocardial infarction, and vascular death without clofibrate.

Effects of interventions

See: [Summary of findings for the main comparison Fibrates compared with control for secondary prevention of cardiovascular disease and stroke](#); [Summary of findings 2 Fibrates compared with control for secondary prevention of cardiovascular disease and stroke - without clofibrate data](#)

Primary outcome

Composite outcome of non-fatal stroke, non-fatal myocardial infarction, and vascular death

All 13 included trials recorded the CVD events during treatment and follow-up period. No major cardiovascular events occurred during follow-up in one trial ([Derosa 2004](#)). We could include 12 trials with 16,064 participants into meta-analysis of the primary composite outcome of non-fatal stroke, non-fatal myocardial infarction (MI), and vascular death ([ACCORD 1999](#); [Acheson 1962](#); [BECAIT 1985](#); [BIP 1990](#); [CDP 1968](#); [HHS Ancillary Study 1987](#); [LEADER 1992](#); [LOCAT 1997](#); [Newcastle Trial 1964](#); [Scottish Trials 1964](#); [VACSA 1966](#); [VA-HIT 1991](#)). Of these 12 trials, 5 used clofibrate as intervention, 3 bezafibrate, 3 gemfibrozil, and 1 fenofibrate. Meta-analysis performed using fixed-effect modelling showed evidence for a protective effect of fibrates for composite outcome of non-fatal stroke, non-fatal MI, and vascular death (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.83 to 0.94; participants = 16,064; studies = 12; $I^2 = 45\%$) ([Analysis 1.1](#)). Random-effects meta-analysis excluding

clofibrate trials showed that fibrates were no longer effective in preventing composite outcome of non-fatal stroke, non-fatal MI, and vascular death (RR 0.90, 95% CI 0.79 to 1.03; participants = 10,320; studies = 7; $I^2 = 50\%$).

Secondary outcome

1. Death from any cause during the treatment and scheduled follow-up period

Data on death from any cause from 10 trials with 13,653 participants was available ([Acheson 1962](#); [BECAIT 1985](#); [BIP 1990](#); [CDP 1968](#); [HHS Ancillary Study 1987](#); [LEADER 1992](#); [Newcastle Trial 1964](#); [Scottish Trials 1964](#); [VACSA 1966](#); [VA-HIT 1991](#)). Of these 10 trials, 5 used clofibrate as intervention, 3 bezafibrate, and 2 gemfibrozil. Meta-analysis performed using fixed-effect modelling showed no evidence of effect of fibrates for the prevention of death from any cause during the treatment and scheduled follow-up period (RR 0.98, 95% CI 0.91 to 1.06; participants = 13,653; studies = 10; $I^2 = 23\%$) ([Analysis 1.7](#)). Meta-analysis excluding clofibrate data showed fibrates remained ineffective against all-cause mortality (RR 1.01, 95% CI 0.91 to 1.12; participants = 7909; studies = 5; $I^2 = 1\%$, fixed effect) ([Analysis 1.2](#)).

2. Death from vascular causes during the treatment and scheduled follow-up period

Data on vascular death from 10 trials with 13,653 participants was available ([Acheson 1962](#); [BECAIT 1985](#); [BIP 1990](#); [CDP 1968](#);

HHS Ancillary Study 1987; LEADER 1992; Newcastle Trial 1964; Scottish Trials 1964; VACSA 1966; VA-HIT 1991). Of these 10 trials, 5 used clofibrate as intervention, 3 bezafibrate, and 2 gemfibrozil. Meta-analysis performed using fixed-effect modelling showed no evidence of effect of fibrates for the prevention of death from vascular causes during the treatment and scheduled follow-up period (RR 0.95, 95% CI 0.86 to 1.05; participants = 13,653; studies = 10; $I^2 = 11\%$) (Analysis 1.8). Meta-analysis excluding clofibrate data showed fibrates remained ineffective against vascular death (RR 0.98, 95% CI 0.84 to 1.15; participants = 7909; studies = 5; $I^2 = 44\%$, fixed effect) (Analysis 1.3).

3. MI (non-fatal or fatal) during the treatment and scheduled follow-up period

Data on MI risk from 10 trials with 13,942 participants was available (BECAIT 1985; BIP 1990; CDP 1968; HHS Ancillary Study 1987; LEADER 1992; LOCAT 1997; Newcastle Trial 1964; Scottish Trials 1964; VACSA 1966; VA-HIT 1991). Of these 10 trials, 4 used clofibrate as intervention, 3 bezafibrate, and 3 gemfibrozil. Meta-analysis performed using fixed-effect modelling showed strong evidence of effect of fibrates for the prevention of MI (non-fatal or fatal) during the treatment and scheduled follow-up period (RR 0.86, 95% CI 0.80 to 0.93; participants = 13,942; studies = 10; $I^2 = 24\%$) (Analysis 1.9). Meta-analysis excluding clofibrate data showed fibrates continued to be effective for preventing MI (RR 0.85, 95% CI 0.76 to 0.94; participants = 8304; studies = 6; $I^2 = 47\%$, fixed effect) (Analysis 1.4).

4. Stroke (ischaemic or haemorrhagic, non-fatal or fatal) during the treatment and scheduled follow-up period

A range of stroke events were recorded in 6 trials with 11,719 participants (Acheson 1962; BIP 1990; CDP 1968; LEADER 1992; VACSA 1966; VA-HIT 1991). Of these 6 trials, 3 used clofibrate as intervention, 2 bezafibrate, and 1 gemfibrozil. Meta-analysis performed using fixed-effect modelling showed no evidence of effect of fibrates for the prevention of stroke (ischaemic or haemorrhagic, non-fatal or fatal) during the treatment and scheduled follow-up period (RR 1.03, 95% CI 0.91 to 1.16; participants = 11,719; studies = 6; $I^2 = 11\%$) (Analysis 1.10). Meta-analysis excluding clofibrate data showed fibrates remained ineffective for preventing stroke (RR 0.94, 95% CI 0.78 to 1.14; participants = 7189; studies = 3; $I^2 = 44\%$, fixed effect) (Analysis 1.5).

5. Change in plasma levels of total cholesterol concentration, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol

All 13 included trials reported change in plasma lipids. However, we could only include data of three trials into meta-analysis of the change in total cholesterol concentration, triglyceride, and high-density lipoprotein cholesterol (HDL-C) (Derosa 2004; LOCAT 1997; VA-HIT 1991), and two trials into meta-analysis of the change in low-density lipoprotein cholesterol (LDL-C) (Derosa 2004; LOCAT 1997). Meta-analysis performed using random-effects modelling showed evidence of an effect of fibrates in reducing total cholesterol concentration (mean difference (MD) -15.00, 95% CI -29.56 to -0.44; participants = 2974; studies = 3; $I^2 = 93\%$) (Analysis 1.11) and triglyceride concentration (MD -43.79, 95% CI -73.75 to -13.83; participants = 2974; studies = 3; $I^2 = 83\%$) (Analysis 1.15) and increasing HDL-C concentration (MD 4.00, 95% CI 1.72 to 6.28; participants = 2974; studies = 3; $I^2 = 84\%$) (Analysis 1.13). Meta-analysis performed using fixed-effect modelling showed evidence

that fibrates increased the plasmal level of LDL-C (MD -17.69, 95% CI -21.81 to -13.58; participants = 443; studies = 2; $I^2 = 0\%$) (Analysis 1.12).

6. Quality of life

None of the included trials collected data on quality of life.

7. Adverse events

In the two trials with 3138 participants that recorded the risk of myopathy (Derosa 2004; BIP 1990), there was no significant difference between the fibrates group and the placebo group (RR 0.86, 95% CI 0.31 to 2.35; $I^2 = 0\%$, fixed effect). One trial reported that five participants receiving placebo and three participants receiving bezafibrate developed diabetes mellitus (BECAIT 1985), but there was no significant difference between arms (RR 0.57, 95% CI 0.15 to 2.26). One trial reported significant liver enzyme elevations in nine gemfibrozil participants and none of the placebo participants (LOCAT 1997). One trial reported raised creatinine concentration in 25 bezafibrate participants and five placebo participants, with a significant difference (RR 5.01, 95% CI 1.93 to 13.03) (LEADER 1992). None of the included trials reported altered estimated glomerular filtration rate (Analysis 1.14).

The most commonly recorded adverse event was gastrointestinal events, which six trials reported (BECAIT 1985; CDP 1968; LOCAT 1997; Newcastle Trial 1964; Scottish Trials 1964; VA-HIT 1991). A total of 1048 participants developed gastrointestinal events in the placebo group and 2566 participants developed gastrointestinal events in the fibrate group. There was no statistically significant difference (RR 1.02, 95% CI 1.00 to 1.04; $I^2 = 42\%$, fixed effect). In addition, one trial recorded that one participant treating with bezafibrate presented with malignant melanoma, and one presented with hypernephroma at nine months after the end of placebo treatment (BECAIT 1985). One trial diagnosed cancer in seven participants with placebo and three participants with gemfibrozil during the study period (LOCAT 1997).

8. Costs

Only one included trial reported costs (Derosa 2004). The cost of fenofibrate plus fluvastatin therapy amounted to GBP 569.4 per year (USD 624.35 per year), and the cost of only fluvastatin therapy amounted to GBP 460.26 per year (USD 460.26 per year). Considering the efficacy of the two therapeutic strategies in reducing LDL-C level and increasing HDL-C level, the incremental cost-effectiveness ratio showed that each 1% decrease in LDL-C level with the combination fenofibrate plus fluvastatin added a cost of GBP 14.97 per year (USD 16.41 per year), and each 1% increase in HDL-C level added a cost of GBP 7.48 per year (USD 8.20 per year).

Subgroup analysis

1. Older versus younger than 65 years

Subgroup analyses of different ages showed evidence for a protective effect of fibrates for the primary outcome in both the older (65 years or older) subgroup (RR 0.77, 95% CI 0.63 to 0.93; participants = 1266; studies = 1; $I^2 = 0\%$) and younger (less than 65 years) subgroup (RR 0.76, 95% CI 0.59 to 0.99; participants = 5746; studies = 4; $I^2 = 77\%$) (Analysis 2.1).

2. Gender

Subgroup analyses of different genders showed evidence for a protective effect of fibrates for the primary outcome in both the male subgroup (RR 0.83, 95% CI 0.73 to 0.94; participants = 5092; studies = 4; $I^2 = 27\%$) and the female subgroup (RR 0.30, 95% CI 0.16 to 0.56; participants = 616; studies = 3; $I^2 = 0\%$) ([Analysis 3.1](#)).

