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Effect of Fenofibrate on plasma apolipoprotein C-III levels: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

Short title. Fenofibrate reduces plasma apoC-III

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Key words: Fenofibrate; fibrate; apoprotein C; triglyceride; meta-analysis.

ABSTRACT

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

Participants. Randomized 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. 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 glycemic parameter confounders.

Results. Meta-analysis of 11 clinical trials involving 507 subjects showed fenofibrate therapy decreased apo C-III levels (weighted mean difference (WMD): -4.56 mg/dL, 95% confidence interval (CI): -6.53, -2.58, $p<0.001$; I^2: 64.67%). 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 ($p<0.001$) 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.

Keywords: fenofibrate; glucose; apolipoprotein C-III; meta-analysis.

Strengths and limitations

- A strength was the use of this meta-analysis to look at the effect of fenofibrate on plasma apo C-III levels, and that showed a significant reduction of apo C-III by fenofibrate.
- The meta-analysis showed that apo C-III reduction by fenofibrate was independent of treatment dose and duration.
- A limitation was that the number of clinical trials was limited to analyse with only 507 subjects in total

INTRODUCTION

Elevated triglycerides have been shown to be an independent marker of coronary artery disease (CAD) [1] [2] [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 ApoC-III messenger RNA and a reduction of apoC-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 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 EPIC-Norfolk prospective population study [7]. It has been suggested that apoC-III may exert atherogenic properties by both direct (via enhancing inflammation) and indirect (*via* promoting hypertriglyceridemia) mechanisms [8].

Fibrates are a therapeutic class of drugs that are used primarily for the treatment of hypertriglyceridemia, but are also for combined dyslipidemias in which both triglycerides and LDL-cholesterol are elevated [9] [10] [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 (PPARα) through modulation of genes expression related to fatty acid and lipoprotein metabolism [22] [23, 24].

This meta-analysis of randomized 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-analysis (PRISMA) 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. The search was limited to articles published in English language. The literature was searched from inception to August 18, 2017.

Study Selection

Original studies were included if they met the following inclusion criteria: (i) being a randomized placebo-controlled clinical trial with either parallel or cross-over design, (ii) investigating the impact of fenofibrate versus placebo on total circulating concentrations of apoC-III, and, (iii) presentation of sufficient information on apoC-III concentrations at baseline and at study end in both intervention and placebo groups or providing the net change values. Exclusion criteria were: (i) non-clinical studies, (ii) uncontrolled OR non-placebo-controlled studies, (iii) observational studies with case-control, cross-sectional or cohort design, (iv) reporting postprandial plasma apoC-III levels, and (v) lack of sufficient information on baseline or follow-up total circulating apoC-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 apoC-III. When apoC-III data were incompletely reported, authors of the respective article were contacted to obtain missing information.

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 (CMA) V2 software (Biostat, NJ). 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. Standard deviations (SDs) of $(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: SD = SEM × 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 standardized mean difference (WMD) and 95% confidence interval (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 (i.e., 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 apoC-III concentrations were entered into a random-effects meta-regression model to explore their association with the estimated effect size on plasma apoC-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.

RESULTS

Overall, 61 articles were found following multi-database search. After screening of titles and abstracts, 22 articles were assessed in full text. Of these 5 articles were excluded because of lack of reporting serum/plasma total apo C-III concentrations, 3 because of duplicate reporting of data from the same population, 2 because of reporting postprandial apo C-III levels, and 1 because of incomplete data on apo C-III levels. Therefore, 11 articles were found to be eligible for inclusion in the meta-analysis (**Figure 1**).

Study characteristics

Data were pooled from 11 randomized placebo-controlled clinical trials comprising a total of 507 subjects, including 280 and 227 participants in the fenofibrate and placebo arms respectively (individuals of the cross-over 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 [38] [34] and 2016. Treatment duration ranged from 2 weeks [36] [40] up to 12 weeks [30] [31] [31] [33] [34]. Study designs of included trials were parallel [30] [41] [34] [36] and cross-over [31] [33] [35] [37] [38] [39, 40]. Selected studies enrolled subjects with metabolic syndrome [30], type 2 diabetes [31] [33], hypertriglyceridemia [32, 35, 38], dyslipidemia [34] [36] and nondiabetic subjects [40]. Characteristics of the included clinical trials are presented in **Table 1**.

