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RESEARCH

Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117 411 patients

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Abstract

Objective To investigate the effects on cardiovascular outcomes of drug interventions that increase high density lipoprotein levels.

Design Meta-analysis.

Studies reviewed Therapeutic benefit of niacin, fibrates, and cholesteryl ester transfer protein (CETP) inhibitors on cardiovascular events (all cause mortality, coronary heart disease mortality, non-fatal myocardial infarction, and stroke).

Results 117 411 patients were randomised in a total of 39 trials. All interventions increased the levels of high density lipoprotein cholesterol. No significant effect was seen on all cause mortality for niacin (odds ratio 1.03, 95% confidence interval 0.92 to 1.15, P=0.59), fibrates (0.98, 0.89 to 1.08, P=0.66), or CETP inhibitors (1.16, 0.93 to 1.44, P=0.19); on coronary heart disease mortality for niacin (0.93, 0.76 to 1.12, P=0.44), fibrates (0.92, 0.81 to 1.04, P=0.19), or CETP inhibitors (1.00, 0.80 to 1.24, P=0.99); or on stroke outcomes for niacin (0.96, 0.75 to 1.22, P=0.72), fibrates (1.01, 0.90 to 1.13, P=0.84), or CETP inhibitors (1.14, 0.90 to 1.45, P=0.29). In studies with patients not receiving statins (before the statin era), niacin was associated with a significant reduction in non-fatal myocardial infarction (0.69, 0.56 to 0.85, P=0.0004). However, in studies where statins were already being taken, niacin showed no significant effect (0.96, 0.85 to 1.09, P=0.52). A significant difference was seen between these subgroups (P=0.007). A similar trend relating to non-fatal myocardial infarction was seen with fibrates: without statin treatment (0.78, 0.71 to 0.86, P<0.001) and with all or some patients taking statins (0.83, 0.69 to 1.01, P=0.07); P=0.58 for difference.

Conclusions Neither niacin, fibrates, nor CETP inhibitors, three highly effective agents for increasing high density lipoprotein levels, reduced all cause mortality, coronary heart disease mortality, myocardial infarction, or stroke in patients treated with statins. Although observational studies might suggest a simplistic hypothesis for high density lipoprotein cholesterol, that increasing the levels pharmacologically would generally reduce cardiovascular events, in the current era of widespread use of statins in dyslipidaemia, substantial trials of these three agents do not support this concept.

Introduction

The discovery that raised low density lipoprotein and low high density lipoprotein levels are associated with an increased cardiovascular mortality[1 2] encouraged the development of targeted drug treatments. The primary aim of these drugs was to increase high density lipoprotein levels or lower low density lipoprotein levels, to prevent an increase in cardiovascular disease, the single greatest cause of death worldwide.[3]

Reduction in low density lipoprotein levels with statins has repeatedly been found to reduce cardiac events and all cause mortality in the setting of both secondary and primary prevention.[4] Statins are available generically at low cost. Attention has now turned to targeting levels of high density lipoprotein in the hope of similar large benefits.

The three main agents proposed to increase high density lipoprotein levels to reduce cardiovascular morbidity and mortality are niacin, fibrates, and the recently developed cholesterylester transfer protein (CETP) inhibitors. We conducted a meta-analysis of randomised controlled trials of these three classes of agents to determine their effects on mortality and cardiovascular events.

Methods

We included all published and unpublished randomised controlled trials that compared niacin, fibrates, or CETP inhibitors against a control with or without concurrent statin

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Appendices 1-7

treatment. No language restrictions were applied. We searched Medline (1966 to 5 May 2013), the Cochrane Central Register of Randomised Controlled Trials (to 5 May 2013), and the WHO International Clinical Trials Registry Platform search portal (to 5 May 2013) using search terms that included randomised controlled trial and drug family names (niacin, fibrates, and CETP inhibitors), and drug names within each class. Supplementary appendix 1 provides the full search terms. We additionally hand searched previous meta-analyses and reviews and included results presented at recent conferences before formal publication.

Two authors (DK and CP) carried out the literature search. Three authors (DK, CP, MJS-S) extracted data and assessed the quality of the trials independently in triplicate using a standardised approach. Disagreements were resolved through consensus with the help of an additional author (DPF). To be eligible for inclusion, the trials had to be completed randomised controlled trials that assessed the effects of the intervention compared with a control group and that reported one or more of our primary or secondary outcomes. We used the Cochrane Collaboration's tool for assessing risk of bias for quality assessment.

The primary outcome was all cause mortality on an intention to treat basis. This endpoint is highly relevant and has the least risk of bias. Secondary outcomes were coronary heart disease mortality, non-fatal myocardial infarction, stroke, and reported important adverse events. Since most patients with abnormalities in lipid levels are currently treated with statins we separated the trials into those in which there was no statin treatment compared with those in which some or all of the participants received statin treatment.

Event rates were extracted from the studies. We used the I^2 statistic to assess for heterogeneity. When no significant heterogeneity was detected we performed a random effects meta-analysis in RevMan (version 5.2) using the Mantel-Haenszel odds ratio and risk difference for harm.

Results

The literature searches identified 387 publications of niacin, 749 of fibrates, and 263 of CETP inhibitors that potentially met our criteria. Of these there were 11 eligible trials of niacin, 20 of fibrates, and eight of CETP inhibitors. Two trials were of niacin and fibrate in combination compared with control (see supplementary appendix 2).

In one trial[9] niacin was part of combination treatment with colestipol, with the control arm receiving neither. In two trials[5 14] niacin and a fibrate were part of a combination treatment, with the control arms receiving neither. We included these two trials in both the niacin and fibrate analyses, and we performed a sensitivity analysis with them excluded (see supplementary appendix 5).

Niacin

Description of included studies

Eleven completed randomised controlled trials[5-15] enrolling 35 301 patients, lasting between six and 60 months, reported the effects of niacin on the included outcomes (table 1⇓). Of these, 30 310 patients[6 7 11-13] were in trials with statin used by some or all the patients, and 4991 patients were in trials with no statin treatment.[5 8-10 14 15] The most recent trial, HPS2-Thrive, has announced its outcome data, which we have included in this meta-analysis.