3. With diabetes mellitus versus without

Subgroup analyses of participants with or without diabetes mellitus showed evidence for a protective effect of fibrates for the primary outcome in both the subgroup with diabetes mellitus (RR 0.85, 95% CI 0.73 to 0.99; participants = 2643; studies = 2; $I^2 = 0\%$) and the subgroup without diabetes mellitus (RR 0.75, 95% CI 0.65 to 0.86; participants = 3118; studies = 3; $I^2 = 0\%$) ([Analysis 4.1](#)).

4. Coronary heart disease versus stroke

Subgroup analyses showed no evidence for a protective effect of fibrates for the primary outcome either in the subgroup with coronary heart disease (RR 0.83, 95% CI 0.68 to 1.01; participants = 8357; studies = 6; $I^2 = 75\%$) or the subgroup with previous stroke (RR 0.99, 95% CI 0.82 to 1.20; participants = 638; studies = 2; $I^2 = 0\%$) ([Analysis 5.1](#)).

5. Each single fibrate versus placebo or no treatment

Four kinds of fibrates were used in the included trials: fenofibrate ([Derosa 2004](#); [ACCORD 1999](#)), bezafibrate ([BECAIT 1985](#); [BIP 1990](#); [LEADER 1992](#)), clofibrate ([Acheson 1962](#); [CDP 1968](#); [Newcastle Trial 1964](#); [Scottish Trials 1964](#); [VACSA 1966](#)), and gemfibrozil ([HHS Ancillary Study 1987](#); [LOCAT 1997](#); [VA-HIT 1991](#)).

We could include data for three kinds of fibrates into meta-analysis: clofibrate, bezafibrate, and gemfibrozil. Subgroup analyses showed no evidence of difference in the preventive effect on the primary outcome across fibrates, that is clofibrate trials (RR 0.86, 95% CI 0.74 to 1.00; participants = 5744; studies = 5; $I^2 = 51\%$), bezafibrate trials (RR 0.90, 95% CI 0.73 to 1.12; participants = 4750; studies = 3; $I^2 = 53\%$), and gemfibrozil trials (RR 1.01, 95% CI 0.62 to 1.64; participants = 3554; studies = 3; $I^2 = 67\%$) ([Analysis 6.1](#)).

We did not undertake the subgroup analysis of fibrate dose because of insufficient data.

Sensitivity analysis

1. Trials with low risk of bias versus trials with high risk of bias

We classified trials with 'low risk' for sequence generation and blinded outcome assessment as trials with low risk of bias and trials with 'unclear risk' or 'high risk' for sequence generation and blinded outcome as trials with high risk of bias. Sensitivity analysis showed evidence of an effect of fibrates in preventing the primary outcome in trials with low risk of bias (RR 0.85, 95% CI 0.79 to 0.91; participants = 11,221; studies = 6; $I^2 = 41\%$) ([Analysis 7.1](#)).

2. New trials versus old (before 1990) trials

We classified trials conducted before 1990 as 'old trials' ([Acheson 1962](#); [BECAIT 1985](#); [CDP 1968](#); [HHS Ancillary Study 1987](#); [Newcastle Trial 1964](#); [Scottish Trials 1964](#); [VACSA 1966](#)). Sensitivity analysis showed evidence of an effect of fibrates in preventing the primary outcome in new (1990 and after) trials (RR 0.88, 95% CI 0.81 to 0.95; participants = 9600; studies = 6; $I^2 = 0\%$) ([Analysis 7.2](#)).

3. Trials with the addition of fibrate to statin therapy

Two trials compared the addition of a fibrate to statin therapy to statin therapy alone. Given its small sample size ($N = 48$) and follow-up of only 12 months, one of these trials reported no cardiovascular events ([Derosa 2004](#)). The second trial compared the addition of fenofibrate to simvastatin to simvastatin alone ([ACCORD 1999](#)). There was no difference in primary composite outcome between arms (RR 0.90, 95% CI 0.74 to 1.09; participants 5518).

We could not undertake other sensitivity analysis (handling of missing data and effect of length of follow-up) due to insufficient data.

see [Summary of findings for the main comparison](#)

DISCUSSION

Summary of main results

We found that, when compared primarily to placebo, fibrates as a class of drugs can have a protective effect for composite outcome of non-fatal stroke, non-fatal MI, and vascular death in people with history of CVD. This protective effect appeared to primarily be the result of a reduction in non-fatal or fatal MI events. Fibrates were not effective in the prevention of stroke or death from any cause or vascular causes. Apart from clofibrate, we found no single fibrate to have a protective effect for secondary prevention of cardiovascular disease and stroke. There was no significant difference between fibrates group and placebo group in reported adverse events. We found no data on the cost-effectiveness of fibrates.

Overall completeness and applicability of evidence

This systematic review included all trials of fibrate therapy. However, as clofibrate was withdrawn in 2002 due to safety concerns, we also undertook an analysis excluding clofibrate trials. Meta-analysis without the clofibrate data showed that fibrates were no longer effective for preventing composite outcome of non-fatal stroke, non-fatal MI, and vascular death in people with history of cardiovascular disease and stroke (RR 0.90, 95% CI 0.79 to 1.03; participants = 10,320; studies = 7; $I^2 = 50\%$, random effects). However, without clofibrate data, fibrates were still effective in preventing MI (RR 0.85, 95% CI 0.76 to 0.94; participants = 8304; studies = 6; $I^2 = 47\%$, fixed effect).

Data in this review were primarily from trials without background treatment with statins (current standard of care) ([Keene 2014](#)). The effect of combined statins and fibrates compared with statins or fibrates alone for CVD therefore remains uncertain.

In addition, the majority of participants in the included trials were diagnosed with coronary heart disease. Only two trials recruited 627 participants with cerebrovascular disease, so caution is required in extrapolating the results of this review to people with stroke.

Quality of the evidence

According to GRADE approach, the quality of evidence with the clofibrate data was moderate for the composite (non-fatal stroke, non-fatal MI, and vascular death) and MI (non-fatal or fatal) outcomes and low for stroke (ischemic or haemorrhagic, non-fatal or fatal) and death from vascular or any cause during the treatment and scheduled follow-up period ([Summary of findings](#)

for the main comparison). The quality of evidence without the clofibrate data was moderate for the MI (non-fatal or fatal) outcome and low for the composite (non-fatal stroke, non-fatal MI, and vascular death), stroke (ischaemic or haemorrhagic, non-fatal or fatal), and death from vascular or any cause outcomes during the treatment and scheduled follow-up period (Summary of findings 2). The moderate-quality evidence was due to studies (more than 75%) not reporting the details of randomisation and four trials withdrawn or loss to follow-up of less than 20%. Only two trials reported a random component in the sequence generation process, and only seven trials provided details of allocation concealment method. Eleven of the included trials reported they were double blind. Withdrawals and attrition was less than 20% in 11 trials (Derosa 2004). The low-quality evidence was a result of the above description in addition to the imprecision of the effect estimate.

Agreements and disagreements with other studies or reviews

Our results are consistent with two previous systematic reviews. Jun et al assessed effects of fibrates on cardiovascular outcomes in the context of both primary and secondary prevention (Jun 2010). They found fibrate therapy produced a 10% RR reduction (95% CI 0 to 18%; $P = 0.05$) for major CVD events and a 13% RR reduction (95% CI 7 to 19; $P < 0.0001$) for coronary events, but had no benefit on the risk of stroke. They also found no effect of fibrate therapy on the risk of all-cause mortality, cardiovascular mortality, sudden death, or non-vascular mortality. More recently, the systematic review conducted by Keene et al also included participants with or without CVD. This later review found no significant difference in all-cause mortality with fibrate treatment (odds ratio (OR) 0.98, 95% CI 0.89 to 1.08, $P = 0.66$). In addition, neither coronary heart disease mortality (OR 0.92, 95% CI 0.81 to 1.04, $P = 0.19$) nor stroke (OR 1.01, 95% CI 0.90 to 1.13, $P = 0.84$) were found to be significantly affected by fibrates across all trials. However, non-fatal MI was reduced (OR 0.80, 0.74 to 0.87, $P < 0.001$) (Keene 2014). Based on the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (ACCORD 1999), the Keene review highlighted that the use of fibrates did not improve CVD outcomes in individuals with CVD already treated with a statin.

In contrast to the findings of this Cochrane review, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial showed no significant reduction in CVD events (that is CVD death, MI, stroke, coronary, or carotid revascularisation) in the subgroup of participants with previous CVD (FIELD 1998). We excluded this study from our review as it focussed on primary prevention of CVD, and

the data for secondary prevention of CVD was not available despite our contacting the authors of this study. The use of statin therapy could partly explain the negative result of this study. Decisions about changes in lipid-lowering therapy were at the discretion of the participant's primary-care or specialist physician, and there was a greater use of statin therapy in placebo participants than in those on fenofibrate (FIELD 1998).

The role of fibrates for the prevention of CVD events remains controversial. The 2014 National Institute for Health and Care Excellence (NICE) in United Kingdom guidance did not recommend fibrates for either primary or secondary prevention of CVD (NICE 2014). However, the International Atherosclerosis Society recommends that if non-HDL-C and triglycerides remain elevated when the LDL-C goal is achieved, consideration could be given to adding a fibrate (IAS 2014), albeit RCTs have not definitively shown efficacy of using fibrates combined with another lipid-lowering drug in the secondary prevention of CVD.

AUTHORS' CONCLUSIONS

Implications for practice

We found evidence that the class of fibrate drugs can have a secondary preventive effect in people with CVD. However, this beneficial effect of the fibrate class was lost after we excluded data from clofibrate, which was discontinued in 2002 due to adverse events.