Table 1. Demographic characteristics of the included studies.

Author	Study design	Target Population	Treatment duration	n	Study groups	Age, years	Female (n,	BMI, (kg/m^2)	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides	ApoC-III

			n			%)		(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)
Belfort et al. (2010)	Randomized, double-blind, placebo-controlled	Metabolic syndrome	12 weeks	16 9	Fenofibrate 200 mg/day Placebo	46±8 46±9	5 (31) 3 (33)	31.6±4 31.5±3	228±72 219±33	109±56 117±30	34±8 34±9	500±284 343±126	52.7±23.2 35.5±12.3
Chan et al. (2010)	Randomized, double-blind, placebo-controlled, cross-over	Type 2 diabetes	12 weeks	15 15	Fenofibrate 145 mg/day Placebo	63±8 63±8	2 (13) 2 (13)	28.6±3.4 28.5±3.0	143.1±14.7 139.2±14.7	73.5±23.2 73.5±23.2	44.9±9.3 41.8±12.0	115.1±53.1 97.4±70.9	14.0±4.6 13.8±5.4
Davidson et al. (2006)	Randomized, double-blind, placebo-controlled	Hypertriglyce-ridemia	8 weeks	96 50	Fenofibrate 130 mg/day Placebo	56.5±9.7 55.3±7.0	37 (38.5) 20 (40.0)	30.8±3.9 31.5±4.9	245±48.9 237±42.4	121±39.1 116±42.4	36±9.7 35±7.0	480±186 479±148	32±9.7 30±7.0
Hamilton et al. (2010)	Randomized, double-blind, placebo-controlled, cross-over	Type 2 diabetes	12 weeks	15 15 15	Overall Fenofibrate 145 mg/day Placebo	63.3±7.8 ND ND	2 (13) ND ND	28.4 (26.8-30.1)* ND ND	150.8±27.1 143.1±14.7 139.2±14.7	77.3±15.5 73.5±23.2 73.5±23.2	45.2±6.6 44.5±5.8 43.7±7.3	124.0 (97.4-159.4)* 115.1±53.1** 97.4±70.9**	ND 13.9±4.8 13.7±5.3
Ishibashi et al. (2016)	Randomized, double-blind, placebo-controlle	Dyslipidemia	12 weeks	36 35	Fenofibrate 100 mg/day Placebo	51.1±11.5 48.7±9.0	3 (8) 1 (3)	26.6±3.0 26.8±2.6	232.0±41.8 225.1±30.5	134.2±35.2 128.4±29.4	40.2±7.3 40.2±6.2	326.0±204.6 309.1±130.2	15.9±4.8 14.9±4.5

	d												
Kazumi et al. (2003)	Randomized, double-blind, placebo-controlled, cross-over	Hypertriglyce-ridemia	8 weeks	43 21 22	Overall Fenofibrate 300 mg/day Placebo	57.1±9.1 ND ND	5 (11) ND ND	24.3±2.6 ND ND	238±45.8 245±51.5	ND ND	40.0±10.0 49.4±23.9	352±274 342±304	17.9±8.2 20.0±11.7
Kosoglou et al. (2004)	Randomized, single-blind, placebo-controlled	Dyslipidemia	2 weeks	8 8	Fenofibrate 200 mg/day Placebo	ND ND	ND ND	ND ND	239.8±10.8 266.8±32.5	197.2±32.8 177.9±32.8	50.3±21.7 46.4±10.8	132.9±50.0 186.0±35.4	28.2±4.8 32.5±14.7
Ooi et al. (2012)	Randomized, double-blind, placebo-controlled, cross-over	Metabolic syndrome	5 weeks	11 11 11	Overall Fenofibrate 200 mg/day Placebo	46.3±6.9	0 (0.0)	30.5±2.6	211.9±21.7 227.4±18.9	143.1±2.8 152.4±27.8	40.2±8.9 36.3±5.0	147.0±78.8 216.1±90.3	12.0±1.4 15.5±1.0
Sasaki et al. (2002)	Randomized, double-blind, placebo-controlled, cross-over	Hypertriglyce-ridemia	8 weeks	50 40 40	Overall Fenofibrate 300 mg/day Placebo	54.6±12.7	19 (38)	ND	241.0±65.7	119.2±49.9	39.9±11.6	431.8±305.5	21.7±9.7
Vega et al. (2003)	Randomized, placebo-controlled, cross-over	Metabolic syndrome	8 weeks	13 13 13	Overall Fenofibrate 200 mg/day	56.5±8.9	0 (0.0)	30.5±4.2	ND	ND	ND	ND	ND

