Effect of fenofibrate on plasma apolipoprotein C-III levels: a systematic review and meta-analysis of randomised placebo-controlled trials

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ABSTRACT

Objectives This meta-analysis of randomised placebo-controlled clinical trials aimed to assess the effect of fenofibrate on apolipoprotein C-III (apo C-III), a key regulator of triglyceride metabolism.

Materials and methods Randomised placebo-controlled trials investigating the impact of fenofibrate treatment on apo C-III levels were searched in PubMed-Medline, Scopus, Web of Science and Google Scholar databases from inception to 18 August 2017. Quantitative data synthesis was determined by a random-effects model and generic inverse variance method. Sensitivity analysis was conducted using the leave-one-out method. A weighted random-effects meta-regression was performed to evaluate glycaemic parameter confounders.

Results Meta-analysis of 10 clinical trials involving 477 subjects showed fenofibrate therapy decreased apo C-III levels (weighted mean difference (WMD) −4.78 mg/dL, 95% CI −6.95 to −2.61, p<0.001; I^2 66.87%). Subgroup analysis showed that fenofibrate reduced plasma apo C-III concentrations in subgroups of trials with treatment durations of either <12 weeks (WMD −4.50 mg/dL, p=0.001) or ≥12 weeks (WMD: −4.73 mg/dL, p=0.009) and doses of fenofibrate <200 mg/day (WMD −6.33 mg/dL, p<0.001) and >200 mg/day (p=0.006), with no significant difference between the subgroups.

Conclusion This meta-analysis found that fenofibrate therapy significantly decreases apo C-III levels, an effect evident with both short-term treatment and doses less than 200 mg/day.

INTRODUCTION

Elevated triglycerides have been shown to be an independent marker of coronary artery disease (CAD).[1–3] Apolipoprotein C-III (apo C-III) is a key regulator of triglyceride metabolism that mediates its effects through lipoprotein lipase (LPL) inhibition. However, indirect LPL-independent mechanisms are also present, shown by inhibition of apo C-III messenger RNA and a reduction of apo C-III levels in patients with LPL deficiency.[4 5] Apo C-III also inhibits hepatic lipase activity that decreases the conversion of very-low-density

Strengths and limitations of this study

► This was the first systematic review to determine the effect of fenofibrate on plasma apolipoprotein C-III (apo C-III).
► The strength of this study was the use of the meta-analysis that used the increased population size compared with individual studies that were small and, in some instances, underpowered to discern if fenofibrate had an effect on plasma apo C-III.
► The limitation was that the small number of trials, lack of studies in patients with hyperapolipoprotein-aemia C-III and lack of presenting gender-stratified results by individual studies.

lipoprotein (VLDL) to intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL).[6] Recently, apo C-III was shown to be significantly associated with incident CAD in the European Prospective Investigation of Cancer (EPIC)-Norfolk prospective population study.[7] It has been suggested that apo C-III may exert atherogenic properties by both direct (via enhancing inflammation) and indirect (*via* promoting hypertriglyceridaemia) mechanisms.[8]

Fibrates are a therapeutic class of drugs that are used primarily for the treatment of hypertriglyceridaemia, but are also for combined dyslipidaemias in which both triglycerides and LDL-cholesterol (LDL-C) are elevated.[9–11] Fibrates also have several pleiotropic activities described recently.[12–18] Fenofibrate is the most commonly used fibrate that induces lipoprotein lipolysis, fatty acid uptake and increase high-density lipoprotein (HDL) production,[19 20] while reducing plasma triglyceride levels by 20%–30%.[21] Mechanistically, fenofibrate activates peroxisome proliferator activated receptor alpha through modulation of genes expression related to fatty acid and lipoprotein metabolism.[22–24]

This meta-analysis of randomised placebo-controlled clinical trials using fenofibrate therapy aimed to determine its effect on apo C-III levels.

METHODS
Search strategy
This study was designed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[25] PubMed-Medline, Scopus and ISI Web of Knowledge databases were searched using the following search terms in titles and abstracts: fenofibrate AND (apoCIII OR apoC-III OR 'apo CIII' OR 'apo C-III' OR apoC3 OR 'apo C3') AND (placebo OR placebo-controlled). The wild-card term '*' was used to increase the sensitivity of the search strategy. An example of the search strategy employed in PubMed-Medline is shown in online supplementary file 1. The search was limited to articles published in English language. The literature was searched from inception to 18 August 2017.

Study selection
Original studies were included if they met the following inclusion criteria: (1) being a randomised placebo-controlled clinical trial with either parallel or cross-over design, (2) investigating the impact of fenofibrate versus placebo on total circulating concentrations of apo C-III and (3) presentation of sufficient information on apo C-III concentrations at baseline and at study end in both intervention and placebo groups or providing the net change values. Exclusion criteria were: (1) non-clinical studies; (2) uncontrolled or non-placebo-controlled studies; (3) observational studies with case–control, cross-sectional or cohort design; (4) reporting postprandial plasma apo C-III levels and (5) lack of sufficient information on baseline or follow-up total circulating apo C-III levels.