Implications for research

Whether fibrates are beneficial in prevention of stroke events needs to be studied further. As only two trials recruiting a total of 627 participants with CVD contributed to this review, it may therefore be inadequately powered to show an effect in this subgroup. The effect of the addition of fibrates to a background of statin treatment (current standard of care) also needs to be examined in future secondary prevention CVD trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ACCORD 1999

Methods	Randomised, placebo-controlled trial, intention-to-treat principle
Participants	Fenofibrate 2765 participants, placebo 2753 participants; type 2 diabetes and a glycated haemoglobin level of 7.5% or more, with or without CVD; 40 to 79 years, if had clinical CVD; 55 to 79 years, if had sub-clinical CVD or at least 2 additional cardiovascular risk factors; an LDL cholesterol level of 60 to 180 mg per deciliter (1.55 to 4.65 mmol per liter), an HDL cholesterol level below 55 mg per deciliter (1.42 mmol per liter) for women and blacks or below 50 mg per deciliter (1.29 mmol per liter) for all other groups, and a triglyceride level below 750 mg per deciliter (8.5 mmol per liter) if they were not receiving lipid therapy or below 400 mg per deciliter (4.5 mmol per liter) if they were receiving lipid therapy
	Countries: the United States and Canada

ACCORD 1999 (Continued)

Interventions	<p>Open-label simvastatin + fenofibrate (160 mg initial, later the dose of fenofibrate was adjusted according to the estimated glomerular filtration rate) or simvastatin + placebo.</p> <p>Mean duration of follow-up was 4.7 years for the primary outcome and 5.0 years for total rates of death.</p>
Outcomes	<p>Primary outcome: the first occurrence of non-fatal MI, non-fatal stroke, or death from cardiovascular causes.</p> <p>Secondary outcomes included the combination of the primary outcome plus revascularisation or hospitalisation for congestive heart failure (termed the "expanded macrovascular outcome"); a combination of a fatal coronary event, non-fatal MI, or unstable angina (termed "major coronary disease events"); non-fatal MI; fatal or non-fatal stroke; non-fatal stroke; death from any cause; death from cardiovascular causes; and hospitalisation or death due to heart failure.</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote "randomization was performed centrally on the trial's Web site with the use of permuted blocks to maintain concealment of study-group assignments"</p> <p>Comment: probably done</p>
Allocation concealment (selection bias)	Low risk	<p>Quote "randomization was performed centrally on the trial's Web site with the use of permuted blocks to maintain concealment of study-group assignments"</p> <p>Comment: central allocation</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Fenofibrate group: lost to follow-up: N = 27, discontinued intervention: N = 61</p> <p>Placebo group: lost to follow-up: N = 29, discontinued intervention: N = 49</p>
Selective reporting (reporting bias)	Low risk	The study protocol was available, and the report included all expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote "randomization was performed centrally on the trial's Web site with the use of permuted blocks to maintain concealment of study-group assignments"</p> <p>Comment: done</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote "ACCORD utilized a centralized adjudication process for all deaths, and hospitalizations for myocardial infarction and strokes"</p> <p>Comment: done</p>

Acheson 1962

Methods	Randomised, placebo-controlled trial; no intention-treat analysis
Participants	<p>106 participants, 53 clofibrate, 53 placebo, both sexes; have focal cerebrovascular disease, cholesterol ≥ 250 mg/ml</p> <p>Country: Great Britain</p>

Acheson 1962 (Continued)

Interventions	Clofibrate (Atromid) (250 mg capsules) first 4 months and then clofibrate (250 mg capsules); females 4 to 6 capsules daily, males 6 to 8 capsules daily. Placebo as control. Duration of the trial: 8.6 ± 3.3 years
Outcomes	Further episode of cerebrovascular disease and serum cholesterol change
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "controlled trial, randomised" Comment: insufficient information to make a judgement
Allocation concealment (selection bias)	Unclear risk	Quote "controlled trial, randomised" Comment: insufficient information to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "The diagnoses were incorrect in 3 patients and 8 patients refused to co-operate during the follow up"
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but the report included all expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote "controlled trial, randomised" Comment: insufficient information to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote "controlled trial, randomised" Comment: insufficient information to make a judgement

BECAIT 1985

Methods	Double-blind, placebo-controlled intervention trial; not intention-to-treat analysis
Participants	92 participants, male survivors of MI younger than 45 years (47 bezafibrate, 45 placebo) Country: Sweden
Interventions	Bezafibrate (200 mg 3 times daily) or placebo Trial duration: 5 years
Outcomes	Primary endpoint: change in mean minimum lumen diameter; lipid, lipoprotein, and apolipoprotein analyses Safety assessments: rates of all-cause mortality, coronary mortality including sudden death, non-fatal reinfarction, and requirement for coronary artery bypass grafting or percutaneous transluminal coronary angioplasty

BECAIT 1985 (Continued)

Notes

This study was supported primarily by a grant from Boehringer Mannheim GmbH, and by supplementary grants from the Karolinska Institutet, the Swedish Heart-Lung Foundation, the Serafimer Foundation, and the Eirs Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from previous reports: "double-blind, placebo-controlled intervention trial" Comment: insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote from previous reports: "double-blind, placebo-controlled intervention trial" Comment: insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 participants (8 in each group) did not complete the 5-year study. The reasons for withdrawal were: lack of co-operation or emigration (4 participants receiving bezafibrate and 2 receiving placebo), referral for CABG (1, 5), adverse events (1 participant in each group), and death (2 participants in the bezafibrate group)
Selective reporting (reporting bias)	Low risk	The protocol was available and all the prescribed outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "double-blind, placebo-controlled intervention trial", "all study personnel were unaware of treatment assignment until the analysis was complete" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "double-blind, placebo-controlled intervention trial", "all study personnel were unaware of treatment assignment until the analysis was complete" Comment: probably done

BIP 1990

Methods	Randomised, double-blind, placebo-controlled trial; intention-to-treat analysis
Participants	3090 participants (placebo 1542, bezafibrate 1548; men 2825, women 265), age 45 to 74 years, history of MI > 6 months but < 5 years before enrolment into the study and/or stable angina pectoris confirmed by coronary angiography and/or radio-nuclear studies or standard exercise tests. In addition, a lipid profile of serum total cholesterol between 180 to 250 mg/dL, LDL-C ≤ 180 mg/dL (≤ 160 mg/dL for participants < 50 years), HDL-C ≤ 45 mg/dL, and TG ≤ 300 mg/dL was required; excluded insulin-dependent diabetes mellitus, severe heart failure, unstable angina pectoris, hepatic or renal failure, known sensitivity to bezafibrate, or current use of lipid-modifying drugs Country: Israel
Interventions	400 mg of bezafibrate per day or placebo Trial duration: a mean of 6.2 years

BIP 1990 (Continued)

Outcomes	<p>Primary endpoints: fatal MI, non-fatal MI, or sudden death (occurring within 24 hours of onset of symptoms)</p> <p>Secondary endpoints: for participants free of primary endpoints, including hospitalisation for unstable angina, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting; stroke and death from any cause were also monitored</p>
Notes	The trial was conducted independent of the sponsor (Boehringer Mannheim GmbH, which is now part of F. Hoffmann-La Roche, Ltd), and it was approved by the Helsinki Committees of each centre and the central national Helsinki Committee

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote "double-blind trial", "Patients were assigned consecutive randomisation numbers"</p> <p>Comment: insufficient information to permit judgement</p>
Allocation concealment (selection bias)	Unclear risk	<p>Quote "double-blind trial", "Patients were assigned consecutive randomisation numbers"</p> <p>Comment: insufficient information to permit judgement</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	For 511 participants (17%), the study medication was withdrawn for reasons other than the occurrence of a primary endpoint or death. Reasons were as follows: lipid levels exceeded predefined limits and necessitated treatment with a lipid-lowering drug (1.5% in the placebo group and 1.0% in the bezafibrate group), adverse events (5.8% and 6.5%, respectively), participant's request to discontinue study medication (7.0% and 7.2%), and other miscellaneous reasons (2.6% and 1.5%)
Selective reporting (reporting bias)	Low risk	The protocol was available and all the prescribed outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote "double-blind trial", "independent Critical Event Committee, whose members were blinded to the treatment assignment, reviewed primary endpoints and all-cause mortality"</p> <p>Comment: probably done</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote "double-blind trial", "independent Critical Event Committee, whose members were blinded to the treatment assignment, reviewed primary endpoints and all-cause mortality"</p> <p>Comment: probably done</p>

CDP 1968

Methods	Randomised, double-blind, placebo-controlled trial; 53 project clinical centres
Participants	8341 males, (1103 clofibrate and 2789 placebo, 1101 conjugated estrogens 2.5 mg/d, 1119 conjugated estrogens, 1110 dextrothyroxine sodium, 1119 niacin 3 mg/d), aged 30 to 64 years, with verified evidence of 1 or more MIs, 3 months beyond their recent MI and free of recent worsening of coronary dis-

CDP 1968 (Continued)

ease, no previous surgery for coronary artery disease, no life-limiting disease other than coronary heart disease, no diseases or conditions that might affect long-term follow-up, such as cerebrovascular disease with mental aberration, psychosis, alcoholism.

No conditions that would contraindicate the use of any of the drugs under study in the Coronary Drug Project, such as active gastric or duodenal ulceration, hypothyroidism requiring thyroid replacement therapy, etc. No anticoagulant therapy, lipid influencing drugs, or insulin at time of entry.

Country: United States

Interventions	Clofibrate 1800 mg/d or placebo Trial duration: at least 54 months, 96% at least 5 years, 63% at least 6 years
Outcomes	Primary endpoint: total mortality Other major endpoints: cause-specific mortality, coronary mortality and sudden death, non-fatal cardiovascular events such as recurrent MI, acute coronary insufficiency, development of angina pectoris, congestive heart failure, stroke, pulmonary embolism, and arrhythmias
Notes	One of the project clinical centres was closed in February 1974. The data in this report are those received at the Coordinating Center through 30 September 1974, and thus are close to being 'final'. It is anticipated that a few additional deaths occurring before 1 September 1974 will yet be reported, a few final follow-up visit forms and additional central lab reports will yet be submitted, and a relatively small number of corrections will be made before finalising the project's data file sometime in 1975. These few results cannot alter the overall findings reported here

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "random permutations of the numbers" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote "allocated bottle number was sent to the clinic in a sealed envelope showing the patient's name and identifying number" Comment: sealed envelope
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "the percentage of dropouts after 5-year follow up was 7.6% for clofibrate and 8.0% for placebo"
Selective reporting (reporting bias)	Low risk	The protocol was available and all the prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "double blinded"; "neither the patient nor the clinic staff was informed of the patient's drug allocation" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "double blinded"; "neither the patient nor the clinic staff was informed of the patient's drug allocation" Comment: probably done