					Placebo								
Wagner et al. (2005)	Randomized, open-label, placebo-controlled, cross-over	Nondiabetic subjects	2 weeks	12 9 9	Overall Fenofibrate 201 mg/day Placebo	24† ND ND	0 (0.0) 0 (0.0) 0 (0.0)	27 (21-34)** ND ND	ND 170.1±30.9 150.8±30.9	ND 100.5±23.2 88.9±27.1	ND 34.8±11.6 38.7±7.7	ND 186.0±106.3 132.9±62.0	ND 14.0±5.7 10.5±2.7

Values are expressed as mean ± SD
*Geometric mean (95% CI)
**Median (IQR)
†Mean only
Abbreviations: ND, no data; BMI, body mass index; IQR; interquartile range.

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 characterized 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**.

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. (2010)	L	U	U	L	L	U

Chan et al. (2010)	U	U	U	L	L	U
Davidson et al. (2006)	U	U	U	L	L	U
Hamilton et al. (2010)	U	U	U	L	L	U
Ishibashi et al. (2016)	L	U	U	L	L	U
Kazumi et al. (2003)	U	U	U	L	L	U
Kosoglou et al. (2004)	U	U	H	L	L	U
Ooi et al. (2012)	U	U	U	L	L	U
Sasaki et al. (2002)	U	L	U	L	L	U
Vega et al. (2003)	U	U	H	L	L	U
Wagner et al. (2005)	U	U	H	L	L	U

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

Quantitative data synthesis

The present meta-analysis of data from 11 randomized 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, -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: -4.50 mg/dL, 95% CI: -7.17, -1.82, p=0.001; I^2: 70.74%) or ≥ 12 weeks (WMD: -4.73 mg/dL, 95% CI: -8.29, -1.18, p=0.009; I^2: 61.44%), with no significant difference between the two subgroups (p=0.917). With respect to fenofibrate dose, significant reductions were observed in both subgroups of trials with administered doses of < 200 mg/day (WMD: -5.53 mg/dL, 95% CI: -8.35, -2.70, p<0.001; I^2: 80.23%) and ≥ 200 mg/day (WMD: -3.70 mg/dL, 95% CI: -6.35, -1.05, p=0.006; I^2: 27.51%). Again, there was no significant difference between the subgroups treated with different fenofibrate doses (p=0.355) (**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 positive association between the apo C-III-lowering effect of fenofibrate and baseline apo C-III concentrations (slope: -0.41; 95% CI: -0.58, -0.23; p<0.001). However, no significant association between the apo C-III-lowering and triglycerides-lowering effects of fenofibrate was found (slope: 0.11; 95% CI: -0.03, 0.25; p=0.134) (**Figure 4**).

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 -4.89 (-6.79, -2.99) (**Figure 5**). Begg's rank correlation (p=0.533) and Egger's regression (p=0.730) tests did not suggest the presence of publication bias. The results of "fail-safe N" test suggested that 174 missing studies would be required to make the observed significant result non-significant.

DISCUSSION

In this meta-analysis of randomized 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.

The reduction of apo C-III levels by fenofibrate therapy may contribute to a reduced risk of CAD achieved with fibrates therapy [42] [43] [44]; however, the mechanism(s) by which apo C-III increases CAD risk remain(s) unclear [7]. Loss of function mutations of the APO3 gene are associated with reduced triglyceride and VLDL levels [45], whereas genetic variations have linked APO3 to CAD risk [46]. Epidemiological studies have found an association between increased apo C-III and CAD that correlated with elevated triglyceride levels [47] [48] [49] [7]. It has been shown that elevated triglycerides and low HDL-cholesterol 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 [42]. 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 [50] [51] [52] 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 [53]. Apo C-III may therefore be seen as a therapeutic target to reduce CAD and anti-sense 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[54, 55]. 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 [56]. 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 apoC-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 apoC-III. Of note, the reduction of apoC-III levels was also observed with fenofibrate doses < 200 mg/day, but it is unclear whether a reduction in apoC-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 characterized by a small population size and a limited number of individuals. However, the pooled population analyzed 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 hyperapolipoproteinemia C-III might be interesting.