Data extraction
Eligible studies were reviewed and the following data were abstracted: (1) first author's name; (2) year of publication; (3) country where the study was performed; (4) study design; (5) number of participants in the statin and control groups; (6) fenofibrate dose; (7) duration of treatment; (8) age, gender and body mass index (BMI) of study participants and (9) baseline and follow-up concentrations of plasma lipids, lipoproteins and apolipoproteins including apo C-III. When apo C-III data were incompletely reported, authors of the respective article were contacted to obtain missing information. Two authors (AS and LES) reviewed the papers, and disagreements were resolved through discussion and consultation with a third author (SLA).

Quality assessment
The quality of involved studies in this meta-analysis was evaluated using the Cochrane criteria. Risk of bias in the studies considered in this meta-analysis was evaluated according to the Cochrane instructions.[26]

Quantitative data synthesis
Meta-analysis was conducted using Comprehensive Meta-Analysis V.2 software (Biostat, New Jersey, USA). A random-effects model (using DerSimonian-Laird method) and the generic inverse variance weighting method were used to compensate for the heterogeneity of studies in terms of study design, treatment duration and the characteristics of populations being studied. SDs of $[(SD_{pre-treatment})^2 + (SD_{post-treatment})^2 - (2R \times SD_{pre-treatment} \times SD_{post-treatment})]$, assuming a correlation coefficient (r)=0.5. Where SE of the mean (SEM) was only reported, SD was estimated using the following formula: $SD=SEM \times sqrt(n)$, where n is the number of subjects. Heterogeneity was assessed quantitatively using Cochrane Q and I^2 statistic. All apo C-III values were collated in mg/L. Effect sizes were expressed as weighted mean difference (WMD) and 95% CI. In order to avoid the double-counting problem in trials comparing multiple treatment arms versus a single control group, the number of subjects in the control group were divided by the number of treatment arms. In order to evaluate the influence of each study on the overall effect size, a sensitivity analysis was conducted using the leave-one-out method (ie, removing one study each time and repeating the analysis).[27 28]

Meta-regression
As potential confounders of treatment response, the duration of treatment and baseline plasma apo C-III concentrations were entered into a random-effects meta-regression model to explore their association with the estimated effect size on plasma apo C-III levels.

Publication bias
Evaluation of funnel plot, Begg's rank correlation and Egger's weighted regression tests were performed to assess the presence of publication bias in the meta-analysis. When there was evidence of funnel plot asymmetry, potentially missing studies were imputed using the 'trim and fill' method.[29] In case of a significant result, the number of potentially missing studies required to make the p value non-significant was estimated using the 'fail-safe N' method as another marker of publication bias.

Patient and public involvement
No patients or public were involved in this study.