Derosa 2004

Methods	Randomised, double-blind controlled trial
Participants	<p>48 participants (24 men, 24 women; mean (SD) age, 60 (5) years; 25 fenofibrate + fluvastatin, 23 fluvastatin)</p> <p>Included criteria: age 18 to 80 years; and type 2 diabetes mellitus (defined using the American Diabetes Association diagnostic criteria); and combined hyperlipidaemia (TC $\geq$ 200 mg/dL, LDL-C $\geq$ 100 mg/dL, and TG $\geq$ 150 mg/dL, according to ATP III I); and CHD, defined as a history of MI (last episode of acute CHD > 2 years prior to study entry)</p> <p>Excluded criteria: uncontrolled hypertension (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg); uncontrolled hypothyroidism; obstructive hepatic or biliary disease; alcoholism (> 3 drinks per day); autoimmune disease; chronic pancreatitis; active liver disease or hepatic dysfunction; concomitant participation in other clinical studies; known hypersensitivity to statins or fibrates; treatment with any lipid-lowering drugs; and/or use of heparin and/or oral anticoagulants and/or drugs associated with rhabdomyolysis in combination with a statin and/or fibrate</p> <p>Country: Italy</p>
Interventions	<p>Intervention: fluvastatin 80 mg + micronised fenofibrate 200 mg. Control: fluvastatin 80 mg</p> <p>Duration of treatment: 12 months</p>
Outcomes	<p>The primary efficacy variables were the plasma lipid levels (LDL-C, HDL-C, TC, and TG levels)</p> <p>The secondary efficacy variable was glycaemic status (HbA1c, fasting plasma glucose, and postprandial plasma glucose; safety profile)</p>
Notes	Outcomes of interest in the review are reported incompletely so that they could not be entered in a meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote "Patients were randomly assigned, using envelopes containing randomisation codes prepared by a statistician"</p> <p>Comment: insufficient information to permit judgement</p>
Allocation concealment (selection bias)	Low risk	<p>Quote "Patients were randomly assigned, using envelopes containing randomisation codes prepared by a statistician"</p> <p>Comment: envelopes containing randomisation codes</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	43 of 48 participants (89.6%) completed the study (22/25 (88.0%) in the combination-therapy group and 21/23 (91.3%) in the monotherapy group). The withdrawal rate was similar between the 2 groups
Selective reporting (reporting bias)	High risk	1 or more outcomes of interest in the review are reported incompletely
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias)	Low risk	Quote "a copy of the randomisation code was provided only to the person responsible for the statistical analysis. The code could be broken only after study conclusion or in emergency cases."

Derosa 2004 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "a copy of the randomisation code was provided only to the person responsible for the statistical analysis. The code could be broken only after study conclusion or in emergency cases."
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HHS Ancillary Study 1987

Methods	Randomised, double-blind controlled trial, intention-to-treat principle	
Participants	Gemfibrozil (n = 311), placebo (n = 317) Individuals who exhibited symptoms and signs of possible CHD; non-HDL-cholesterol ≥ 5.2 mmol/l at 2 consecutive visits Country: Finland	
Interventions	Gemfibrozil 600 mg twice daily or matching placebo Duration of treatment: 5 years	
Outcomes	Fatal and non-fatal MI and cardiac death were the principal endpoints Coronary artery bypass grafting was used as an ancillary endpoint	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "randomly allocated" Comment: insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote "randomly allocated" Comment: insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	100 participants in the placebo group (31.5%) and 119 in the gemfibrozil group (38.3%) withdrew from the trial
Selective reporting (reporting bias)	Low risk	The protocol was not available but all the prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "randomized to receive gemfibrozil 600 mg twice daily and 317 subjects to receive a matching placebo over 5 years in a double-blind fashion"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "all the end-points were analysed blindly without knowledge of the treatment group"

LEADER 1992

Methods	Randomised, double-blind, placebo-controlled trial; intention-to-treat basis
Participants	<p>1568 men, 783 bezafibrate and 785 placebo, mean age 68.2 years (range 35 to 92), men with possible lower extremity arterial disease. Excluded unstable angina, unless or until it was controlled; serum total cholesterol less than 3.5 mmol/l or more than 8.0 mmol/l; significant renal or hepatic disease; a known hepatitis B or C or HIV positive status; malignant disease (other than non-melanoma skin cancer) within the past 5 years; taking or likely to need lipid-lowering agents or monamine oxidase inhibitors; unlikely to comply with trial treatment or procedures; in another trial; or at the discretion of the general practitioner for other reasons, upper or lower age limits</p> <p>Country: United Kingdom</p>
Interventions	<p>Bezafibrate 400 mg daily (as Bezalip Mono, Roche) for men with creatinine plasma concentrations < 135 mmol/l, men with creatinine concentrations of 135 to 149 mmol/l at entry took 400 mg on alternate days. Placebo.</p> <p>Duration of the trial: 3 to 8 years. Creatinine concentrations rose to > 170 mmol/l, in which case men were withdrawn from trial treatment</p>
Outcomes	<p>Primary endpoint: combination of all CHD events (nonfatal and fatal) and all strokes</p> <p>Secondary endpoints: all coronary events, fatal and nonfatal coronary events separately, and strokes alone</p>
Notes	<ol style="list-style-type: none"> 1. In men taking daily treatment (i.e. creatinine < 135 mmol/l at entry), this was changed to alternate day treatment if concentrations rose to 155 mmol/l unless and until concentrations rose to > 170 mmol/l, in which case men were withdrawn from trial treatment. These changes were made for all men, whether they were on active or placebo treatment. 2. Those who had had a MI or stroke were eligible for the trial provided that their general management was stable, again at the discretion of the general practitioner. 3. Decisions regarding treatment with a statin were left to the general practitioners' discretion.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote "random assignment of trial treatment was initiated, balanced between active and placebo treatment within each practice or hospital clinic"; "labels identifying containers with either active or placebo tablets were removed at the trial coordinating centre, labelled with the man's name and trial number, and sent to the practices and hospital clinics"</p> <p>Comment: insufficient information to permit judgement</p>
Allocation concealment (selection bias)	Low risk	<p>Quote "labels identifying containers with either active or placebo tablets were removed at the trial coordinating centre, labelled with the man's name and trial number, and sent to the practices and hospital clinics"</p> <p>Comment: labels identifying containers with the man's name and trial number</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote "369 (47.1%) in the treatment group and 403 (51.3%) in the placebo group withdrawn"
Selective reporting (reporting bias)	Low risk	The protocol was available and all the prespecified outcomes were reported

LEADER 1992 (Continued)

Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "double blind placebo controlled randomised trial"; "labels identifying containers with either active or placebo tablets were removed at the trial co-ordinating centre, labelled with the man's name and trial number, and sent to the practices and hospital clinics" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "all possible endpoint episodes notified were documented and assessed independently and without knowledge of trial treatment allocation" Comment: probably done

LOCAT 1997

Methods	Randomised, parallel-group, double-blind, placebo-controlled trial
Participants	395 men $\leq$ 70 years old (197 intervention, 198 control) who had previously (within 3 to 48 months) undergone coronary bypass surgery without valve replacement and fulfilled the following criteria: HDL cholesterol $\leq$ 1.1 mmol/L (42.5 mg/dL), LDL cholesterol $\leq$ 4.5 mmol/L (174 mg/dL), and serum TG $\leq$ 4.0 mmol/L (354 mg/dL); blood pressure $\leq$ 160/95 mm Hg; body mass index $\leq$ 30 kg/m ² ; left ventricular ejection fraction $\geq$ 35%; no history of diabetes and fasting serum glucose concentration $<$ 7.8 mmol/L (140 mg/dL); and no conditions requiring therapy with calcium channel blockers, angiotensin-converting-enzyme inhibitors, or diuretics; smoked $\leq$ 20 cigarettes/wk. Country: Finland
Interventions	Slow-release gemfibrozil (Lopid SR) 1200 mg/d or placebo Duration of the trial: average 2.5 years after randomisation
Outcomes	Primary: change in the average diameter of segment index; change in the minimum luminal diameter index; number of new lesions. Secondary: per-participant change in mean percent diameter stenosis and the stenosis flow reserve in the lesions of the primary segments; changes in the graft-affected segments and changes in bypass grafts; per-participant classification into those with progression only, with regression only, both progression and regression (a mixed response), and no significant change in the primary segments and primary segment stenoses
Notes	1. This study was supported by grants from Parke-Davis, a division of Warner Lambert; the Finnish Foundation for Cardiovascular Research; the Aarne Koskelo Foundation; and the Finnish Society of Angiology. 2. One or more outcomes of interest in the review were reported incompletely so that they cannot be entered in a meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from previous reports: "a randomised, parallel-group, double-blind, placebo controlled study; carried out in three university hospitals in Finland" Comment: insufficient information to permit judgement

LOCAT 1997 (Continued)

Allocation concealment (selection bias)	Unclear risk	Quote from previous reports: "a randomised, parallel-group, double-blind, placebo controlled study; carried out in three university hospitals in Finland" Comment: insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Low risk	The protocol was available and all the prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote from previous reports: "a randomised, parallel-group, double-blind, placebo controlled study; carried out in three university hospitals in Finland" Comment: insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote from previous reports: "a randomised, parallel-group, double-blind, placebo controlled study; carried out in three university hospitals in Finland" Comment: insufficient information to permit judgement

Newcastle Trial 1964

Methods	Randomised, placebo-controlled, double-blind study
Participants	<p>497 participants, age < 65 years, 244 (192 men and 52 women) to the clofibrate group, 253 (208 men and 45 women) to the placebo group; they either had symptoms of angina or had had a MI or both, no limits set on the duration of the angina or on the number of infarctions, but at least 6 weeks had elapsed from the time of the last episode of infarction pain.</p> <p>Excluded:</p> <ol style="list-style-type: none"> aged 65 or over; valvular heart disease, cardiovascular syphilis, myxoedema (treated or untreated), diabetics on insulin or oral hypoglycaemics, idiopathic or familial hypercholesterolaemia (serum cholesterol exceeding 400 mg/100 ml or xanthomatosis, or both), chronic nephritis, significant hypertension (blood pressure 200/100 mm Hg on more than 1 occasion or people receiving therapy for hypertension), incipient or established heart failure; people with serious intercurrent diseases or with diseases requiring other drug treatment such as to make it unlikely that they would take the trial capsules regularly; people who had taken part in earlier trials of clofibrate or who had been treated with it at any time; and people whose co-operation seemed doubtful. <p>Country: England</p>
Interventions	<p>Clofibrate (250 mg capsules), 6 capsules daily for those weighing less than 140 lb (63.5 kg) and 8 capsules daily for participants weighing more than that</p> <p>Duration of the trial: about 5 years</p>
Outcomes	<p>Deaths: fatal infarct, non-cardiac causes were excluded, death due to congestive heart failure, all other sudden death</p> <p>New non-fatal infarctions. Lipoprotein levels</p>