Assessment of quality

Concealing allocation with niacin is challenging because of the high risk of flushing. In one attempt to ameliorate this unavoidable unblinding, participants were given a small dose of niacin in the placebo[6] on the assumption that this would be enough to cause flushing but not enough to prevent events. Another approach has been to add agents to inhibit the flushing effect, such as aspirin[9 11] or laropiprant.[12] Laropiprant is thought to work by modifying prostaglandin pathways. It is possible, however, that its effect could confound the effect of niacin. One study did not make a special attempt to obscure this effect and might therefore be argued to be unblinded.[14] A higher cessation of treatment was seen in the niacin compared with the placebo group in most of the studies,[6 8 10-12 14] predominantly as a result of the unpleasant side effect of facial flushing.

The assessment of risk of bias can be found in supplementary appendix 3a.

Efficacy on cardiovascular endpoints

Overall, niacin had no net effect on all cause mortality (odds ratio 1.03, 95% confidence interval 0.92 to 1.15, P=0.59). No statistically significant difference (P=0.10) was seen in studies conducted with statin treatment (1.10, 1.00 to 1.21, P=0.06) or without (0.86, 0.65 to 1.14, P=0.29, fig 1⇓).

Neither was there any significant effect across all trials on the secondary outcomes of coronary heart disease mortality (0.93, 0.76 to 1.12, P=0.44), non-fatal myocardial infarction (0.85, 0.72 to 1.01, P=0.07), or stroke (0.96, 0.75 to 1.22, P=0.72, see table 4).

In studies conducted without statin treatment a significant benefit was seen for the outcomes of non-fatal myocardial infarction (0.69, 0.56 to 0.85, P=0.0004) and stroke (0.78, 0.61 to 1.00, P=0.05). This effect was not, however, seen in studies conducted with statin treatment (0.96, 0.85 to 1.09, P=0.52 and 1.10, 0.70 to 1.74, P=0.68, respectively). The difference between these subgroups was statistically significant for non-fatal myocardial infarction (P=0.007) but not for stroke (P=0.19).

Reported adverse events

Niacin is known to cause flushing. This was clearly reported on in four trials.[6 11-13] Of these trials, one gave a small dose of niacin to the placebo group,[6] one recommended that participants took aspirin,[11] one gave laropiprant,[12] and one was unblinded.[13] Across these trials, the risk difference in the development of an adverse skin effect was 0.05 (95% confidence interval 0.03 to 0.07, P<0.001), and heterogeneity between trials was significant (I^2=86%).

The HPS2-Thrive study reported multiple new signals for possible harm, including infection, gastrointestinal complications, bleeding, complications of diabetes, and musculoskeletal side effects (see supplementary appendix 7).

Fibrates

Description of included studies

Twenty completed randomised controlled trials[5 8 14 16-32] enrolling 46 099 patients, lasting between 12 and 85 months, reported the effects of fibrates on the included outcomes (table 2⇓). One study had to be excluded as it did not report extractable data on our endpoints.[19] In two of the studies[26 28] some or all of the patients were receiving statin treatment (100% and 26%, respectively).

Assessment of quality

Early trials[14 20 22-24] presented limited data on the key aspects of trial quality, such as randomisation and maintenance of blinding. More recent trials[17 26-28] showed better evidence of good quality design, with satisfactory central randomisation using block design stratification with clear central event adjudication, and methods in place to ensure maintenance of double blinding. Dropout rates were high in several trials[14 26 31] partly perhaps because of publicity surrounding the published WHO Clofibrate study,[25] which reported an increased mortality for patients receiving fibrates.

The assessment of risk of bias can be found in supplementary appendix 3b.

Effect on cardiovascular endpoints

All cause mortality was not found to be significantly affected by fibrate treatment (odds ratio 0.98, 95% confidence interval 0.89 to 1.08, P=0.66). Heterogeneity across the 20 trials was moderate (I^2=33%). No statistically significant difference was seen in all cause mortality in studies conducted with statin treatment (1.01, 0.83 to 1.24, P=0.12)[26 28] or without (0.96, 0.86 to 1.09, P=0.55)[5 8 14 16-18 20-27]; P=0.67 for difference between the subgroups (fig 2⇓).

Neither coronary heart disease mortality (0.92, 0.81 to 1.04, P=0.19) nor stroke (1.01, 0.90 to 1.13, P=0.84) were found to be significantly affected by fibrates across all trials. Overall, however, non-fatal myocardial infarction was found to be reduced (0.80, 0.74 to 0.87, P<0.001) (see table 4). This effect was statistically significant in the trials without statin treatment (0.78, 0.71 to 0.86, P<0.001), but not in those with statin treatment (0.83, 0.69 to 1.01, P=0.07). The difference between these subgroups was not significant (P=0.58).

Reported adverse events

Across three trials, fibrates were associated with a small statistical increase in pulmonary emboli (risk difference 0.01, 95% confidence interval 0.00 to 0.01, P=0.002). Other reported adverse effects are included in supplementary appendix 7.

CETP inhibitors

Description of included studies

Eight completed randomised controlled trials[33-40] enrolling 36 011 patients examined three agents in this class: anacetrapib, dalcetrapib, and torcetrapib (table 3⇓). All randomisations were between the addition of CETP inhibitor and placebo, with virtually all patients receiving statin treatment. Duration of follow-up ranged from eight months to 31 months. Two more trials, ACCELERATE (NCT01687998) and HPS3/TIMI-55 (REVEAL, NCT01252953), are underway, and are expected to finish in January 2016 and January 2017, respectively.

Assessment of quality

Most trials used electronic central random sequence generation.[33-35 40] In many[33 34 36-38] there was an external adjudication committee blinded to the endpoint. In all studies both the patients and the assessors were blinded. In six studies patients and staff were also blinded to follow-up cholesterol levels.[33-36 39 40] In one study[37] the CETP inhibitor arm had a higher dropout rate than the control arm, as well as a higher adverse event rate, including more hypertension and diarrhoea. Two of the studies involving torcetrapib [37 40] were stopped early because of adverse events in the treatment arms, and one involving dalcetrapib[33] due to futility.