RESULTS
Overall, 61 articles were found following multidatabase search. After screening of titles and abstracts, 22 articles were assessed in full text. Of these five articles were excluded because of lack of reporting serum/plasma total apo C-III concentrations, four because of duplicate reporting of data from the same population, two because of reporting postprandial apo C-III levels and one because of incomplete data on apo C-III levels. Therefore, 10 articles were found to be eligible for inclusion in the meta-analysis (figure 1).
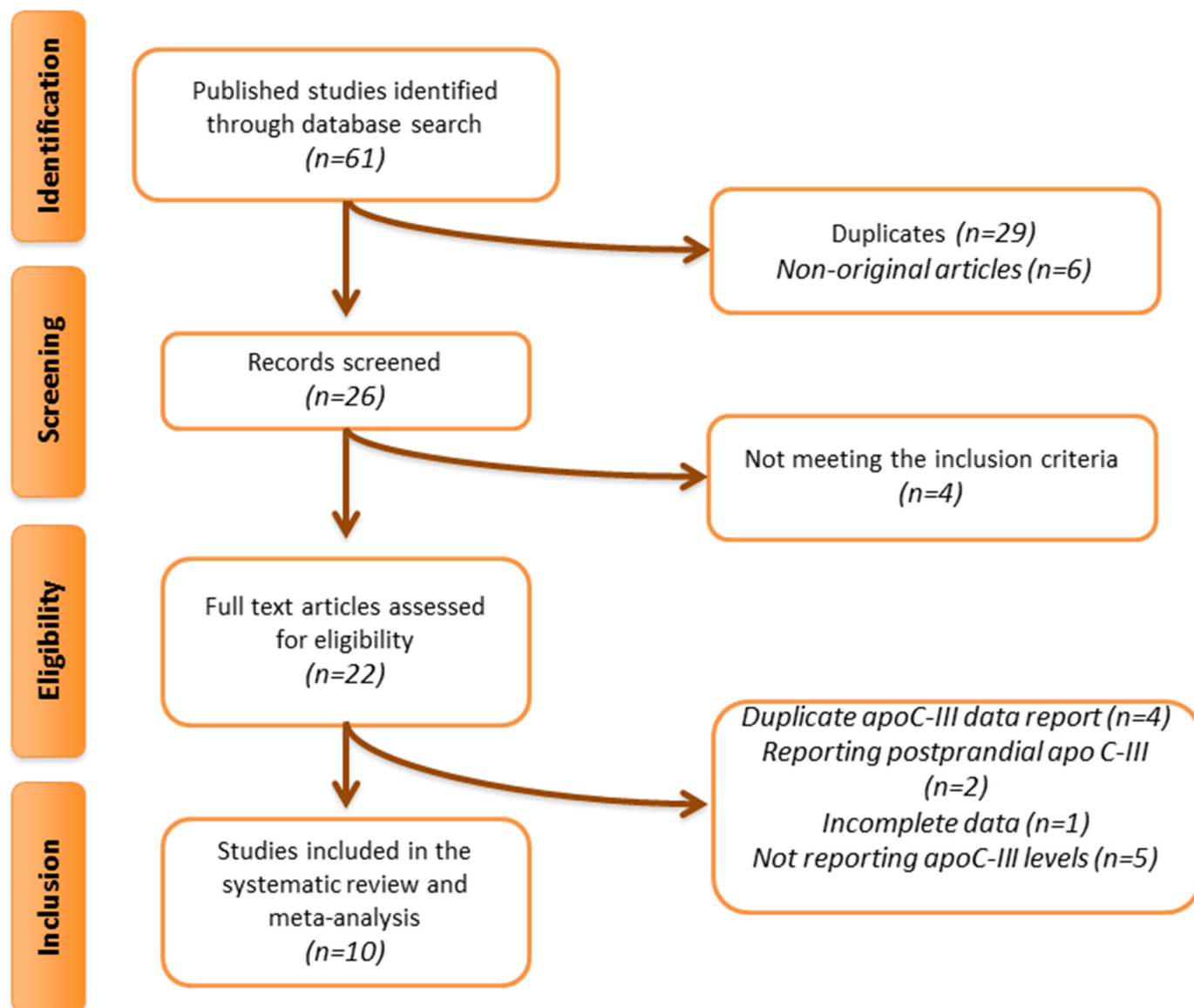
Figure 1 Flow chart of the number of studies identified and included into the meta-analysis. Apo C-III, apo C-III.

Study characteristics

Data were pooled from 10 randomised placebo-controlled clinical trials comprising a total of 477 subjects, including 265 and 212 participants in the fenofibrate and placebo arms respectively (individuals of the crossover trials were considered in the treatment and control groups).[30–40] Clinical trials reported different doses of fenofibrate. The included studies were published between 2002[34 38] and 2016. Treatment duration ranged from 2 weeks[36 40] to 12 weeks.[30–34] Study designs of included trials were parallel[30 34 36 41] and crossover.[31 33 35 37–40] Selected studies enrolled subjects with metabolic syndrome,[30] type 2 diabetes,[31 33] hypertriglyceridaemia,[32 35 38] dyslipidaemia[34 36] and non-diabetic subjects.[40] Characteristics of the included clinical trials are presented in table 1.

Risk of bias assessment

Most of the included studies showed insufficient information regarding the sequence generation and allocation concealment. Moreover, three trials had high risk of bias concerning blinding of participants, personnel and outcome assessors.[36 40] Nevertheless, all selected studies were characterised by a low risk of bias for incomplete outcome data and selective outcome reporting. Details of the risk of bias assessment are shown in table 2.

Quantitative data synthesis

The present meta-analysis of data from 11 randomised placebo-controlled trials found a significant reduction of apo C-III plasma concentrations following treatment with fenofibrate (WMD: −4.56 mg/dL, 95% CI −6.53 to −2.58, $p<0.001$; I^2 64.67%) (figure 2). The effect size was robust in the leave-one-out sensitivity analysis (figure 2) and not mainly driven by any single study. Subgroup analysis showed significant decreases in plasma apo C-III levels caused by fenofibrate in subgroups of trials with treatment durations of either <12 weeks (WMD −4.48 mg/dL, 95% CI −7.32 to −1.64, $p=0.002$; I^2 70.74%) or ≥12 weeks