Newcastle Trial 1964 (Continued)

Notes Anticoagulant treatment was discouraged, but if a physician was anxious to continue long-term anti-coagulant treatment already started, he was asked to do so throughout the trial. Since clofibrate alters anticoagulant requirements, arrangements were made for another clinician to supervise the anticoagulant therapy. If a physician wished to treat a fresh infarct with anticoagulants, he was to do so for 3 to 4 weeks only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "double-blind", "The patients were allotted to one or other treatment group by means of a randomisation scheme prepared by Professor D. J. Newell, of the Department of Industrial Health, University of Newcastle, and supervised by the pharmacists of the hospitals taking part in the trial" Comment: insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote "double-blind", "allocation envelopes", "The patients were allotted to one or other treatment group by means of a randomisation scheme prepared by Professor D. J. Newell, of the Department of Industrial Health, University of Newcastle, and supervised by the pharmacists of the hospitals taking part in the trial" Comment: allocation envelopes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "44/244 patients were withdrawn from the clofibrate group and 29/253 from the placebo group"
Selective reporting (reporting bias)	Low risk	The protocol was not available but all the prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote "double-blind study" Comment: insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "To ensure uniformity therefore the organizing secretary, while still ignorant of group allocations, made the decision on the basis of all the information which could be obtained" Comment: probably done

Scottish Trials 1964

Methods	Randomised, double-blind, placebo-controlled trial in 19 hospitals
Participants	717 participants (350 clofibrate and 367 placebo), either sex, aged 40 to 69 years; people with <ol style="list-style-type: none"> 1 MI (WHOECG criteria) between 8 and 16 weeks before the start of the trial; 2. angina of a duration of 3 to 24 months, provided their ECG showed signs of myocardial ischaemic at rest or after exercise; and 3. 1 recent MI and pre-existing angina as defined above.

Scottish Trials 1964 (Continued)

Excluded: people who had cardiac failure that required treatment with digoxin or diuretics or both, and people with diabetes mellitus

Country: Scotland

Interventions	<p>Clofibrate 1.6 g or 2 g daily (specially prepared 400 mg capsules) according to weight (less than or more than 140 lb; 63-5 kg) or placebo (olive oil)</p> <p>Duration: essentially 6 years, duration of groups varied</p> <p>Follow-up: unclear</p>
Outcomes	The only events assessed in this study were sudden death, fatal MI, and non-fatal definite and non-fatal probable MI
Notes	<p>There were 2 groups of participants in the trial:</p> <ol style="list-style-type: none"> 1. Double-blind group. This comprised 537 participants not receiving anticoagulants. Neither the participants nor the examining doctors were aware of the "treatment" group to which the participant had been allocated. 2. Anticoagulant group. This comprised 180 participants also given warfarin sodium. Due to the potential difficulties in controlling the prothrombin time in participants receiving clofibrate and warfarin sodium, the examining doctors knew which participants were allocated to the treatment group; this information was not available to the participants themselves.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote "patients were allocated at random"; "The pharmacist in each hospital was supplied with a list of the names of each patient, their allocated numbers, and the code concerning treatment group"; "The physicians knew only the serial number allocated"</p> <p>Comment: insufficient information to permit judgement</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "The pharmacist in each hospital was supplied with a list of the names of each patient, their allocated numbers, and the code concerning treatment group"</p> <p>Comment: central allocation</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "88 (46/350 clofibrate, 42/367 placebo) patients withdrawn"; "In the double-blind group more younger men withdrew from the clofibrate than from the placebo group"
Selective reporting (reporting bias)	Low risk	The protocol was not available but all the prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote "the double-blind group without the physician being aware of their contents"; "Neither the patients nor the examining doctors were aware of the 'treatment' group to which the patient had been allocated"</p> <p>Comment: probably done</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "the double-blind group without the physician being aware of their contents"; "Neither the patients nor the examining doctors were aware of the 'treatment' group to which the patient had been allocated"

Scottish Trials 1964 (Continued)

Comment: probably done

VA-HIT 1991

Methods	Placebo-controlled, double-blind, randomised trial conducted in 20 Veterans Affairs medical centres; intention-to-treat analysis
Participants	2531 males (1264 gemfibrozil and 1267 placebo), < 74 years with history of CHD (defined as a history of MI, angina corroborated by objective evidence of ischaemia, coronary revascularisation, or angiographic evidence of stenosis greater than 50% of the luminal diameter in 1 or more major epicardial coronary arteries), HDL cholesterol level < 40 mg/dl (1.0 mmol/l), LDL cholesterol level < 140 mg/dl (3.6 mmol/l), and TG level < 300 mg/dl (3.4 mmol/l), without other life-threatening medical illness, alcohol or other substance abuse, cholelithiasis, marked left ventricle dysfunction Country: United States
Interventions	Gemfibrozil (Lopid SR, Parke-Davis) 1200 mg once daily, later regular gemfibrozil (Lopid, Parke-Davis), 600 mg twice daily; a matching placebo Duration of the trial: median follow-up 5.1 years (range 0 to 6.9 years)
Outcomes	Primary endpoint: occurrence of either MI or death from coronary artery disease Secondary outcome: instances of stroke, death from any cause, transient ischaemic attack, revascularisation procedures, carotid endarterectomy, and hospitalisation for unstable angina or congestive heart failure

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "the Cooperative Studies Program Coordinating Center randomly assigned patients", "a permuted-block design with stratification according to center" Comment: insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote "the Cooperative Studies Program Coordinating Center randomly assigned patients", "a permuted-block design with stratification according to center" Comment: central allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	219/1264 gemfibrozil withdrew or died, 275/1267 placebo withdrew or died
Selective reporting (reporting bias)	Low risk	The protocol was available and all the prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias)	Low risk	Quote "all patients and local study personnel were blinded to treatment assignment" Comment: probably done

VA-HIT 1991 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "all patients and local study personnel were blinded to treatment assignment", "Clinical events are reviewed by a masked end points adjudication committee" Comment: probably done
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VACSA 1966

Methods	Randomised, double-blind, placebo-controlled trial
Participants	532 participants (268 clofibrate, 264 placebo), < 70 years (mean 64 ± 7 years), male veterans with 1 or more cerebral infarctions or transient ischaemic attack were eligible. Less than 12 months between the onset of the qualifying event and entrance into the study. Excluded: people with cerebral embolism or haemorrhage and brain tumours, major medical disorders such as accelerated hypertension, severe diabetes, cancer, serious nonvascular neurological conditions, dementia and personality disturbances Country: United States. 20 Veterans Administration hospitals
Interventions	Clofibrate 500 mg 4 times daily or a placebo Duration of the trial: up to 4.5 years
Outcomes	Mortality of all causes, vascular events, toxic effects, lipid values
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "patients were assigned by a prearranged random procedure to treatment and control regimens" Comment: insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote "patients were assigned by a prearranged random procedure to treatment and control regimens" Comment: insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote "127 patients were lost to follow-up, but their data were included in the analysis to the point of drop-out. Of these, 70/268 were on clofibrate and 57/264 received the placebo. Information on a patient was not included if he did not take the assigned drug for two months or longer."
Selective reporting (reporting bias)	Low risk	The protocol was not available but all the prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote "double-blind", "At each return visit, patients were evaluated, without knowledge of whether they were receiving clofibrate, both for possible episodes of vascular disease and for side effects." Comment: probably done

VACSA 1966 (Continued)

Blinding of outcome assessment (detection bias)
All outcomes

Low risk

Quote "double-blind", "At each return visit, patients were evaluated, without knowledge of whether they were receiving clofibrate, both for possible episodes of vascular disease and for side effects."

Comment: probably done

CHD: coronary heart disease
CVD: cardiovascular disease ECG: electrocardiogram
HbA1c: glycosylated haemoglobin
HDL-C: high-density lipoprotein cholesterol
HIV: human immunodeficiency virus
LDL-C: low-density lipoprotein cholesterol
MI: myocardial infarction
SD: standard deviation
TC: total cholesterol
TG: triglycerides

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
DAIS 2001	Recruited participants with type 2 diabetes, not focussed on secondary prevention, and the data of secondary prevention was not available even after we contacted the study authors. The Diabetes Atherosclerosis Intervention Study was not designed as a clinical endpoint study, nor did it have the statistical power to determine whether fenofibrate reduced major cardiac endpoints
FIELD 1998	Recruited participants with type 2 diabetes, focussed on primary prevention of CVD, and the data of secondary prevention of CVD was not available even after we contacted the study authors
FIRST 2008	Recruited participants with mixed dyslipidaemia and a history of coronary heart disease or risk equivalent, the separate outcome data of participants with a history of coronary heart disease was not available even after we contacted the study authors
Hanefeld 1991	Primary prevention of CVD
HHS 1987	Primary prevention of CVD
Li 2013	Just reported the results of laboratory test without clinical endpoints
Rottiers 1975	Primary prevention of CVD
SENDCAP 1998	Recruited participants with type 2 diabetes without a history of clinical CVD, focussed on primary prevention of CVD
Tonelli 2004	Just reported the results of laboratory test without clinical endpoints

CVD: cardiovascular disease

Characteristics of ongoing studies [ordered by study ID]

[NCT01956201](#)

Trial name or title	Efficacy and safety of fenofibrate added on to atorvastatin compared with atorvastatin in mixed hypercholesterolemic patient (CKD-337)
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NCT01956201 (Continued)

Methods	Randomised, parallel assignment
Participants	> 19 years old, high-risk patient to CHD, applied to 1 or more of the following CHD risk factors: <ol style="list-style-type: none"> 1. person with CHD 2. person with carotid artery disease, peripheral blood vessel disease, abdominal aneurysm 3. person with diabetes (HbA1C ≤ 8.0%) 4. 10-year risk of CHD > 20% (by Framingham 10-year risk score calculation)
Interventions	Atorvastatin 20 mg + fenofibrate 160 mg vs Atorvastatin 20 mg + placebo
Outcomes	Primary outcome measures: mean percent change of non-HDL cholesterol
Starting date	30 September 2013
Contact information	Hyun-Kyung Oh 82221940469, hkoh@ckdpharm.com
Notes	