The assessment of risk of bias can be found in supplementary appendix 3c.

Effect on cardiovascular endpoints

Torcetrapib was found to significantly increase mortality (odds ratio 1.53, 95% confidence interval 1.12 to 2.09, P=0.007). This effect was not seen with anacetrapib (1.38, 0.55 to 3.45, P=0.49) or with dalcetrapib (0.98, 0.81 to 1.18, P=0.82). The differences between these subgroups was significant (I^2=67.4%, P=0.05, fig 3⇓). When considering only anacetrapib and dalcetrapib, mortality was found not to be significantly affected (0.99, 0.83 to 1.19, P=0.93).

CETP inhibitors were found to have no significant effect on coronary heart disease mortality (1.00, 0.80 to 1.24, P=0.31), non-fatal myocardial infarction (1.05, 0.93 to 1.18, P=0.41), or stroke (1.14, 0.90 to 1.45, P=0.29). Table 4⇓ summarises these results.

Reported adverse events

As well as the increased risk of mortality associated with torcetrapib, the rate of hypertension was found to be increased (risk difference 0.10, 95% confidence interval 0.06 to 0.14). This effect was not seen with the other CETP inhibitors. Dalcetrapib was associated with a significant increase in diarrhoea (0.02, 0.02 to 0.03, P<0.001). Supplementary appendix 7 shows the other reported side effects.

Forest plots for all endpoints are available in supplementary appendix 4. A funnel plot for each agent for the endpoint of all cause mortality is shown in supplementary appendix 6. The funnel plots did not suggest publication bias.

Discussion

The three classes of agents studied in this meta-analysis (niacin, fibrates, and cholesteryl ester transfer protein (CETP) inhibitors), targeted at increasing high density lipoprotein levels, were not associated with a significantly reduced risk of all cause mortality and coronary heart disease mortality. This was the case in both the pre-statin era and the present era of widespread use of statins for cardiovascular event reduction. One agent for increasing high density lipoprotein levels, torcetrapib, did significantly change mortality, but this was an increase.

The statin era

Without background treatment with statins, fibrates were seen to reduce non-fatal myocardial infarction, and niacin to reduce both non-fatal myocardial infarction and stroke. However, in the modern era when treatment with statins is standard, this effect has not been apparent (fig 4⇓). Attempts at risk reduction through these treatments to increase high density lipoprotein levels on top of statin treatment have been unsuccessful so far.

Over-simplistic high density lipoprotein hypothesis?

With the impending flooding of the marketplace with low cost generic statins, it was rational for investment in preventive lipid modifying treatment to be directed towards non-statin interventions. The consistent finding in observational studies,[41-44] that an increased high density lipoprotein cholesterol level is associated with lower cardiovascular risk, made the increasing of high density lipoprotein levels a logical aim in drug development.

However it seems that in the statin era these three agent classes to increase high density lipoprotein levels have not been able to prevent clinically important events. This is despite the observational association that each 0.1 mmol/L higher high density lipoprotein level is associated with a 50-80% reduction[44] in coronary heart disease events.

For example, in the DEFINE study of anacetrapib,[36] the effect size on high density lipoprotein level was 1.4 mmol/L, which would correspond to a 66% to 89% reduction in cardiovascular events, quite apart from any event reduction through other mechanisms (for example, low density lipoprotein was approximately halved).

It could be argued that the studies so far have selected inappropriate candidates to study. Individual doctors sometimes feel confident that they can make better selections in daily practice. It should be remembered, however, that the companies planning substantial investment in trials took considerable care to select appropriate cohorts. None of these selections delivered net benefit on clinical endpoints in the statin era.

A strength of our analysis is that the mechanisms through which these three classes of agents increase high density lipoprotein levels are distinctly different, and have different pleiotropic effects. It is possible that, in each of the three cases a different off-target effect may have neutralised an underlying benefit of the drug. However, an alternative and arguably simpler interpretation might be that interventions targeted at raising high density lipoprotein levels should not be assumed to be beneficial.

It could also be argued that the CETP inhibitors show promise, with long term outcome trials underway. However, unless they find event rates reduced by 75% to 95%, which is what would be expected if the therapeutic impact of the changes in high density and low density lipoprotein levels matched the observational relations, we will never know whether the benefits are mediated through raising high density lipoprotein levels, lowering low density lipoprotein levels, or neither.

High density lipoprotein has subtypes and the molecule can vary in degree of function. This study cannot comment about whether an intervention that rebalances the distribution between subtypes, or alters their function, would reduce cardiovascular events. Adequately powered specific trials for this are as yet unavailable. A genome wide mendelian randomisation study[45] has provided a mechanistic basis for the observations in this meta-analysis by finding numerous genes that affect high density lipoprotein cholesterol levels without affecting the incidence of myocardial infarction. This has removed a major premise supporting the strategic aim of using drugs to increase high density lipoprotein levels.

Causation

Caution is needed before a conclusion can be made that the statins reduce mortality and the agents targeted at high density lipoprotein do not. The possibility cannot be excluded that high density lipoprotein targeted agents have a beneficial mortality effect but simultaneously abolish the statin benefit, leaving a net neutral effect. Nevertheless, how such abolition might occur is unknown.

Multiple convincing molecular mechanisms

High density lipoprotein has been reported to have a panoply of favourable properties,[46 47] including anti-inflammatory, antioxidant, and antithrombotic, and facilitating cholesterol transport out of lesions. Nevertheless, some of these agents have been associated with worrying signals. In the trials of torcetrapib,[37 38] which increased mortality, blood pressure was also noted to be increased and it was hoped that this might be the cause of the adverse outcomes so that these events could be reduced by using an alternative agent. Unfortunately, and as pointed out by the authors themselves, the increased mortality was in patients with lower, not higher, blood pressure. Furthermore, no mortality benefit was seen with the other two agents in the class, which did not share this blood pressure raising tendency.