Table 1 Demographic characteristics of the included studies

Author	Study design	Target population	Treatment duration	Total population (n)	Study groups	Age, years	Female/male (n)	BMI, (kg/m²)	Total cholesterol (mg/dL)	LDL cholesterol (mg/dL)	HDL cholesterol (mg/dL)	Triglycerides (mg/dL)	Apo C-III (mg/dL)
Belfort et al[30]	Randomised, double-blind, placebo-controlled.	Metabolic syndrome	12 weeks	16	Fenofibrate 200mg/day	46±8	5/11	31.6±4	228±72	109±56	34±8	500±284	52.7±23.2
				9	Placebo	46±9	3/6	31.5±3	219±33	117±30	34±9	343±126	35.5±12.3
Chan et al[31]	Randomised, double-blind, placebo-controlled, crossover.	Type 2 diabetes	12 weeks	15	Fenofibrate 145mg/day	63±8	2/13	28.6±3.4	143.1±14.7	73.5±23.2	44.9±9.3	115.1±53.1	14.0±4.6
				15	Placebo	63±8	2/13	28.5±3.0	139.2±14.7	73.5±23.2	41.8±12.0	97.4±70.9	13.8±5.4
Davidson et al[32]	Randomised, double-blind, placebo-controlled.	Hypertriglyceridaemia	8 weeks	96	Fenofibrate 130mg/day	56.5±9.7	37/59	30.8±3.9	245±48.9	121±39.1	36±9.7	480±186	32±9.7
				50	Placebo	55.3±7.0	20/30	31.5±4.9	237±42.4	116±42.4	35±7.0	479±148	30±7.0
Ishibashi et al[34]	Randomised, double-blind, placebo-controlled.	Dyslipidaemia	12 weeks	36	Fenofibrate 100mg/day	51.1±11.5	3/33	26.6±3.0	232.0±41.8	134.2±35.2	40.2±7.3	326.0±204.6	15.9±4.8
				35	Placebo	48.7±9.0	1/34	26.8±2.6	225.1±30.5	128.4±29.4	40.2±6.2	309.1±130.2	14.9±4.5
Kazumi et al[35]	Randomised, double-blind, placebo-controlled, crossover.	Hypertriglyceridaemia	8 weeks	43	Overall	57.1±9.1	5/38	24.3±2.6					
				21	Fenofibrate 300mg/day	ND	ND	ND	238±45.8	ND	40.0±10.0	352±274	17.9±8.2
				22	Placebo	ND	ND	ND	245±51.5	ND	49.4±23.9	342±304	20.0±11.7
Kosoglou et al[36]	Randomised, single-blind, placebo-controlled.	Dyslipidaemia	2 weeks	8	Fenofibrate 200mg/day	ND	ND	ND	239.8±10.8	197.2±32.8	50.3±21.7	132.9±50.0	28.2±4.8
				8	Placebo	ND	ND	ND	266.8±32.5	177.9±32.8	46.4±10.8	186.0±35.4	32.5±14.7
Ooi et al[37]	Randomised, double-blind, placebo-controlled, crossover.	Metabolic syndrome	5 weeks	11	Overall	46.3±6.9	0/11	30.5±2.6					
				11	Fenofibrate 200mg/day				211.9±21.7	143.1±22.8	40.2±8.9	147.0±78.8	12.0±1.4
				11	Placebo				227.4±18.9	152.4±27.8	36.3±5.0	216.1±90.3	15.5±1.0
Sasaki et al[38]	Randomised, double-blind, placebo-controlled, crossover.	Hypertriglyceridaemia	8 weeks	50	Overall	54.6±12.7	19/31	ND	241.0±65.7	119.2±49.9	39.9±11.6	431.8±305.5	21.7±9.7
				40	Fenofibrate 300mg/day								
				40	Placebo								
Vega et al[39]	Randomised, placebo-controlled, crossover.	Metabolic syndrome	8 weeks	13	Overall	56.5±8.9	0/13	30.5±4.2	ND	ND	ND	ND	ND
				13	Fenofibrate 200mg/day								
				13	Placebo								
Wagner et al[40]	Randomised, open-label, placebo-controlled, crossover.	Non-diabetic subjects	2 weeks	12	Overall	24*	0/12	27 (21–34)†	ND	ND	ND	ND	ND
				9	Fenofibrate 201mg/day	ND	0/9	ND	170.1±30.9	100.5±23.2	34.8±11.6	186.0±106.3	14.0±5.7
				9	Placebo	ND	0/9	ND	150.8±30.9	88.9±27.1	38.7±7.7	132.9±62.0	10.5±2.7

Values are expressed as mean±SD.
Geometric mean (95% CI).
*Mean only.
†Median (IQR).
Apo C-III, apo C-III; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ND, no data.

