Fibrates for primary prevention of cardiovascular disease events

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the clinical benefit and harm of fibrates versus placebo or usual care or fibrates plus other lipid-modifying drugs versus other lipid-modifying drugs alone for the primary prevention of CVD events and mortality.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is the most common cause of death, illness, disability and reduced quality of life in industrialized countries (Thom 2006). With the increasing incidence of obesity, metabolic syndrome and type 2 diabetes mellitus, the disease burden of CVD may escalate further in the years to come (Shaw 2010). One of the major risk factors for CVD is elevated low-density lipoprotein cholesterol (LDL-C). In individuals with elevated LDL-C, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) are considered to be the first choice of pharmacological therapy, since they reduce CVD events total mortality independently of baseline LDL-C levels in primary and secondary prevention of CVD (4S 1994; Baigent 2005; Graham 2007; Heart Protection Study 2002; Hooper 2001; Lestra 2005; Mills 2010). The finding of elevated serum triglycerides and low high-density lipoprotein cholesterol (HDL-C) can identify persons who are at increased risk for CVD and who might benefit from further lipid modifying therapy (Graham 2007; NCEP 2002). Several causes underlie elevated triglycerides and low HDL-C in the general population: overweight and obesity, physical inactivity, cigarette smoking, excess alcohol intake, very high-carbohydrate diets (>60 percent of total energy),

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DECLARATIONS OF INTEREST The authors have nothing to declare.

type 2 diabetes, chronic renal failure, nephrotic syndrome, certain drugs (corticosteroids, pro-tease inhibitors for HIV, beta-adrenergic blocking agents, estrogens) and genetic factors (Chait 1990; Stone 1994). When triglyceride levels are 200 mg/dL, the presence of increased quantities of atherogenic remnant lipoproteins can heighten coronary heart disease (CHD) risk substantially beyond that predicted by LDL cholesterol alone (Steiner 1987).

Many prospective epidemiological studies have reported a positive relationship between serum triglyceride levels and incidence of CHD (Assmann 1998; Austin 1998). Although early multivariate analyses generally did not identify serum triglycerides as an independent risk factor for CHD (Hulley 1980), more recent meta-analyses suggest that raised triglycerides are in fact an independent risk factor for CHD (Assmann 1998; Austin 1998). In patients with type 2 diabetes mellitus, the United Kingdom Prospective Diabetes Study (UKPDS) identified low HDL-C (<40 mg/dL in men, <45 mg/dL in women) as the second most important coronary risk factor after LDL-C (Turner 1998). However, it remains unclear if therapeutic interventions to raise HDL-C indeed translate into CVD risk reduction (Briel 2009).

Fibrates are effective for modifying atherogenic dyslipidemia, and particularly for lowering serum triglycerides (Graham 2007; NCEP 2002). In addition, they produce moderate elevations of HDL cholesterol. Current guidelines consider fibrate therapy as an option for treatment of persons at high risk of CVD (i.e. SCORE >5% for CVD death or 10-year Framingham risk score >20% for CVD events) who have low levels of LDL-cholesterol and atherogenic dyslipidemia, and in persons who have elevated LDL-cholesterol and atherogenic dyslipidemia in combination with statin therapy (Graham 2007; Grundy 2004; NCEP 2002). However, any potential benefit of fibrate therapy must be weighed against potential harms and side effects such as changes in serum creatinine, myositis/ rhabdomyolysis, transaminases, pancreatitis, venous thrombotic events, and gallbladder disease (since fibrates increase the cholesterol content of bile), and in combination with statin therapy rhabdomyolysis leading to renal failure. In contrast to another registered Cochrane protocol (Meza 2008) that focuses on combination therapy of statins and fibrates in individuals with dyslipidemia only and one that focuses on the secondary prevention of cardiovascular disease and stroke (Wang 2012), our review will investigate fibrate therapy in any individuals at increased risk of cardiovascular events.