Surrogate endpoint trials

Alongside trials of dichotomous endpoints, other trials have also measured quantitative markers such as atheroma burden through carotid intima media thickness, brachial flow mediated dilation, coronary atheroma quantification by intravascular ultrasonography, calculated angiographic lesion dimensions, and angiographic percentage stenosis. In the pre-statin era many of these trials[9 10 15 16 27] showed a significant beneficial effect on these surrogate markers when high density lipoproteins were increased by drug treatment compared with placebo. Despite impressive reductions in plaque burden being shown by these studies, the decrease has not translated into reduction of cardiovascular events. This mismatch is unexplained.

More recently the effect of these high density lipoprotein targeted treatments on lesion characteristics used rigorous techniques conducted in the statin era with a confirmed noticeable increase in high density lipoprotein showed no significant benefit on plaque burden.[19 35 38-40 48]

Clinical implications

A simple hypothesis that any drug intervention that successfully increases high density lipoprotein levels will give additional protection against important clinical events seems to be incorrect. Trials are underway with agents that simultaneously raise high density lipoprotein and lower low density lipoprotein levels.

For now, we suggest that clinicians quantifying high density lipoprotein for risk stratification should resist assuming that patients' cardiovascular risk will be reduced by using the three classes of agents assessed here to raise high density lipoprotein.

Implications for research

Equally an over-simplistic hypothesis for low density lipoprotein could also be considered doubtful. Only one class of agents, the statins, has a large effect on low density lipoprotein cholesterol levels and provides a large reduction in events. With statin treatment in place, no incremental manipulation of cholesterol, low density lipoprotein, or high density lipoprotein levels with a non-statin agent has been found to prevent events so far.

Higher strength statin regimens do reduce events further in secondary prevention,[49] but this is not proof that the accompanying lower low density lipoprotein level is the mechanism of benefit. The multiple effects of statins might be correlated in intensity across drug and dose. If so, effects on lipids and effects on cardiovascular events would be correlated, without the lipid reduction being the cause for the event reduction.

Notably, fine grained temporal analysis shows reduction in events from use of statins long before the plausible time at which lower lipid levels could mediate slower accumulation of atheroma and thereby could have had an effect.[50] Whether the decrease in low density lipoprotein cholesterol level is the

principal mechanism for the reduction of acute events by statins is, therefore, unknown.

Limitations of this study

Events were not necessarily adjudicated in the same way across all trials. They were, however, adjudicated consistently within individual trials and it was only the odds ratios from the trials that we combined, which should minimise the impact of differences in definitions between trials.

In our meta-analysis we only considered randomised controlled trials with available results. We cannot exclude the possibility that there were trials showing positive results but that these were not reported, although such a direction of publication bias is unusual.

We did not include non-randomised or uncontrolled studies because of the potential for confounding and bias that can be much larger than generally expected.[51]

Some trials had only a small numbers of events. Some used niacin and fibrate in combination: we considered these to be members of both the niacin and the fibrate groups. Sensitivity analyses (see supplementary appendix 5) showed that without these trials of combination treatment the effects are still neutral. Follow-up duration varied considerably across the trials; not all published a clear time to event analysis that might have allowed effects to be explored more fully.

Meta-analyses of such outcome data do not allow elucidation of mechanisms. Heterogeneity is reported in the particle size, charge, and composition of high density lipoprotein, and therefore level alone may be deemed an inadequate marker for functionality. However, despite this, the three drug agents studied were each considered to have a favourable effect on the high density lipoprotein profile, yet all failed to achieve a reduction in events when statin treatment was already in place.

Conclusions

The simple hypothesis that any agent that raises high density lipoprotein levels should decrease cardiovascular events may not be correct. Trials are underway of agents that raise high density lipoprotein levels while simultaneously reducing low density lipoprotein levels.

For patients who are unable to take statins, fibrates have been shown to reduce non-fatal myocardial infarction, and niacin has been shown to reduce both stroke and non-fatal myocardial infarction, despite neither reducing all cause mortality. These effects were, however, not seen in the current era of statin treatment.

Attempts to reduce cardiovascular events or mortality by raising high density lipoprotein levels using three dissimilar classes of agents has, when trialled in the statin era, so far been unsuccessful.

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Ethical approval: Not required.

Data sharing: Additional data are available from the corresponding author at drkeene@doctors.org.uk.

Transparency: DPF affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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What is already known on this topic

Increased levels of high density lipoprotein in observational studies correlate with improved cardiovascular outcomes

Three classes of agent aim to increase high density lipoprotein levels

What this study adds

In patients already prescribed a statin, neither niacin, fibrates, or cholesteryl ester transfer protein inhibitors improved cardiovascular outcomes

In patients not prescribed a statin, fibrates have been shown to reduce non-fatal myocardial infarction but not all cause mortality

In patients not prescribed a statin, niacin has been shown to reduce both stroke and non-fatal myocardial infarction but not all cause mortality