Table 2 Quality of bias assessment of the included studies according to the Cochrane guidelines

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Belfort et al[30]	L	U	U	L	L	U
Chan et al[31]	U	U	U	L	L	U
Davidson et al[32]	U	U	U	L	L	U
Ishibashi et al[34]	L	U	U	L	L	U
Kazumi et al[35]	U	U	U	L	L	U
Kosoglou et al[36]	U	U	H	L	L	U
Ooi et al[37]	U	U	U	L	L	U
Sasaki et al[38]	U	L	U	L	L	U
Vega et al[39]	U	U	H	L	L	U
Wagner et al[40]	U	U	H	L	L	U

H, high risk of bias; L, low risk of bias; U, unclear risk of bias.

(WMD −5.66 mg/dL, 95% CI −10.15 to −1.16, p=0.014; I^2 69.61%), with no significant difference between the two subgroups (p=0.664). With respect to fenofibrate dose, significant reductions were observed in both subgroups of trials with administered doses of <200 mg/day (WMD −6.33 mg/dL, 95% CI −10.38 to −2.27, p=0.002; I^2 83.26%) and ≥200 mg/day (WMD −3.47 mg/dL, 95% CI −5.51 to −1.42, p=0.001; I^2 27.51%). Again, there was no
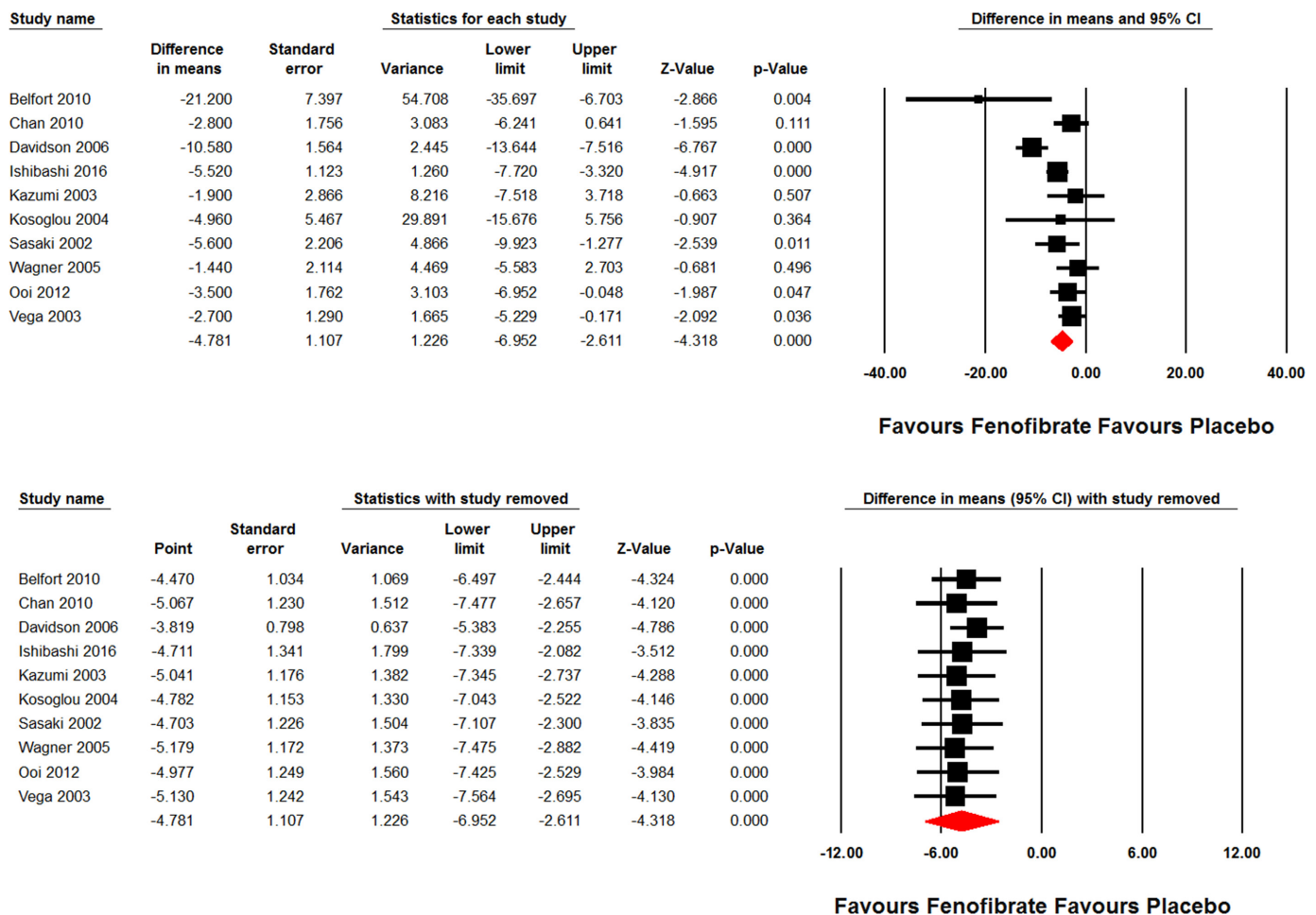