Description of the intervention

In this systematic review and meta-analysis we will evaluate the effects of fibrates vs. placebo or usual care, or fibrates plus other lipid-modifying drugs versus other lipid-modifying drugs alone or fibrates versus placebo or usual care on patient-relevant clinical outcomes. Currently available fibrates in North America and/or Europe include: gemfibrozil, fenofibrate, fenofibric acid, bezafibrate and ciprofibrate. Recent investigations indicate that the effects of fibrates are mediated, at least in part, through alterations in transcription of genes encoding for proteins that control lipoprotein metabolism (Staels 1998). Fibrates activate specific transcription factors belonging to the nuclear hormone receptor superfamily, termed peroxisome proliferator-activated receptors (PPARs). The PPAR- α form mediates fibrate action on HDL-C levels via transcriptional induction of synthesis of the

major HDL apolipoproteins, apoA-I and apoA-II. Fibrates lower hepatic apoC-III production and increase lipoprotein lipase-mediated lipolysis via PPAR. Fibrates stimulate cellular fatty acid uptake, conversion to acyl-CoA derivatives, and catabolism by the β -oxidation pathways, which, combined with a reduction in fatty acid and triglyceride synthesis, results in a decrease in VLDL production. In summary, both enhanced catabolism of triglyceride-rich particles and reduced secretion of VLDL underlie the hypotriglyceridemic effect of fibrates, whereas their effect on the HDL metabolism is associated with changes in HDL apolipoprotein expression.

Potential side or adverse effects from fibrate therapy are increased venous thrombotic events, pancreatitis, reversible rise in creatinine (described with all fibrates except gemfibrozil), rise in homo-cysteine, and elevations in transaminases and myositis/rhabdomyolysis in particular for combinations of gemfibrozil with statins (Davidson 2007; Wierzbicki 2010).

How the intervention might work

Fibrates primarily reduce levels of triglycerides, modestly increase high-density lipoprotein (HDL) cholesterol, and have limited ability to lower LDL-cholesterol and chylomicron remnants (Abourbih 2009; Jun 2010). Improvement of these surrogate markers may result in a reduction of CVD events.

Why it is important to do this review

Evidence that fibrates reduce all-cause or CVD mortality is lacking, although fibrates reduced non-fatal coronary events in two recently published meta-analyses (Abourbih 2009; Jun 2010). In one meta-analysis fibrates were more efficacious than placebo at preventing nonfatal myocardial infarction (odds ratio=0.78; 95% confidence interval [CI], 0.69-0.89), but not all-cause mortality (odds ratio= 1.05; 95% CI, 0.95-1.15) (Abourbih 2009). In the other meta-analysis including 18 trials providing data for 45 058 participants, fibrate therapy produced a 10% relative risk reduction (95% CI, 0-18%) for major CVD events ($p=0.048$) and a 13% relative risk reduction (95% CI, 7-19%) for coronary events ($p<0.0001$), but had no benefit on stroke (relative risk reduction -3%; 95% CI, -16 to 9%; $p=0.69$) (Jun 2010). There was no effect of fibrate therapy on the risk of all-cause mortality (relative risk reduction 0%; 95% CI, -8 to 7%; $p=0.92$) or CVD mortality (relative risk reduction 3%; 95% CI, -7 to 12%; $p=0.59$). Both meta-analyses did not report separate outcomes for the effect of fibrates in primary or secondary prevention.

The main evidence for clinical benefit comes from placebo-controlled trials with older fibrates such as gemfibrozil (for which some safety concerns were raised primarily when used in combination with statin therapy) and clofibrate (which is no longer available due to safety concerns) (Graham 2004; Jones 2005; Rubins 1999). Recently, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial failed to show a reduction in CVD events when patients with type 2 diabetes were treated with fenofibrate plus statins rather than with statins alone (Ginsberg 2010). Thus, there remains uncertainty whether fibrates alone or as add-on therapy to statins are effective in reducing CVD events in primary prevention.

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

Limited health care resources demand an unbiased appreciation of the available evidence about the benefit and harm of fibrate therapy. In the United States, annual sales of fibrates sum up to more than \$1 billion (Bloomberg 2011). Since current evidence about the effectiveness of fibrate therapy in the primary prevention of CVD is missing, the results of this systematic review and meta-analysis will serve as a basis for decision-making in health care.

In this systematic review and meta-analysis we aim to summarize currently available evidence on the effects of fibrates as monotherapy or as add-on therapy to other lipid-modifying drugs for the primary prevention of CVD morbidity and mortality in patients at risk of cardiovascular events.

OBJECTIVES

To assess the clinical benefit and harm of fibrates versus placebo or usual care or fibrates plus other lipid-modifying drugs versus other lipid-modifying drugs alone for the primary prevention of CVD events and mortality.

METHODS

Criteria for considering studies for this review

Types of studies—We will include randomized controlled trials (published and unpublished) that document clinical outcome data and have a length of treatment of at least six months.