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Tables

Table 1| Description of included studies of niacin

Reference	Trial drugs and dose	Control	Follow-up (months)	No enrolled (No intervention, No control)	Statin use (%)	Men (No intervention, No control)	Mean (SD) age (years) (intervention, control)	White ethnicity (%)	Increase in HDL from baseline in active arm (%)
AFREGS[5] 2005	Niacin 240 mg to 3 g, gemfibrozil 600 mg twice daily (cholestyramine 2 g/d titrated to 16 g once daily if LDL increased)	Placebo (cholestyramine if LDL high)	30	143 (71, 72)	0	64, 68	63.3 (7.5), 63.1 (6.8)	NR	36
AIM HIGH[6] 2011	Niacin 1500-2000 mg, simvastatin 40-80 mg with or without ezetimibe as required	Placebo (contained 50 mg of immediate release niacin in each tablet), simvastatin 40-80 mg with or without ezetimibe as required	36	3414 (1718, 1696)	100	1465, 1445	63.7 (8.8), 63.7 (8.7)	92	25
ARBITER 2[7] 2004	Niacin extended release 500 mg for 30 days then 1000 mg and statin	Placebo and statin	12	167 (87, 80)	100	78, 74	67 (10), 68 (10)	NR	21
CDP 5 YR[8] 1975	Niacin 3 g	Lactose placebo 3.8 g daily	60	3908 (1119, 2789)	0	1119, 2789	NR	93	NR
CLAS[9] 1987	Niacin 3-12 g and 30 g colestipol	Placebo	24	188 (94, 94)	0	94, 94	53.9 (0.5), 54.5 (0.5)	94	37
FATS[10] 1990	Niacin 1 g four times daily and colestipol 10 g three times daily	Placebo (with or without colestipol if LDL increased)	30	100 (48, 52)	0	36, 46	47 (NR), 47 (NR)	NR	43
GUYTON[11] 2008	Niacin titrated to 2 g and ezetimibe 10 mg and simvastatin 20 mg	Ezetimbibe 10 mg once daily, simvastatin 20 mg one daily	6	948 (676, 272)	100	324, 152	56.9 (10.9), 57.5 (10.3)	87	30.2
HPS 2 THRIVE[12] 2013 (unpublished)	Niacin extended release 2 g and laropiprant 40 mg, simvastatin 40 mg with or without ezetimibe 10 mg	Placebo, simvastatin 40 mg with or without ezetimibe 10 mg	48	25673 (12 838, 12 835)	100	10 656, 10 653	64.9 (NR), 64.9 (NR)	NR	17
SANG[13] 2009	Niacin extended release 500 mg for 30 days then 1 g for 12 months and atorvastatin 10 mg	Atorvastatin 10 mg	12	108 (52, 56)	100	27, 39	72.88 (6.88), 68.83 (10.01)	NR	29
STOCKHOLM[14] 1988	Niacin up to 1 g three times daily and clofibrate 1 g twice daily	Conventional treatment	60	555 (279, 276)	0	219, 223	61.1 (NR), 60.7 (NR)	NR	NR
UCSF-SCOR[15] 1990	Niacin up to 7.5 g daily, colestipol 30 g daily, losuvastatin was offered towards end of trial	Conventional treatment with or without colestipol	26	97 (48, 49)	0	18, 13	41.4 (12), 42.4 (13)	NR	28

HDL=high density lipoprotein; LDL=low density lipoprotein; NR=not reported.

Table 2| **Description of included studies of fibrates**

Reference	Trial drugs and dose	Control	Follow-up (months)	No enrolled (No intervention, No control)	Statin use (%)	Men (No intervention, No control)	Mean (SD) age (years) (intervention, control)	White ethnicity (%)	Increase in HDL from baseline in active arm (%)
Becait[16] 1998	Bezafibrate 200 mg three times daily	Placebo	60	92 (47, 45)	0	47, 45	41 (NR), 41 (NR)	NR	9
SENDCAP[19] 1998	Bezafibrate 400 mg daily	Placebo	36	164 (81, 83)	0	61, 56	50.8 (8.0), 50.9 (8.1)	56	6
LEADER[18] 2002	Bezafibrate 400 mg daily	Placebo	74	1568 (783, 785)	0	783, 785	68.4 (8.9), 68.0 (8.8)	NR	8
BIP[17] 2000	Bezafibrate retard 400 mg (colestipol added if LDL >180 from 1994)	Placebo (colestipol added if LDL >180 from 1994)	74	3090 (1548, 1542)	0	1412, 1413	60.1 (6.8), 60.1 (6.7)	NR	18
Newcastle[22] 1971	Clofibrate 1.5-2 g	Placebo	60	497 (244, 253)	0	192, 208	52 (NR), 54 (NR)	NR	NR
Scottish[23] 1971	Clofibrate 1.6-2 g	Placebo	72	717 (350, 367)	0	288, 305	NR	NR	NR
WHO Clofibrate[25] 1978	Clofibrate 1.6 g	Placebo	63	10 627 (5331, 5296)	0	5331, 5296	45.9 (0.1), 45.8 (0.1)	NR	NR
Hanefeld (Diabetes Intervention Study)[21] 1991	Clofibrate 1.6 g	Placebo	60	662 (334, 328)	0	198, 231	45.8 (8.8), 46.2 (7.0)	NR	NR
CDP fibrate 5yr[8] 1975	Clofibrate 1.8 g	Placebo	60 month data reported	3892 (1103, 2789)	0	1103, 2789	NR	93	NR
Stockholm[14] 1988	Clofibrate 1 g twice daily and niacin up to 1 g three times daily	Conventional treatment	60	555 (279, 276)	0	219, 223	61.1 (NR), 60.7 (NR)	NR	NR
Acheson[20] 1972	Clofibrate 25 0mg (4 to 8× daily dependent on body weight)	Matching corn oil tablets for first 20 months. Then swapped to placebo tablets	85	95 (47, 48)	0	*68% overall	NR	NR	NR
VA Neuro[24] 1973	Clofibrate 500 mg four times daily	Placebo	54	532 (268, 264)	0	268, 264	NR	75.5	NR
Accord[26] 2010	Fenofibrate 160 mg once daily and open label simvastatin	Placebo and open label simvastatin	56	5518 (2765, 2753)	100	1914, 1910	62.2 (6.7), 62.3 (6.9)	68	8
Field[28] 2005	Fenofibrate 200 mg once daily	Placebo	60	9795 (4895, 4900)	26	3071, 3067	62.2 (6.8), 62.2 (2.9)	93	5
Dais[27] 2001	Fenofibrate 200 mg once daily	Placebo	36	418 (207, 211)	0	149, 156	57.4 (5.7), 56.3 (6.2)	96	9
VA-HIT[32] 1999	Gemfibrozil 1200 mg once daily	Placebo	61	2531 (1264, 1267)	0	1264, 1267	64 (7), 64 (7)	89.5	6
LOCAT[31] 1997	Gemfibrozil 1200 mg once daily	Placebo	32	395 (197, 198)	0	197, 198	58.8 (7.3), 59.5 (6.2)	NR	21
HHS[29] 1987	Gemfibrozil 600 mg twice daily	Placebo	60	4081 (2051, 2030)	0	2051, 2030	47.2 (4.6), 47.4 (4.6)	NR	10
HHS Exclusions[30] 1993	Gemfibrozil 600 mg twice daily	Placebo	60	628 (311, 317)	0	311, 317	48.7 (NR), 48.6 (NR)	NR	8.6
AFREGS[5] 2005	Gemfibrozil 600 mg twice daily, niacin 240 mg to 3 g once daily (cholestyramine 2 g/d titrated to 16 g once daily if LDL increased)	Placebo (cholestyramine if LDL increased)	30	143 (71, 72)	0	64, 68	63.3 (7.5), 63.1 (6.8)	NR	36