Figure 2 Forest plot displaying weighted mean difference and 95% CIs for the effects of fenofibrate on circulating apolipoprotein C-III concentrations. The lower plot shows the results of leave-one-out sensitivity analysis. Analyses were performed using a random-effects model.
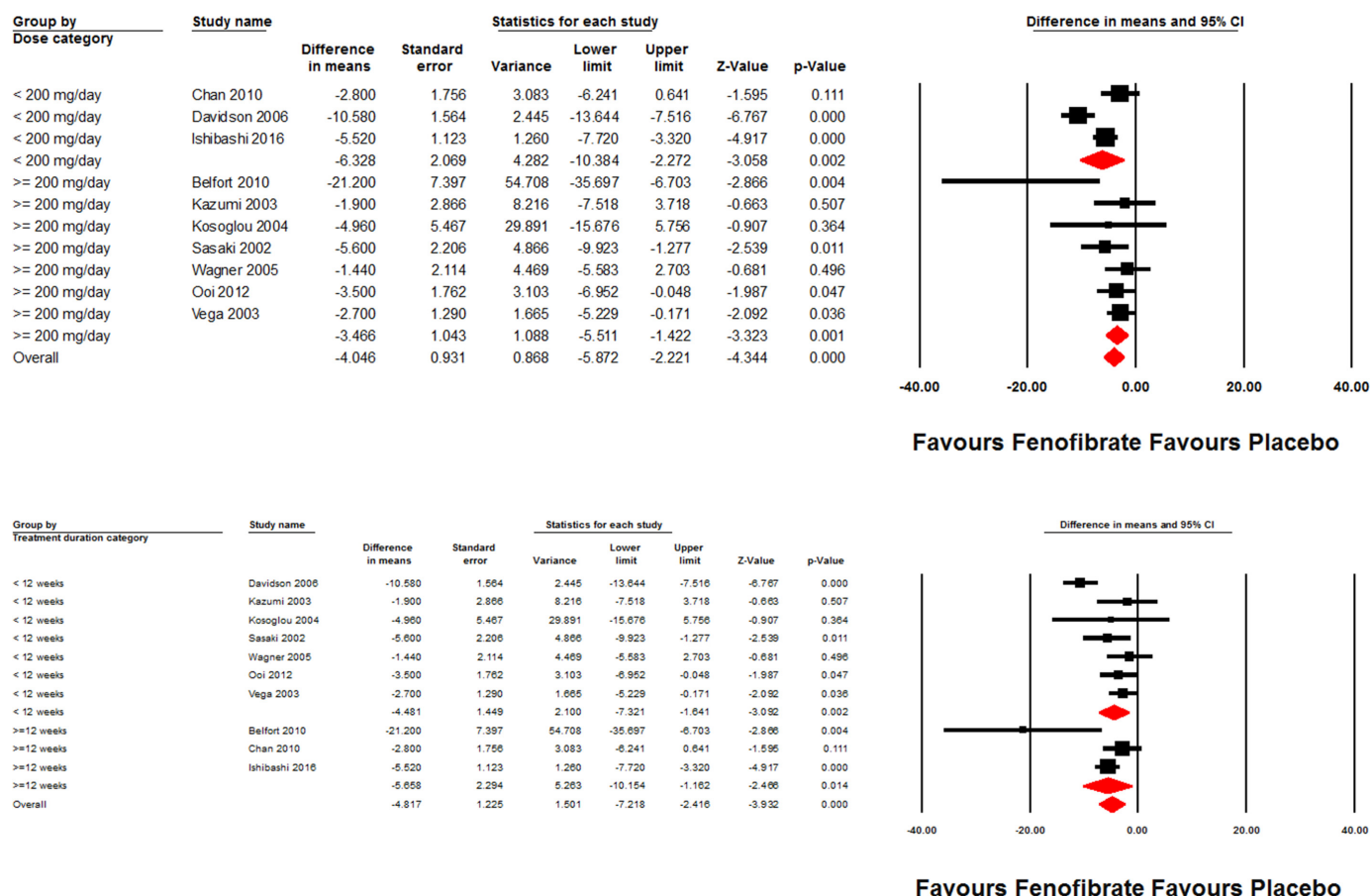
Figure 3 Forest plot displaying weighted mean difference and 95% CIs for the effects of different doses (<200 mg/day vs ≥200 mg/day) and durations (<12 weeks vs ≥12 weeks) of treatment with fenofibrate on circulating apolipoprotein C-III concentrations. Analyses were performed using a random-effects model.

significant difference between the subgroups treated with different fenofibrate doses (p=0.217) (figure 3).