NCT019562011

Trial name or title	Efficacy and safety of fenofibrate added on to atorvastatin compared with atorvastatin
Methods	Multicentre, randomised, double-blind, parallel-group, therapeutic confirmatory study
Participants	> 19 years old, high-risk patient to CHD, applied to 1 or more of the following CHD risk factors: <ol style="list-style-type: none"> 1. person with CHD 2. person with carotid artery disease, peripheral blood vessel disease, abdominal aneurysm 3. person with diabetes (HbA1C = 9.0%) 4. 10-year risk of CHD > 20% (by Framingham 10-year risk score calculation)
Interventions	Experimental: atorvastatin 20 mg, fenofibrate 160 mg orally every day Active comparator: atorvastatin 20 mg, placebo orally every day
Outcomes	Mean percent change of non-HDL cholesterol
Starting date	30 September 2013
Contact information	Contact: Hyun-Kyung Oh, hkoh@ckdpharm.com
Notes	

NCT02015988

Trial name or title	Simvastatin and fenofibrate vs simvastatin alone in patients with type 2 diabetes mellitus and acute coronary syndrome
Methods	Randomised
Participants	Type 2 diabetes mellitus

NCT02015988 (Continued)

- Fasting triglycerides = 1.7 mmol/l
- Acute coronary syndrome at least a minimum of 5 days and a maximum 21 days before the inclusion

Interventions	Simvastatin 40 mg once daily and fenofibrate 145 mg once daily orally for 52 weeks (1 year) vs simvastatin 40 mg once daily orally for 52 weeks (1 year)
Outcomes	Percentage change from baseline in triglycerides at week 12 [Time Frame: Baseline, Week 12] [Designated as safety issue: No]
Starting date	14 December 2013
Contact information	Contact: Olena A Koval, MD, PhD, 380676320919, koval_olena@ukr.net
Notes	380676320919

CHD: coronary heart disease
HbA1c: glycosylated haemoglobin
HDL: high-density lipoprotein

DATA AND ANALYSES

Comparison 1. Fibrates vs control in cardiovascular disease and stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Composite outcome of non-fatal stroke, non-fatal MI, and vascular death without clofibrate	7	10320	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.79, 1.03]
2 Death from any cause during the treatment and scheduled follow-up period without clofibrate	5	7909	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.91, 1.12]
3 Death from vascular causes during the treatment and scheduled follow-up period without clofibrate	5	7909	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.15]
4 MI (non-fatal or fatal) during the treatment and scheduled follow-up period without clofibrate	6	8304	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.76, 0.94]
5 Stroke (ischaemic or haemorrhagic, non-fatal or fatal) during the treatment and scheduled follow-up period without clofibrate	3	7189	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.14]
6 Composite outcome of non-fatal stroke, non-fatal MI, and vascular death	12	16064	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.81, 0.97]
7 Death from any cause during the treatment and scheduled follow-up period	10	13653	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Death from vascular causes during the treatment and scheduled follow-up period	10	13653	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.86, 1.05]
9 MI (non-fatal or fatal) during the treatment and scheduled follow-up period	10	13942	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.80, 0.93]
10 Stroke (ischaemic or haemorrhagic, non-fatal or fatal) during the treatment and scheduled follow-up period	6	11719	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.91, 1.16]
11 change in plasma levels of total cholesterol concentration	3	2974	Mean Difference (IV, Random, 95% CI)	-15.00 [-29.56, -0.44]
12 Change in plasma levels of LDL-C	2	443	Mean Difference (IV, Fixed, 95% CI)	-17.69 [-21.81, -13.58]
13 Change in plasma levels of HDL-C	3	2974	Mean Difference (IV, Random, 95% CI)	4.00 [1.72, 6.28]
14 adverse events	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 myopathy	2	3138	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.31, 2.39]
14.2 worsening of diabetes control	1	92	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.15, 2.26]
14.3 altered liver function tests	1	395	Risk Ratio (M-H, Random, 95% CI)	19.10 [1.12, 325.86]
14.4 Gastrointestinal events	5	5593	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.78, 2.14]
14.5 raised creatinine concentration	1	1568	Risk Ratio (M-H, Random, 95% CI)	5.01 [1.93, 13.03]
15 Change in plasma levels of TG	3	2974	Mean Difference (IV, Random, 95% CI)	-43.79 [-73.75, -13.83]

Analysis 1.1. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 1 Composite outcome of non-fatal stroke, non-fatal MI, and vascular death without clofibrate.

Study or subgroup	fibrates n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ACCORD 1999	163/1008	182/1008		20.39%	0.9[0.74,1.09]
BECAIT 1985	3/47	11/45		1.18%	0.26[0.08,0.88]
BIP 1990	317/1548	337/1542		25.87%	0.94[0.82,1.07]
HHS Ancillary Study 1987	35/311	24/317		6.03%	1.49[0.91,2.44]
LEADER 1992	150/783	160/785		19.76%	0.94[0.77,1.15]
LOCAT 1997	7/197	7/198		1.61%	1.01[0.36,2.81]
			Favours [fibrate] 0.01 0.1 1 10 100 Favours [placebo]

Analysis 1.2. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 2 Death from any cause during the treatment and scheduled follow-up period without clofibrate.

Analysis 1.3. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 3 Death from vascular causes during the treatment and scheduled follow-up period without clofibrate.

Analysis 1.4. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 4 MI (non-fatal or fatal) during the treatment and scheduled follow-up period without clofibrate.

Analysis 1.5. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 5 Stroke (ischaemic or haemorrhagic, non-fatal or fatal) during the treatment and scheduled follow-up period without clofibrate.

Analysis 1.6. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 6 Composite outcome of non-fatal stroke, non-fatal MI, and vascular death.

Analysis 1.7. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 7 Death from any cause during the treatment and scheduled follow-up period.

Analysis 1.8. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 8 Death from vascular causes during the treatment and scheduled follow-up period.

Analysis 1.9. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 9 MI (non-fatal or fatal) during the treatment and scheduled follow-up period.

Analysis 1.10. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 10 Stroke (ischaemic or haemorrhagic, non-fatal or fatal) during the treatment and scheduled follow-up period.

Analysis 1.11. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 11 change in plasma levels of total cholesterol concentration.

Analysis 1.12. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 12 Change in plasma levels of LDL-C.

Analysis 1.13. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 13 Change in plasma levels of HDL-C.

Analysis 1.14. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 14 adverse events.

Analysis 1.15. Comparison 1 Fibrates vs control in cardiovascular disease and stroke, Outcome 15 Change in plasma levels of TG.

Comparison 2. Subgroup analysis 1: different ages

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary outcome	4	7012	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.64, 0.94]
1.1 older than 65 years	1	1266	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.63, 0.93]
1.2 younger than 65 years	4	5746	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.59, 0.99]

Analysis 2.1. Comparison 2 Subgroup analysis 1: different ages, Outcome 1 primary outcome.

Comparison 3. Subgroup analysis 2: different genders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary outcome	5	5708	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.61, 0.92]
1.1 males	4	5092	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.73, 0.94]
1.2 female	3	616	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.16, 0.56]

Analysis 3.1. Comparison 3 Subgroup analysis 2: different genders, Outcome 1 primary outcome.

Comparison 4. Subgroup analysis 3: with versus without diabetes mellitus

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary outcome	4	5761	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.72, 0.88]
1.1 with diabetes mellitus	2	2643	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.73, 0.99]
1.2 without diabetes mellitus	3	3118	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.65, 0.86]

Analysis 4.1. Comparison 4 Subgroup analysis 3: with versus without diabetes mellitus, Outcome 1 primary outcome.

Comparison 5. Subgroup analysis 4: coronary heart disease versus stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary outcome	8	8995	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.75, 1.01]
1.1 Ischaemic heart disease and coronary heart disease	6	8357	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.68, 1.01]
1.2 stroke	2	638	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.82, 1.20]

Analysis 5.1. Comparison 5 Subgroup analysis 4: coronary heart disease versus stroke, Outcome 1 primary outcome.

Comparison 6. Subgroup analysis 5: each fibrate versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary outcome	11	14048	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.98]
1.1 clofibrate	5	5744	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.74, 1.00]
1.2 bezafibrate	3	4750	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.73, 1.12]
1.3 gemfibrozil	3	3554	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.62, 1.64]

Analysis 6.1. Comparison 6 Subgroup analysis 5: each fibrate versus placebo or no treatment, Outcome 1 primary outcome.

Comparison 7. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Trials with low-risk of bias versus with high-risk of bias on primary outcome	12	16064	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.83, 0.94]
1.1 low-risk of bias	6	11221	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.79, 0.91]
1.2 high-risk of bias	6	4843	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.86, 1.07]
2 New trials versus old trials on primary outcome	12	16064	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.81, 0.97]
2.1 new trials	5	9600	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.81, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 old trials	7	6464	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.73, 1.05]

Analysis 7.1. Comparison 7 Sensitivity analysis, Outcome 1 Trials with low-risk of bias versus with high-risk of bias on primary outcome.

Analysis 7.2. Comparison 7 Sensitivity analysis, Outcome 2 New trials versus old trials on primary outcome.