HDL=high density lipoprotein; LDL=low density lipoprotein; NR=not reported.

Table 3| **Description of included studies of cholesteryl ester transfer protein (CETP) inhibitors**

Reference	Trial drugs and dose	Control	Follow-up (months)	No enrolled (No intervention, No control)	Statin use (%)	Men (No intervention, No control)	Mean (SD) age (years) (intervention, control)	White ethnicity (%)	Increase in HDL from baseline in active arm (%)
Dal-OUTCOMES[33] 2012	Dalcetrapib 600 mg daily	Placebo	31	15 871 (7938, 7933)	97	6365, 6436	60.3 (9.1), 60.1 (9.1)	88	40
Dal-PLAQUE[34] 2011	Dalcetrapib 600 mg daily	Placebo	24	130 (64, 66)	87	51, 55	62.6 (8.2), 64.6 (7.8)	92	31
Dal-VESSEL[35] 2012	Dalcetrapib 600 mg daily	Placebo	8	476 (239, 237)	95	211, 211	62.3 (7.05), 61.9 (7.92)	NR	31
Define[36] 2010	Anacetrapib 100 mg daily	Placebo	18	1623 (811, 812)	99	629, 618	62.5 (8.7), 62.9 (9.0)	83	138
Illuminate[37] 2007	Torcetrapib 60 mg daily	Placebo	18	15 054 (7528, 7526)	100	5854, 5861	61.3 (7.6), 61.3 (7.6)	93	72
Illustrate[38] 2007	Torcetrapib 60 mg daily	Placebo	24	1188 (591, 597)	100	416, 421	56.9 (9.1), 57 (9.2)	NR	61
Radiance 1[39] 2007	Torcetrapib 60 mg daily	Placebo	24	850 (423, 427)	100	214, 232	46.8 (12.0), 45.2 (12.9)	NR	52
Radiance 2[40] 2007	Torcetrapib 60 mg daily	Placebo	20	752 (377, 375)	100	237, 245	57.9 (8.1), 56.5 (8.2)	NR	63

HDL=high density lipoprotein; NR=not reported.

Table 4| **Combined results of meta-analysis showing effect of niacin, fibrate, and cholesteryl ester transfer protein (CETP) inhibitors on risk of all cause mortality, coronary heart disease mortality, non-fatal myocardial infarction, and stroke**

	No of events/Total			
Events by drug class	**Intervention**	**Placebo**	**Odds ratio (Mantel-Haenszel random (95% CI)**	**P value**
Niacin				
All cause mortality:				
All trials	1194/17 030	1486/18 271	1.03 (0.92 to 1.15)	0.59
Non-statin trials	299/1659	669/3332	0.86 (0.65 to 1.1.4)	0.29
Statin trials	895/15 371	817/14 939	1.10 (1.00 to 1.21)	0.06
Coronary heart disease mortality:				
All trials	565/16 795	852/18 034	0.93 (0.76 to 1.12)	0.44
Non-statin trials	2225/1563	527/3231	0.75 (0.48 to 1.18)	0.21
Statin trials	340/15 232	325/14 803	1.05 (0.90 to 1.22)	0.57
Non-fatal myocardial infarction:				
All trials	645/17030	921/18271	0.85 (0.72 to 1.01)	0.07
Non-statin trials	136/1659	399/3332	0.69 (0.56 to 0.85)	0.0004
Statin trials	509/15371	527/14939	0.96 (0.85 to 1.09)	0.52
Stroke:				
All trials	620/16 788	797/18 020	0.96 (0.75 to 1.22)	0.72
Non-statin trials	92/1517	278/3189	0.78 (0.61 to 1.00)	0.05
Statin trials	528/15 319	519/14 883	1.10 (0.70 to 1.74)	0.68
Fibrates				
All cause mortality:				
All trials	1763/22 140	2123/23 795	0.98 (0.89 to 1.08)	0.66
Non-statin trials	1204/14 480	1579/16 142	0.96 (0.86 to 1.09)	0.55
Statin trials	559/7660	544/7653	1.01 (0.83 to 1.24)	0.89
Coronary heart disease mortality:				
All trials	704/21 886	1032/23 536	0.92 (0.81 to 1.04)	0.19
Non-statin trials	582/14 226	925/15 883	0.88 (0.78 to 1.00)	0.05
Statin trials	122/7660	107/7653	1.14 (0.88 to 1.49)	0.32
Non-fatal myocardial infarction:				
All trials	1104/21 896	1574/23 549	0.80 (0.74 to 0.87)	<0.001
Non-statin trials	773/14 236	1181/15 896	0.78 (0.71 to 0.86)	<0.001
Statin trials	331/7660	393/7653	0.83 (0.69 to 1.01)	0.07
Stroke:				
All trials	610/20 784	772/22 404	1.01 (0.90 to 1.13)	0.84
Non-statin trials	401/13 124	549/14 751	1.06 (0.91 to 1.23)	0.48
Statin trials	209/7660	223/7653	0.94 (0.77 to 1.13)	0.49
CETP inhibitors				
All trials:				
All cause mortality	340/18 003	307/18 008	1.16 (0.93 to 1.44)	0.19
Coronary heart disease mortality	163/18 003	163/18 008	1.00 (0.80 to 1.24)	0.99
Non-fatal myocardial infarction	582/18 003	553/18 008	1.05 (0.93 to 1.18)	0.41
Stroke	143/18 003	127/18 008	1.14 (0.90 to 1.45)	0.29