Types of participants—Adults older than 18 years at increased risk of CVD events (e.g. individuals with type 2 diabetes and/or dyslipidemia) without established CVD (primary prevention).

Types of interventions—

- Combination therapy fibrates plus other lipid-modifying drug(s) versus other lipid-modifying drug(s) alone
- Fibrate monotherapy versus placebo or usual standard care

Types of outcome measures—Clinical outcomes and side effects.

Primary outcomes: Major CVD events (CVD death, non-fatal myocardial infarction, non-fatal stroke, revascularization procedures such as bypass grafts and angioplasty) as a composite endpoint.

Secondary outcomes:

- Overall mortality
- Coronary heart disease mortality or non-fatal myocardial infarction as a composite endpoint
- Non-CVD mortality
- Diabetic retinopathy
- Progression to albuminuria
- Patient perceived quality of life (only measured using validated scales)

In addition we will descriptively report side effects of fibrate therapy (especially changes in serum creatinine, myositis/rhabdomyolysis, transaminases, pancreatitis, venous thrombotic events, gall-bladder disease and in combination with statin therapy rhabdomyolysis leading to renal failure, and the percentage of individuals discontinuing therapy due to side effects.

Search methods for identification of studies

Electronic searches—We will search MEDLINE (Ovid), EMBASE (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, and CINAHL (EBSCO) (all from their inception) with the help of an experienced professional librarian. We will use Cochrane sensitive search strategies for randomized controlled trials (Lefebvre 2011). No language restrictions will be imposed. The search strategy that has been developed to search MEDLINE (OVID) together with the Cochrane Heart Group can be found in Appendix 1. It will be adapted where necessary to search the other databases listed. In addition, we will search the Conference Proceedings Citation Index- Science (CPCI-S) on ISI Web of Science for eligible trials published as abstracts at conferences.

Searching other resources—Reference lists of identified articles, published editorials, reviews on the topic will also be searched for further eligible studies. We will search trial registries (www.clinicaltrials.gov; www.controlled-trials.com; isrctn.org) and will contact authors of included studies to find out about missing data, ongoing and unpublished trials.

Data collection and analysis

Selection of studies—Investigators, working in teams of two, will independently review potentially eligible titles and abstracts. If either reviewer believes the study may be eligible, we will obtain the full report. After obtaining full reports of the candidate studies (either in full peer-reviewed publication or press article) two reviewers will independently assess eligibility from full text papers. Discrepancies will be resolved by reviewers' consensus or, if needed, by third party arbitration.

Data extraction and management—Two reviewers will use pre-piloted forms to independently extract all relevant data on baseline characteristics of trials, patient populations, outcomes and probably additional data provided by original trial investigators. If available, we will collect data on total cholesterol, LDL-cholesterol, HDL-cholesterol, and

triglycerides at baseline and follow-up. Any disagreement between reviewers will be resolved by consensus. Details of included and excluded trials will be provided in a table.

Assessment of risk of bias in included studies—Working in teams of two, we will independently assess the quality of each included trials with respect to concealment of treatment allocation; random sequence generation; blinding of patients, care-givers, or assessors of clinical outcomes; completeness of follow-up; and selective reporting of outcomes (Cochrane Handbook 2011). Possible disagreement will be resolved by consensus of third party arbitration if needed. We will explore the influence of individual quality criteria in a sensitivity analysis.

Measures of treatment effect—Relative risks and accompanying 95% CI.

Unit of analysis issues—We will use aggregated outcome data for analysis. RCTs will be the unit of analysis.

Dealing with missing data—In case of unpublished, incomplete data, or published data that can not be directly integrated into our analysis we will contact the investigators of the original trials and ask for the relevant information.

Assessment of heterogeneity—We will test for heterogeneity with the Cochran's Q-test and use I^2 to measure inconsistency of treatment effects across different lipid-lowering interventions (Cochrane Handbook 2011; Higgins 2002; Higgins 2003).

Assessment of reporting biases—We will check for outcome reporting bias by comparing reported outcomes to outcomes mentioned in corresponding trial protocols, outcomes mentioned in trial registries, or outcomes mentioned in the Methods section of publications. We will investigate the presence of publication bias by means of funnel plots (Sterne 2001).

Data synthesis—We will pool treatment effects across studies and calculate a weighted average risk ratios for all outcomes in the treatment and control groups by using a random effects model.