APPENDICES

Appendix 1. Search strategies

CENTRAL and DARE

```
#1MeSH descriptor Fibric Acids explode all trees
#2 "fibrin acid*"
#3(fibrate*)
#4"2-phenoxy isobutyric acid*"
#5" methyl-2-phenoxypropanoic acid derivative*"
#6"2 phenoxy 2 methylpropionic acid derivative*"
#7(bezafibrat*)
#8(durabezur)
#9(sklerofibrat)
#10(regadrin)
#11(befizal)
#12"beza puren"
#13(bezapuren)
#14(beza-puren)
#15(bm15?075)
#16"bm 15?075"
#17(bm-15?075)
#18(bezamerck)
#19(reducterol)
```


#20(bezabeta)
#21(bezalande)
#22"beza lande"
#23 beza-lande
#24(bezalip)
#25(bezafisal)
#26(eulitop)
#27(bezacur)
#28(solibay)
#29 cedur
#30(azufibrat)
#31(difaterol)
#32(lipox)
#33(clofenapate)
#34 methylclofenapate
#35(ici55695)
#36"ici 55695"
#37(ici-55695)
#38"clofibric acid"
#39"clofibrinic acid"
#40(nsc1149)
#41"nsc 1149"
#42(nsc-1149)
#43"p-chlorophenoxyisobutyric acid"
#44(p-chlorophenoxyisobutyrate)
#45"2-?4-chlorophenoxy?-2-methylpropionic acid"
#46(clofibrat*)
#47"ethyl chlorophenoxyisobutyrate"
#48(mis?leron)
#49(athromidin)
#50 atromid
#51(fenofibrat*)
#52(procetofen*)
#53(fenofanton)
#54(cil)
#55(livesan)
#56(liparison)
#57(lipidil-ter)
#58(durafenat)
#59(supralip)
#60(lofibra)
#61"lf 178"
#62(lf178)
#63(lf-178)
#64(lipanthyl)
#65(fenobeta)
#66(lipantil)
#67(tricor)
#68 controlip
#69(lipidil)
#70(phenofibrate)
#71(normalip)
#72"apo feno micro"
#73(apo-feno-micro)
#74 secalap
#75(gemfibrozil)
#76(gemfibro?il*)
#77(lipazil)
#78(lopil)
#79(bolutol)
#80(ausgem)
#81(nugemfibrozil)

#82(jezil)
 #83"lipox gemfi"
 #84(pilder)
 #85(litarek)
 #86(apogemfibrozil)
 #87(ci719)
 #88"ci 719"
 #89(ci-719)
 #90(lipur)
 #91"gemfi 1a pharma"
 #92(decrelip)
 #93(trialmin)
 #94(gemhexal)
 #95(ciprofibrat*)
 #96(#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 OR #55 OR #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 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95)
 #97MeSH descriptor Cardiovascular Diseases explode all trees
 #98(isch?emi*)
 #99(emboli*)
 #100(myocardi*)
 #101(arrhythmi*)
 #102(thrombo*)
 #103(heart*)
 #104(cardio*)
 #105(cardia*)
 #106(coronary*)
 #107(pericard*)
 #108 "atrial fibrillat*"
 #109(vascul*)
 #110 tachycardi*
 #111"ventricular fibrillat*"
 #112(endocardi*)
 #113(angina*)
 #114"sick sinus"
 #115MeSH descriptor Hypertension explode all trees
 #116(hypertensi*)
 #117"high blood pressure"
 #118MeSH descriptor Hyperlipidemias explode all trees
 #119(hyperlipid*)
 #120(hypercholesterol*)
 #121(hypercholester?emia*)
 #122(hyperlip?emia*)
 #123(hypertriglycerid?emia*)
 #124(hyperlipoprotein?emia*)
 #125MeSH descriptor Stroke explode all trees
 #126(stroke or strokes)
 #127(cerebrovascular)
 #128(apoplexy)
 #129"brain vascular"
 #130(cerebral near/3 infarct*)
 #131(brain near/3 infarct*)
 #132(#97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131)
 #133(#96 AND #132)

MEDLINE

1 exp Fibric Acids/
2 fibric acid*.tw.
3 fibrate*.tw.
4 2-phenoxy isobutyric acid*.tw.
5 methyl-2-phenoxypropanoic acid derivative*.tw.
6 2 phenoxy 2 methylpropionic acid derivative*.tw.
7 bezafibrat*.tw.
8 durabezur.tw.
9 sklerofibrat.tw.
10 regadrin b.tw.
11 befizal.tw.
12 beza puren.tw.
13 bezapuren.tw.
14 beza-puren.tw.
15 bm15?075.tw.
16 bm 15?075.tw.
17 bm-15?075.tw.
18 bezamerck.tw.
19 reducterol.tw.
20 bezabeta.tw.
21 bezalande.tw.
22 beza lande.tw.
23 beza-lande.tw.
24 bezalip.tw.
25 bezafisal.tw.
26 eulitop.tw.
27 bezacur.tw.
28 solibay.tw.
29 cedur.tw.
30 azufibrat.tw.
31 difaterol.tw.
32 lipox.tw.
33 clofenapate.tw.
34 methylclofenapate.tw.
35 ici55695.tw.
36 ici 55695.tw.
37 ici-55695.tw.
38 clofibric acid.tw.
39 clofibrinic acid.tw.
40 nsc1149.tw.
41 nsc1149.tw.
42 nsc-1149.tw.
43 p-chlorophenoxyisobutyric acid.tw.
44 p-chlorophenoxyisobutyrate.tw.
45 2-?4-chlorophenoxy?-2-methylpropionic acid.tw.
46 clofibrat*.tw.
47 ethyl chlorophenoxyisobutyrate.tw.
48 mis?leron.tw.
49 athromidin.tw.
50 atromid.tw.
51 fenofibrat*.tw.
52 procetofen*.tw.
53 fenofanton.tw.
54 cil.tw.
55 livesan.tw.
56 liparison.tw.
57 lipidil-ter.tw.
58 durafenat.tw.
59 supralip.tw.
60 lofibra.tw.

61 lf 178.tw.
 62 lf178.tw.
 63 lf-178.tw.
 64 lipanthyl.tw.
 65 fenobeta.tw.
 66 lipantil.tw.
 67 tricor.tw.
 68 controlip.tw.
 69 lipidil.tw.
 70 phenofibrate.tw.
 71 normalip.tw.
 72 apo feno micro.tw.
 73 apo-feno-micro.tw.
 74 secalap.tw.
 75 gemfibrozil.tw.
 76 gemfibro?il*.tw.
 77 lipazil.tw.
 78 lopid.tw.
 79 bolutol.tw.
 80 ausgem.tw.
 81 nugemfibrozil.tw.
 82 jezil.tw.
 83 lipox gemfi.tw.
 84 pilder.tw.
 85 litarek.tw.
 86 apogemfibrozil.tw.
 87 ci719.tw.
 88 ci 719.tw.
 89 ci-719.tw.
 90 lipur.tw.
 91 gemfi 1a pharma.tw.
 92 decrelip.tw.
 93 trialmin.tw.
 94 gemhexal.tw.
 95 ciprofibrat*.tw.
 96 or/1-95
 97 exp Cardiovascular Diseases/
 98 isch?emi*.tw.
 99 emboli*.tw.
 100 myocardi*.tw.
 101 arrhythmi*.tw.
 102 thrombo*.tw.
 103 heart*.tw.
 104 cardio*.tw.
 105 cardia*.tw.
 106 coronary*.tw.
 107 pericard*.tw.
 108 atrial fibrillat*.tw.
 109 vascul*.tw.
 110 tachycardi*.tw.
 111 ventricular fibrillat*.tw.
 112 endocardi*.tw.
 113 angina*.tw.
 114 (sick adj sinus).tw.
 115 exp Hypertension/
 116 hypertensi*.tw.
 117 high blood pressure.tw.
 118 exp Hyperlipidemias/
 119 hyperlipid*.tw.
 120 hypercholesterol*.tw.
 121 hypercholester?emia*.tw.
 122 hyperlip?emia*.tw.

123 hypertriglycerid?emia*.tw.
 124 hyperlipoprotein?emia*.tw.
 125 exp Stroke/
 126 (stroke or strokes).tw.
 127 cerebrovascular.tw.
 128 apoplexy.tw.
 129 brain vascular.tw.
 130 (cerebral adj3 infarct*).tw.
 131 (brain adj3 infarct*).tw.
 132 or/97-131
 133 96 and 132
 134 randomized controlled trial.pt.
 135 controlled clinical trial.pt.
 136 randomized.ab.
 137 placebo.ab.
 138 drug therapy.fs.
 139 randomly.ab.
 140 trial.ab.
 141 groups.ab.
 142 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141
 143 exp animals/ not humans.sh.
 144 142 not 143
 145 133 and 144

EMBASE

1 exp Fibric Acid Derivative/
 2 fibric acid*.tw.
 3 fibrate*.tw.
 4 2-phenoxy isobutyric acid*.tw.
 5 methyl-2-phenoxypropanoic acid derivative*.tw.
 6 2 phenoxy 2 methylpropionic acid derivative*.tw.
 7 bezafibrat*.tw.
 8 durabezur.tw.
 9 sklerofibrat.tw.
 10 regadrin b.tw.
 11 befizal.tw.
 12 beza puren.tw.
 13 bezapuren.tw.
 14 beza-puren.tw.
 15 bm15?075.tw.
 16 bm 15?075.tw.
 17 bm-15?075.tw.
 18 bezamerck.tw.
 19 reducerol.tw.
 20 bezabeta.tw.
 21 bezalande.tw.
 22 beza lande.tw.
 23 beza-lande.tw.
 24 bezalip.tw.
 25 bezafisal.tw.
 26 eulitop.tw.
 27 bezacur.tw.
 28 solibay.tw.
 29 cedur.tw.
 30 azufibrat.tw.
 31 difaterol.tw.
 32 lipox.tw.
 33 clofenapate.tw.
 34 methylclofenapate.tw.
 35 ici55695.tw.
 36 ici 55695.tw.

37 ici-55695.tw.
38 clofibrac acid.tw.
39 clofibrinic acid.tw.
40 nsc1149.tw.
41 nsc1149.tw.
42 nsc-1149.tw.
43 p-chlorophenoxyisobutyric acid.tw.
44 p-chlorophenoxyisobutyrate.tw.
45 2-?4-chlorophenoxy?-2-methylpropionic acid.tw.
46 clofibrat*.tw.
47 ethyl chlorophenoxyisobutyrate.tw.
48 mis?leron.tw.
49 athromidin.tw.
50 atromid.tw.
51 fenofibrat*.tw.
52 procetofen*.tw.
53 fenofanton.tw.
54 cil.tw.
55 livesan.tw.
56 liparison.tw.
57 lipidil-ter.tw.
58 durafenat.tw.
59 supralip.tw.
60 lofibra.tw.
61 lf 178.tw.
62 lf178.tw.
63 lf-178.tw.
64 lipanthyl.tw.
65 fenobeta.tw.
66 lipantil.tw.
67 tricolor.tw.
68 controlip.tw.
69 lipidil.tw.
70 phenofibrate.tw.
71 normalip.tw.
72 apo feno micro.tw.
73 apo-feno-micro.tw.
74 secalip.tw.
75 gemfibrozil.tw.
76 gemfibro?il*.tw.
77 lipazil.tw.
78 lopid.tw.
79 bolutol.tw.
80 ausgem.tw.
81 nugemfibrozil.tw.
82 jezil.tw.
83 lipox gemfi.tw.
84 pilder.tw.
85 litarek.tw.
86 apogemfibrozil.tw.
87 ci719.tw.
88 ci 719.tw.
89 ci-719.tw.
90 lipur.tw.
91 gemfi 1a pharma.tw.
92 decrelip.tw.
93 trialmin.tw.
94 gemhexal.tw.
95 ciprofibrat*.tw.
96 or/1-95
97 exp Cardiovascular Diseases/
98 isch?emi*.tw.