Figures

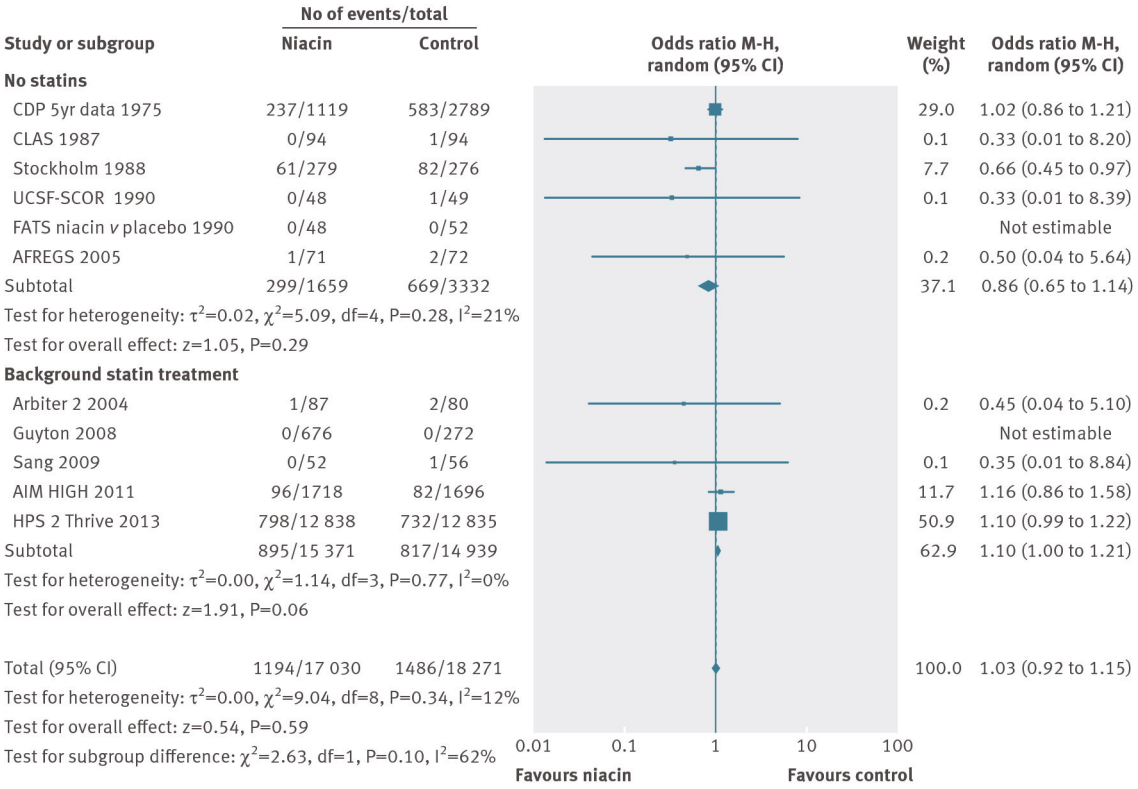

Fig 1 Forest plot showing effect of niacin on risk of all cause mortality, stratified by use of statin in trial