Conclusion

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

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Conflict of interest. NK has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra Zeneca, Boehringer Ingelheim, Elpen, MSD, Novartis, NovoNordisk, Sanofi and WinMedica. MB has served on speaker's bureau and as an advisory board member for Amgen, Sanofi-Aventis and Lilly. Dr. Majeed is the Founder & Chairman of Sabinsa Corporation and Sami Labs Limited.

Author Contribution statement.

AS and LESM contributed to the literature search, article screening, data acquisition and abstraction. AS contributed to the statistical analysis. SLA, AS and LESM contributed to interpretation of the results and drafting of the manuscript. NK, ZR, MB and MP contributed to critical revision of the manuscript. All authors approved the final version of the manuscript for submission.

Data sharing

All data is available on request to Professor Amirhossein Sahebkar

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FIGURE LEGENDS

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the effects of fenofibrate on circulating apolipoprotein C-III concentrations. The lower plot shows the results of leave-one-out sensitivity analysis.

Figure 3. Forest plot displaying weighted mean difference and 95% confidence intervals 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.

Figure 4. Meta-regression bubble plots of the association between mean changes in plasma apolipoprotein C-III concentrations with baseline apolipoprotein C-III levels and percent change in circulating triglycerides levels. The size of each circle is inversely proportional to the variance of change.

Figure 5. Funnel plot detailing publication bias in the studies reporting the impact of fenofibrate on plasma apo C-III concentrations.