99 emboli*.tw.
 100 myocardi*.tw.
 101 arrhythmi*.tw.
 102 thrombo*.tw.
 103 heart*.tw.
 104 cardio*.tw.
 105 cardia*.tw.
 106 coronary*.tw.
 107 pericard*.tw.
 108 atrial fibrillat*.tw.
 109 vascul*.tw.
 110 tachycardi*.tw.
 111 ventricular fibrillat*.tw.
 112 endocardi*.tw.
 113 angina*.tw.
 114 (sick adj sinus).tw.
 115 exp Hypertension/
 116 hypertensi*.tw.
 117 high blood pressure.tw.
 118 exp Hyperlipidemias/
 119 hyperlipid*.tw.
 120 hypercholesterol*.tw.
 121 hypercholester?emia*.tw.
 122 hyperlip?emia*.tw.
 123 hypertriglycerid?emia*.tw.
 124 hyperlipoprotein?emia*.tw.
 125 exp Stroke/
 126 (stroke or strokes).tw.
 127 cerebrovascular.tw.
 128 apoplexy.tw.
 129 brain vascular.tw.
 130 (cerebral adj3 infarct*).tw.
 131 (brain adj3 infarct*).tw.
 132 or/97-131
 133 96 and 132
 134 random\$.tw.
 135 factorial\$.tw.
 136 crossover\$.tw.
 137 cross over\$.tw.
 138 cross-over\$.tw.
 139 placebo\$.tw.
 140 (doubl\$ adj blind\$).tw.
 141 (singl\$ adj blind\$).tw.
 142 assign\$.tw.
 143 allocat\$.tw.
 144 volunteer\$.tw.
 145 crossover procedure/
 146 double blind procedure/
 147 randomized controlled trial/
 148 single blind procedure/
 149 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148
 150 (animal/ or nonhuman/) not human/
 151 149 not 150
 152 133 and 151

Web of Science

#34#33 AND #32
 #33TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
 #32#31 AND #30
 #31TS=("fibric acid*" or fibrate*)

#30#29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #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
#29TS=(hypertensi* or "high blood pressure")
#28TS=(arteriosclerosis or cholesterol or "coronary risk factor*" or "blood pressure")
#27TS=(hyperlipoprotein?emia* or hypertriglycerid?emia*)
#26TS=(hypercholester?emia*)
#25TS=(hypercholesterol*)
#24TS=(hyperlip?emia*)
#23TS=(hyperlipid*)
#22TS=((brain* or cerebral or lacunar) near/2 infarct)
#21TS=(brain near/2 accident*)
#20TS=(apoplexy)
#19TS=("cerebral vascular")
#18TS=(cerebrovasc*)
#17TS=(stroke or strokes)
#16TS=("sick sinus")
#15TS=(endocardi*)
#14TS=(tachycardi*)
#13TS=((atrial fibrillat*))
#12TS=(thrombo*)
#11TS=(arrhythmi*)
#10TS=(emboli*)
#9TS=(isch?em*)
#8TS=(pericard*)
#7TS=(myocard*)
#6TS=(ventric*)
#5TS=(angina*)
#4TS=(coronary*)
#3TS=(heart*)
#2TS=(cardia*)
#1TS=(cardio*)

CBM

56 #55 and #46 and #34

55 #54 or #53 or #52 or #51 or #50 or #49 or #48 or #47

54 关键词:随机

53 关键词:安慰剂

52 关键词:盲法

51 关键词:三盲

50 关键词:双盲

49 关键词:单盲

48 主题词:随机分配/全部树/全部副主题词

47 主题词:随机对照试验/全部树/全部副主题词

46 #45 or #44 or #43 or #42 or #41 or #40 or #39 or #38 or #37 or #36 or #35

45 主题词:血脂异常/全部树/全部副主题词

44 主题词:动脉硬化/全部树/全部副主题词

43 主题词:颅内出血/全部树/全部副主题词

42 主题词:脑缺血/全部树/全部副主题词

41 关键词:脑中风

40 主题词:卒中/全部树/全部副主题词

39 主题词:脑梗死/全部树/全部副主题词

38 主题词:心肌缺血/全部树/全部副主题词

37 关键词:心肌梗塞

36 关键词:缺血性心脏病

35 关键词:心脏病, 缺血性

34 #33 or #32 or #31 or #30 or #29 or #28 or #27 or #26 or #25 or #24 or #23 or #22 or #21 or #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

33 英文标题:gemfibrozil

32 英文标题:fenofibrate

31 英文标题:clofibrate

30 英文标题:bezafibrate

29 关键词:纤维酸%

28 关键词:贝特%

27 关键词:贝特类

26 关键词:%吉非罗奇

25 关键词:%吉非贝奇

24 关键词:乐衡

23 关键词:优瑞脂

22 关键词:洛衡

21 关键词:洁脂

20 关键词:吉非?齐

19 关键词:吉非罗齐

18 关键词:阿贝他

17 关键词:?平脂

16 关键词:?平之

15 关键词:立平脂

14 关键词:力平%

13 关键词:力平之

12 关键词:力平脂

11 关键词:非诺贝%

10 关键词:非诺贝特%

9 关键词:非诺贝特

8 关键词:安妥明%

7 关键词:安妥明

6 关键词:冠心平

5 关键词:氯贝特

4 关键词:必降脂%

3 关键词:必降脂

2 关键词:苯扎贝特%

1 主题词:氯贝酸/全部树/全部副主题词

VIP

(K=苯扎贝特+K=必降脂+K=氯贝酸+K=氯贝丁酯+K=氯贝特+K=对氯苯氧异丁酸+K=安妥明+K=普鲁脂芬+K=非诺贝特+K=力平脂+K=力平之+K=立平脂+K=苯酰降脂丙酯+K=二甲苯氧庚酸+K=吉非贝齐+K=吉非罗齐+K=乐衡+K=氯苯甲酯+K=贝特类+K=纤维素+K=纤维素衍生物+K=苯氧酸)*(K=冠心病+K=心肌梗死+K=心绞痛+K=脑梗死+K=脑出血+K=卒中+K=外周血管疾病+K=血脂异常+K=高脂血症)*(K=随机对照试验+K=对照临床试验+K=随机分配+K=双盲法+K=单盲法+K=临床试验+K=临床观察+K=临床研究+K=临床评价+K=临床评估+K=单盲+K=三盲+K=盲法+K=随机)

CNKI

(KY=苯扎贝特 OR KY=必降脂 OR KY=氯贝酸 OR KY=氯贝丁酯 OR KY=氯贝特 OR KY=对氯苯氧异丁酸 OR KY=安妥明 OR KY=普鲁脂芬 OR KY=非诺贝特 OR KY=力平脂 OR KY=力平之 OR KY=立平脂 OR KY=苯酰降脂丙酯 OR KY=二甲苯氧庚酸 OR KY=吉非贝齐 OR KY=吉非罗齐 OR KY=乐衡 OR KY=氯苯甲酯 OR KY=贝特类 OR KY=纤维素 OR KY=纤维素衍生物 OR KY=苯氧酸) AND (KY=冠心病 OR KY=心肌梗死 OR KY=心绞痛 OR KY=脑梗死 OR KY=脑出血 OR KY=卒中 OR KY=外周血管疾病 OR KY=血脂异常 OR KY=高脂血症) AND (KY=随机对照试验 OR KY=对照临床试验 OR KY=随机分配 OR KY=双盲法 OR KY=单盲法 OR KY=临床试验 OR KY=临床观察 OR KY=临床研究 OR KY=临床评价 OR KY=临床评估 OR KY=单盲 OR KY=三盲 OR KY=盲法 OR KY=随机)

WHO International Clinical Trial Registry Platform (ICTRP)

"coronary* OR myocardi* OR heart* OR cardi* OR vascul* OR angina* OR hyperlipid* OR hypercholester* OR stroke OR cerebr*OR brain vascular" in the condition and "fenofibrate OR clofibrate OR gemfibrozil OR bezafibrate OR ciprofibrate" in the intervention

ClinicalTrials.gov

ischaemic heart disease OR coronary heart disease OR angina OR transient ischemic attack OR stroke OR cerebral* | fenofibrate OR clofibrate OR gemfibrozil OR bezafibrate OR ciprofibrate

Current Controlled Trials

fenofibrate in the intervention

clofibrate in the intervention

gemfibrozil in the intervention

bezafibrate in the intervention

ciprofibrate in the intervention

WHAT'S NEW

Date	Event	Description
12 April 2018	Amended	Abstract - minor correction of year when use of clofibrate was discontinued

CONTRIBUTIONS OF AUTHORS

All review authors were involved in the development of the protocol, interpretation of data, and drafting the review.

Fibrates for secondary prevention of cardiovascular disease and stroke (Review)

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DW, BL, ZH: literature search and data collection.

DW, BL, ML: literature selection, assessment of study quality, and data analysis.

DECLARATIONS OF INTEREST

DW: None known.

BL: None known.

WT: None known.

ZH: None known.

ML: None known.

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Internal sources

- West China Hospital, Sichuan University, China.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we determined that if the I^2 was less than 40%, we would consider heterogeneity as not important; 30% to 60% as moderate; and more than 50% as substantial or considerable heterogeneity, which were not specific, so we determined that if the I^2 was less than 30%, we would consider heterogeneity as not important; 30% to 50% as moderate; and more than 50% as substantial or considerable heterogeneity in the review.

BL replaced WT in searching and selecting literature and in assessing the quality of papers and collecting data. BL was added to analyse and interpret data and write the review. DW and BL contributed equally to finishing the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticholesteremic Agents [*therapeutic use]; Bezafibrate [therapeutic use]; Cardiovascular Diseases [mortality] [*prevention & control]; Cause of Death; Cholesterol, HDL; Clofibrate [therapeutic use]; Coronary Disease [mortality]; Fenofibrate [therapeutic use]; Fibric Acids [adverse effects] [*therapeutic use]; Gemfibrozil [therapeutic use]; Hypertriglyceridemia [drug therapy]; Myocardial Infarction [mortality] [prevention & control]; Randomized Controlled Trials as Topic; Secondary Prevention [*methods]; Stroke [mortality] [prevention & control]

MeSH check words

Adult; Aged; Aged, 80 and over; Female; Humans; Male; Middle Aged