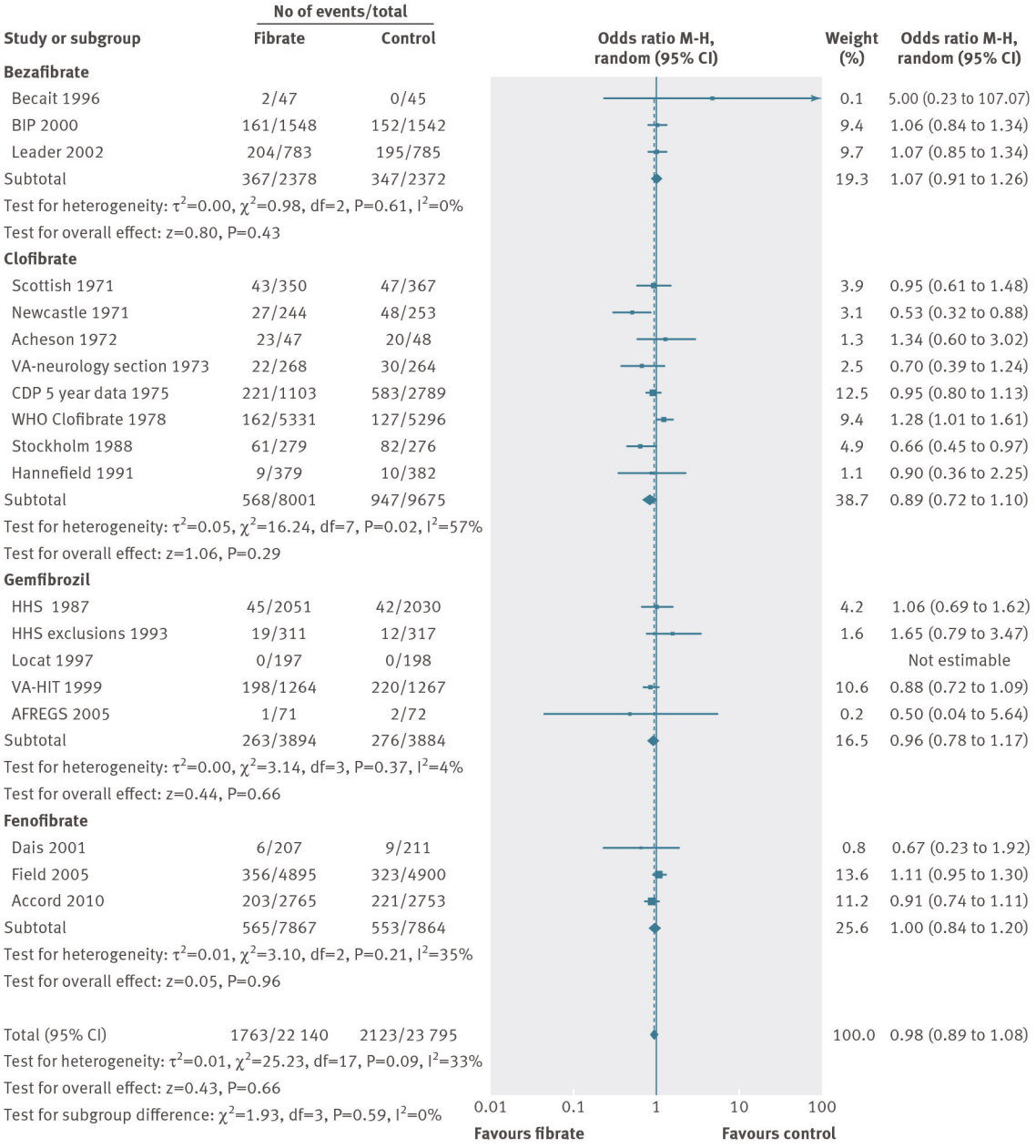

Fig 2 Forest plot showing effect of fibrates on risk of all cause mortality stratified by different fibrate agents

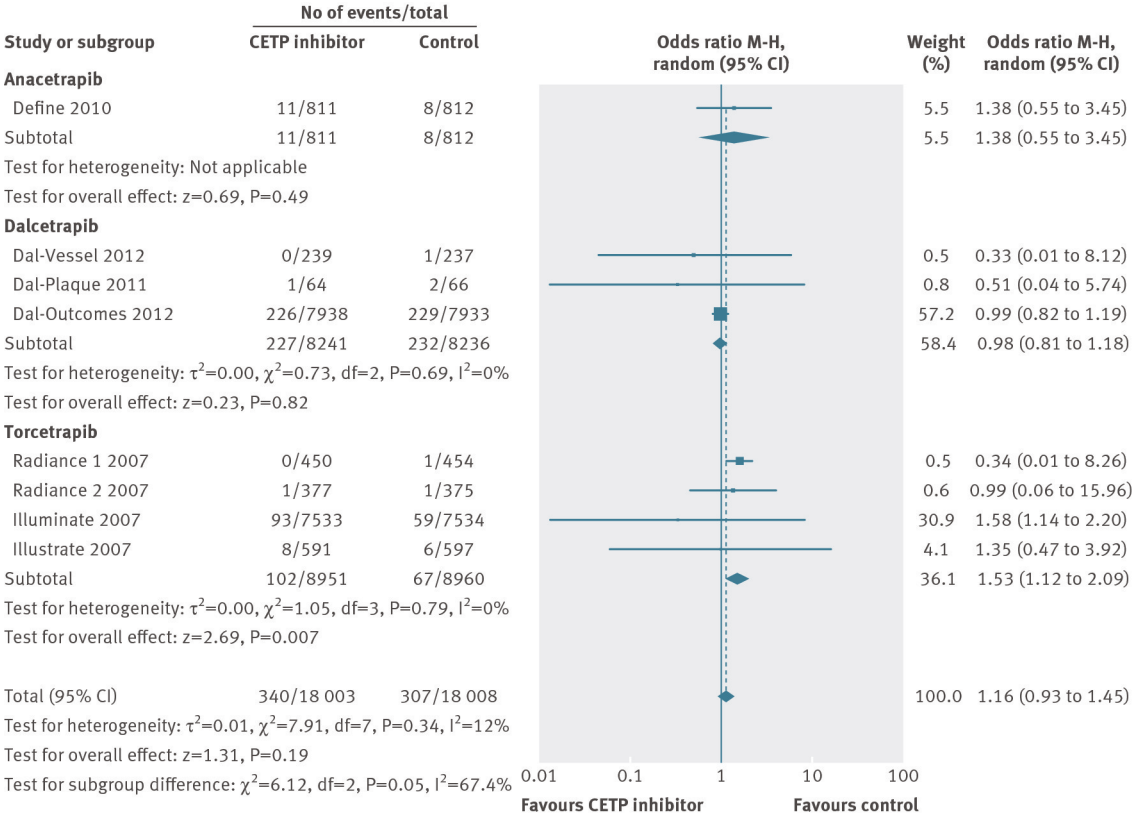

Fig 3 Forest plot showing effect of cholesteryl ester transfer protein (CETP) inhibitors on risk of all cause mortality stratified by CETP inhibitors

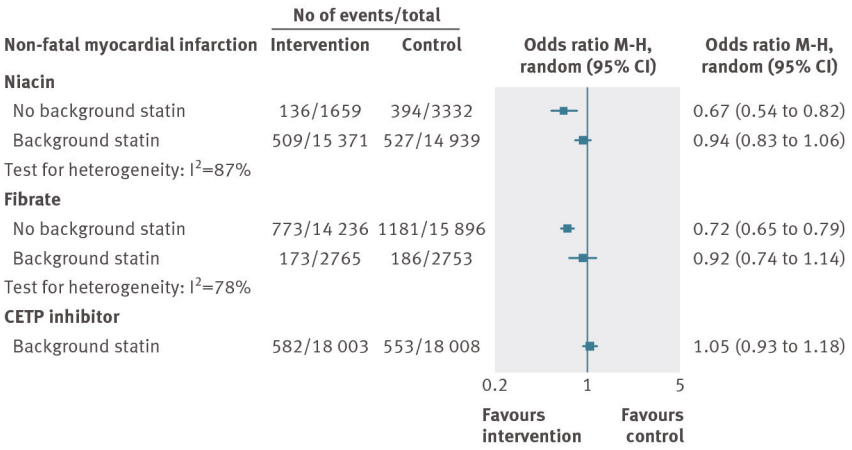

Fig 4 The statin revolution: without background statin treatment, fibrates and niacin were found to reduce non-fatal myocardial infarction. In the modern era, however, when background treatment of patients with dyslipidaemia typically includes statins, this effect was not apparent