Meta-regression

Random-effects meta-regression was performed to assess the impact of potential confounders on the effects of fenofibrate on plasma apo C-III levels. The results suggested a significant association between the apo C-III-lowering effect of fenofibrate with baseline apo C-III (slope −0.40; 95% CI −0.58 to −0.22; p<0.001) and baseline triglyceride (slope −0.02; 95% CI −0.03 to −0.01; p=0.001) concentrations. However, no significant association between the apo C-III-lowering and triglyceride-lowering effects of fenofibrate was found (slope 0.11; 95% CI −0.05 to 0.27; p=0.185) nor were there any association with baseline LDL-C (slope −0.02; 95% CI −0.12 to 0.08; p=0.677), HDL-cholesterol (HDL-C) (slope 0.35; 95% CI −0.29 to 0.98; p=0.284) and BMI (slope −0.75; 95% CI −2.08 to 0.58; p=0.269).

Publication bias

Visual inspection of Begg's funnel plots revealed a slight asymmetry in the meta-analysis of fenofibrate's effect on plasma apo C-III levels that was imputed by one potentially missing study at the left side of the plot using 'trim and fill' method that yielded an adjusted effect size of −5.18 (−7.28 to −3.09) (figure 4). Begg's rank correlation (p=0.592) and Egger's regression (p=0.718) tests did not suggest the presence of publication bias. The results of 'fail-safe N' test suggested that 153 missing studies would be required to make the observed significant result non-significant.

DISCUSSION

In this meta-analysis of randomised placebo-controlled clinical trials, fenofibrate therapy was related to a significant reduction of apo C-III levels. Subanalyses revealed that this effect was observed even in those trials whose duration was less than 12 weeks and for doses of fenofibrate both higher and lower than 200 mg/day. Moreover, the apo C-III-lowering effect of fenofibrate was found to be directly proportional to baseline apo C-III and triglycerides levels, suggesting that greater effects on plasma apo C-III levels are anticipated in populations with hyperapolipoproteinaemia C-III hypertriglyceridaemia. However, there were no associations between apo C-III-lowering effect of fenofibrate with baseline BMI, LDL-C and HDL-C, and the changes in plasma triglycerides levels. The latter finding on the lack of any association between changes in plasma apo C-III and
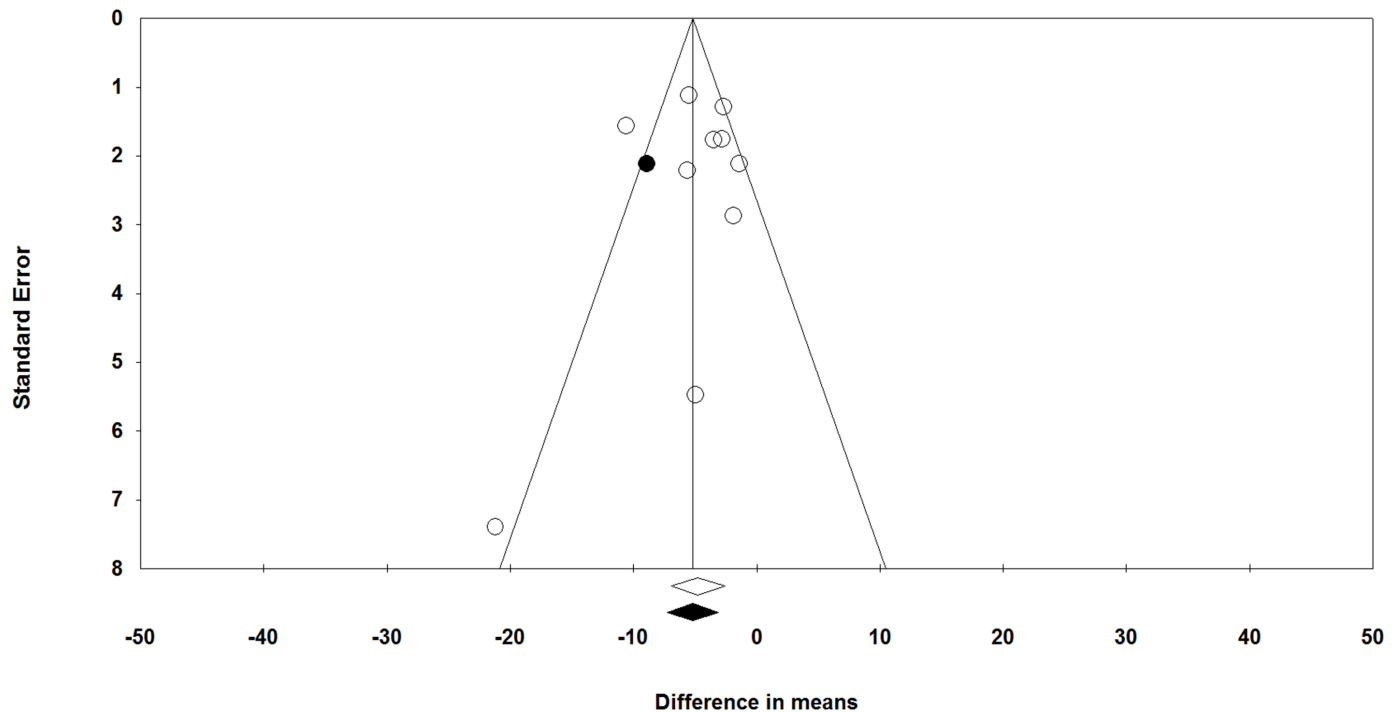
Figure 4 Random-effects funnel plot detailing publication bias in the studies reporting the impact of fenofibrate on plasma apo C-III concentrations.