Numbers needed to treat per year to prevent one event will be calculated by multiplication of the averaged weighted mean annual baseline risk with the mean relative risk reduction in each intervention category (Marx 2003).

The percentage of any change in lipid-levels for each trial will be calculated as the difference in the mean change from baseline to end of follow-up in the intervention and control groups.

All analyses will be conducted with Review Manager 5.1 (Cochrane Collaboration) and Stata 9.2 (StataCorp, College Station/Texas, USA).

Subgroup analysis and investigation of heterogeneity—If available data allow, we will use inverse variance-weighted meta-regression analysis (Thompson 1999) to investigate

any association between the outcomes and the extent of cholesterol and triglycerides reduction, items about trial quality, individuals with type 2 diabetes versus individuals without type 2 diabetes, and the type and duration of lipid-modifying intervention.

Sensitivity analysis—For sensitivity analysis we will examine treatment effects according to quality components in lipid reducing trials (presence versus absence of reported concealed treatment allocation, reported blinding of patients & caregivers versus not reported, reported blinded outcome assessment versus not reported), trials including only patients with type 2 diabetes versus trials not including patients with type 2 diabetes, and trials using fibrates in addition to other lipid-modifying drugs versus using fibrates as monotherapy.

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Internal sources

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External sources

- Ciber de Epidemiología y Salud Publica (CIBERESP), Spain. Spanish Ministry of Science, Spain. A competitive grant

Appendix 1. MEDLINE search strategy

The following search strategy was developed for MEDLINE (Ovid) together with the Cochrane Heart Group; it will be adapted for other electronic databases:

1. Exp Fibric Acid or fibrate\$.mp. or fibric acid\$.tw.or exp Clofibrac Acid/
2. gemfibrozil.mp. or Gemfibrozil/ or gemfibrocil.tw
3. bezafibrate/ or clofibrate/ or ciprofibrat\$
4. fenofibrate.mp. or Procetofen/
5. (bezafibrate or clofibrate).mp.
6. bezafibrate/ or bezafibrate.mp. or 41859-67-0.rn. or asufibrat.mp. or azufibrat.mp. or (bm-15075 or bm15075).rn,mp.
7. (befibrat or befizal or beza or bezabeta or bezacur or bezafibratum).mp.
8. (bezafisal or bezagen or beza-lande or bezalande or bezalex or bezalip).mp.
9. (bezamerck or bezamil or beza-puren or bezapuren or bezastad or bezatol).mp.
10. (bionolip or cedur or colser or difaterol or durabezur or eulitop).mp.
11. (hadiel or klestran or (lo-44 or lo44) or liparol or lipitrol or lipocin).mp.
12. (lipox or norlip or pms-bezafibrate or polyzalip or redalip).mp.

13. (reducterol or regadrin b or sklerofibrat or solibay or wayfrato).mp.
14. (zafibril or zimbacol or ciprofibrate or 52214-84-3 or bi-liponor).mp,rn.
15. (hyperlipen or cirpol or lipanor or modalim or oroxadin).mp. or (win-35833 or win35833).mp,rn.
16. clofibrate.mp. or 637-07-0.rn. or 882-09-7.rn. or abitrate.mp. or amotril.mp.
17. (anparton or anti-lipide-ratiopharm or apolan or arterioflexin).mp.
18. (arteriosan or artevil or ateculon or ateriosan or atheroprnt).mp.
19. (atromidin or atromid-s).mp. or (ay-61123 or ay61123).mp,rn. or azionly.mp.
20. (bioscleran or cartagyl or claripex or clobren or clofibril).mp.
21. (clofibrat or clofibratum or clofirem or clofi or clofibrin or clofibrinic acid or clofinit or clofenapate or methylclofenapate).mp.
22. (colebron or col or geromid or hyclorate).mp. or (ici-28257 or ici28257 or ici55695 or ici-55695 or nsc1149 or nsc-1149).mp,rn.
23. (liaptene or lipavil or lipavlon or lipilim or lipofacton or lipomid).mp.
24. (liprinal or miscleron or misclerone or neo-atromid or athromidin or normet).mp.
25. (regulipid or sinteriod or serotoninex or sklerepmexe or skleromexe).mp.
26. (s trat os or stratos or sklero-tablinene or sklerolip or ticlobran).mp. (3)
27. (xyduril or gemfibrozil).mp. or 25812-30-0.rn. or apo-gemfibrozil.mp. or ausgem.mp.
28. bolutol.mp. or (ci-719 or ci719).mp,rn. or decrelip.mp. or deopid.mp. or dom-gemfibrozil.mp.
29. (dropid or elmogan or emfib or fibrociit or fibros or gemcor).mp.
30. (gemfibril or gemfibromax or gemhexal or gemizol or gemlipid).mp.
31. (gemnpid or gen-gemfibrozil or nugemfibrozil or genlip or genozil or genozil).mp.
32. (gozid or hidil or ipolipid or jezil or lipazil or lipidys or lipox gemfi or gemfi 1a pharma or lipidil or lofibra or lipison).mp.
33. (lipofor or lipogen or lipoite or lipozid or lipozil or lipur).mp.
34. (litarek or locholes or lopid or lopizid or mariston or med-gemfibrozil).mp.
35. (norpid or novo-gemfibrozil or pilder or pms-gemfibrozil or poli-fibrozil).mp.
36. (polyxit or recozil or riva-gemfibrozil or synbrozil or taborcil).mp.
37. (tentroc or tiba or trialmin or fenofibrate or procetofen).mp.
38. 49562-28-9.rn. or apofen.mp. or ankebin.mp. or apo-fenofibrate.mp. or apo-feno-micro.mp.
39. (catalip or cil or controlip or dom-fenofibrate or durafenat).mp.