triglycerides levels could be attributed to the fact that not all VLDL particles (as the main carriers of apo C-III in plasma) contain apo C-III. It has been estimated that apo C-III is present in about 50% of plasma VLDL particles. This might justify the lack of apo C-III reduction proportional to triglycerides reduction following fenofibrate therapy.[42]

The reduction of apo C-III levels by fenofibrate therapy may contribute to a reduced risk of CAD achieved with fibrates therapy[43–45]; however, the mechanism(s) by which apo C-III increases CAD risk remain(s) unclear.[7] Loss of function mutations of the *APOC3* gene are associated with reduced triglyceride and VLDL levels,[46] whereas genetic variations have linked *APOC3* to CAD risk.[47] Epidemiological studies have found an association between increased apo C-III and CAD that correlated with elevated triglyceride levels.[7 48–50] It has also been shown that accumulation of apo C-III and triglycerides in the necrotic core predisposes to plaque vulnerability in patients with stable CAD[51]; hence, the significant lowering effect of fenofibrate on both of these parameters might justify its potential efficacy in preventing plaque rupture and acute CV events, as shown for statin therapy.[52] In addition, there is evidence in vivo showing the stabilising and regressing effects of fenofibrate[53 54] on the atherosclerotic plaque. It has been shown that elevated triglycerides and low HDL-C are not only associated with macrovascular atherosclerotic changes such as CAD, but they are also risk factors for microvascular disease in type 2 diabetes mellitus.[43] Indeed, in addition to the association with elevated triglyceride-rich particles such as VLDL number and size, increased apo C-III levels were also related to increased IDL particles numbers and a shift to more atherogenic small dense LDL

particles.[7 20] Small dense LDL exerts atherogenic properties and has been linked to increased cardiovascular risk as well as to the presence of metabolic disorders including obesity, metabolic syndrome and type 2 diabetes.[55–57] Some speculate that it is quite unlikely that elevated triglycerides per se might be associated with an increased risk of CAD. However, triglyceride-rich particles such as VLDL and IDL could accumulate in the intima, and can be further catabolised and ingested by macrophages to form foam cells, resulting in progression of the atherosclerotic lesion.[58] Apo C-III may therefore be seen as a therapeutic target to reduce CAD, and antisense RNA inhibition has shown dramatic decreases in triglyceride levels.[4 5]

In the EPIC study, mediation analysis showed that a large part of the increased CAD risk associated with apo C-III was attributable to the triglyceride-rich remnant particle levels.[7] This fits well with the mechanism proposed above. It has been also proven that fenofibrate decreases triglyceride-rich remnant particles.[59 60] However, it was also shown that apo C-III was associated with an increased C reactive protein, a marker of inflammation that may represent an independent predictor of increased CAD risk.[61] This finding may also reflect the LPL-independent mechanism of increased CAD risk by apo C-III.

The present meta-analysis suggested that the effect of apo C-III lowering was relatively rapid as it was observed within 12 weeks, thus indicating the early potential benefit of fibrate therapy. However, no data exist that relate triglycerides reduction and remnant particles changes induced by apo C-III. Of note, the reduction of apo C-III levels was also observed with fenofibrate doses <200 mg/day, but it is unclear whether a reduction in apo C-III may

occur even if in the absence of a therapeutic decrease in triglyceride levels.

The main limitation of the present meta-analysis is that several trials were characterised by a small population size and a limited number of individuals. However, the pooled population analysed was sufficiently robust due to other studies that provided a large population size. In addition, included studies did not define elevated plasma apo C-III levels among the inclusion criteria and hence future trials specifically defined in populations with hyperapolipoproteinaemia C-III might be interesting. Finally, included the trials did not provide gender-stratified results for the impact of fenofibrate on plasma apo C-III levels; therefore, the presence of any gender effect on the apo C-III-lowering activity of fenofibrate needs to be evaluated in further studies.

Conclusion

The results of the present meta-analysis showed that fenofibrate treatment significantly decreases apo C-III levels, even with short-term treatment and doses <200 mg daily.

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