40. (elasterin or fegenor or fenobeta or fenobrate or fenogal or fenofanton or phenofibrate).mp.
41. (fenolip or fenotard or feno-micro-200 or fulcro or gen-fenofibrate).mp.
42. lexemin.mp. or (1f-179 or 1f179).mp,rn. or (1f-178 or 1f178).mp,rn. or lipanon.mp. or lipanthyl.mp.
43. (lipantil or liparison or lipcor or lipidax or lipidil or lipil).mp.
44. (lipirex or lipoclar or lipofene or lipofen or lipo red or liposit).mp.
45. (lipovas or lipsin or livesan or nolipax or normalip or procetofene).mp.
46. (qualecon or scleril or procetoken or protolipan or secalip).mp.
47. (supralip or tilene or tricor or volutine or tocofibrate).mp. or 50465-39-9.rn.
48. (transferal or theofibrate or etofylline clofibrate).mp. or 54504-70-0.rn.
49. duolip.mp. or (ml-1024 or ml1024).mp,rn. or theofol.mp.
50. or/1-49
51. exp Cardiovascular Diseases/
52. exp Cerebrovascular Disorders/
53. coronary.mp.
54. (heart adj (disease\$ or attack\$)).mp.
55. (coronary adj (disease\$ or event\$)).mp.
56. (cerebrovascular\$ or cardiovasc\$).mp.
57. (myocardial adj (infarct\$ or re?vascular\$ or ischemi\$)).mp.
58. (stroke\$ or mortal\$).mp.
59. (morbid adj5 (heart\$ or cardiovascula\$ or coronary\$ or isch?em\$ or myocard \$)).mp.
60. (cardio\$ or cardia\$ or heart\$ or coronary\$ or angina\$ or ventric\$ or myocard\$ or pericard\$ isch?em\$).tw.
61. (apoplexy or (brain adj2 accident\$).tw.
62. ((brain\$ or cerebral or lacunar) adj2 infarct\$).tw.
63. exp Hypertension/
64. (hypertensi\$ or peripheral arter\$ disease\$).tw.
65. peripheral arter\$ disease\$.tw.
66. ((high or increased or elevated) adj2 blood pressure).tw.
67. exp Hyperlipidemias/

68. (hyperlipid\$ or hyperlip?emia\$ or hypercholesterol\$ or hypercholester?emia\$ or hyperlipoprotein?emia\$ or hypertriglycerid? emia\$).tw.
69. (emboli\$ or arrhythmi\$ or thrombo\$ or atrial fibrillat\$ or tachycardi\$ or endocardi\$ or (sick adj sinus)).tw.
70. or/51-69
71. randomized controlled trial\$.mp.
72. randomized controlled trial.pt.
73. controlled clinical trial.pt.
74. randomized.ab.
75. placebo.ab.
76. drug therapy.fs.
77. randomly.ab.
78. trial.ab.
79. groups.ab.
80. or/71-79
81. exp animals/ not humans.sh.
82. 80 not 81
83. 70 and 82
84. 83 and 50

HISTORY

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