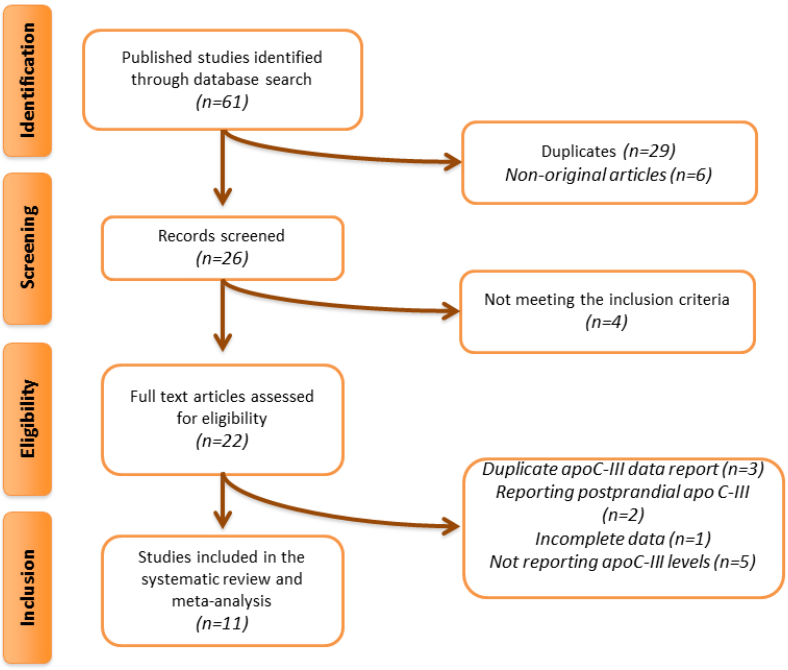

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

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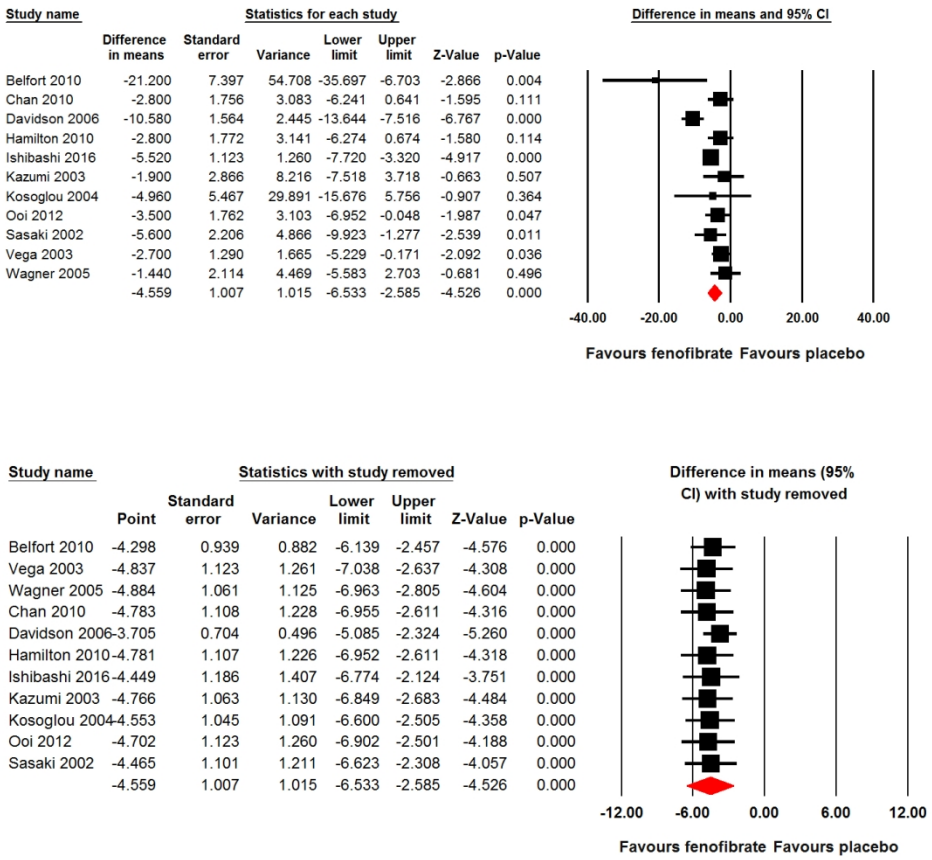

Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the effects of fenofibrate on circulating apolipoprotein C-III concentrations. The lower plot shows the results of leave-one-out sensitivity analysis.

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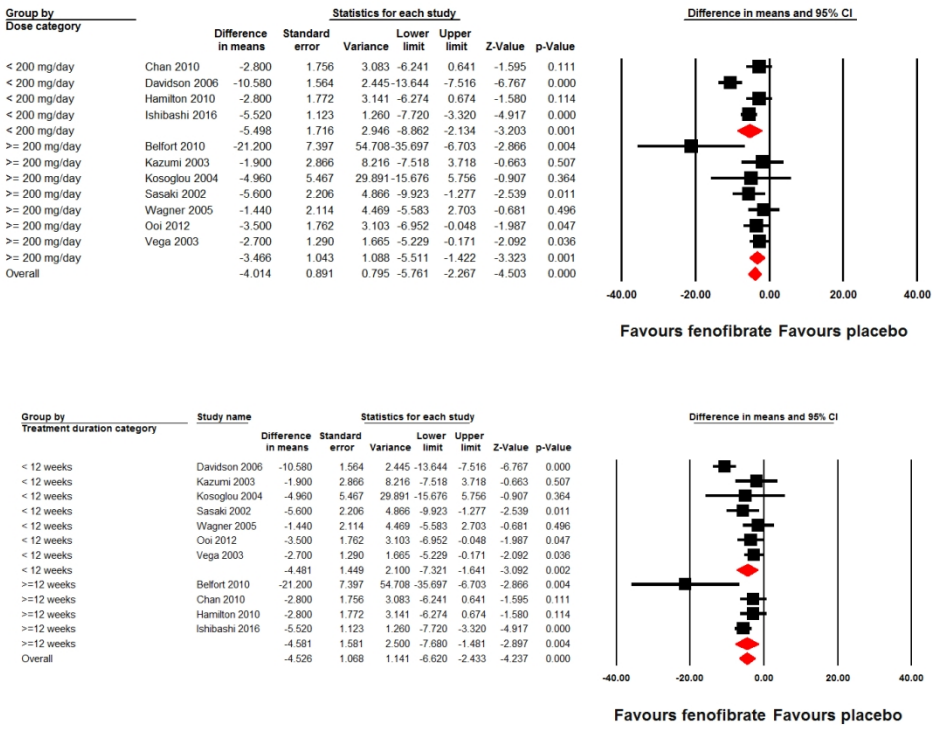

Figure 3. Forest plot displaying weighted mean difference and 95% confidence intervals for the effects of different doses (< 200 mg/day vs. ≥ 200 mg/day) and durations (< 12 weeks vs. ≥ 12 weeks) of treatment with fenofibrate on circulating apolipoprotein C-III concentrations.

124x100mm (300 x 300 DPI)

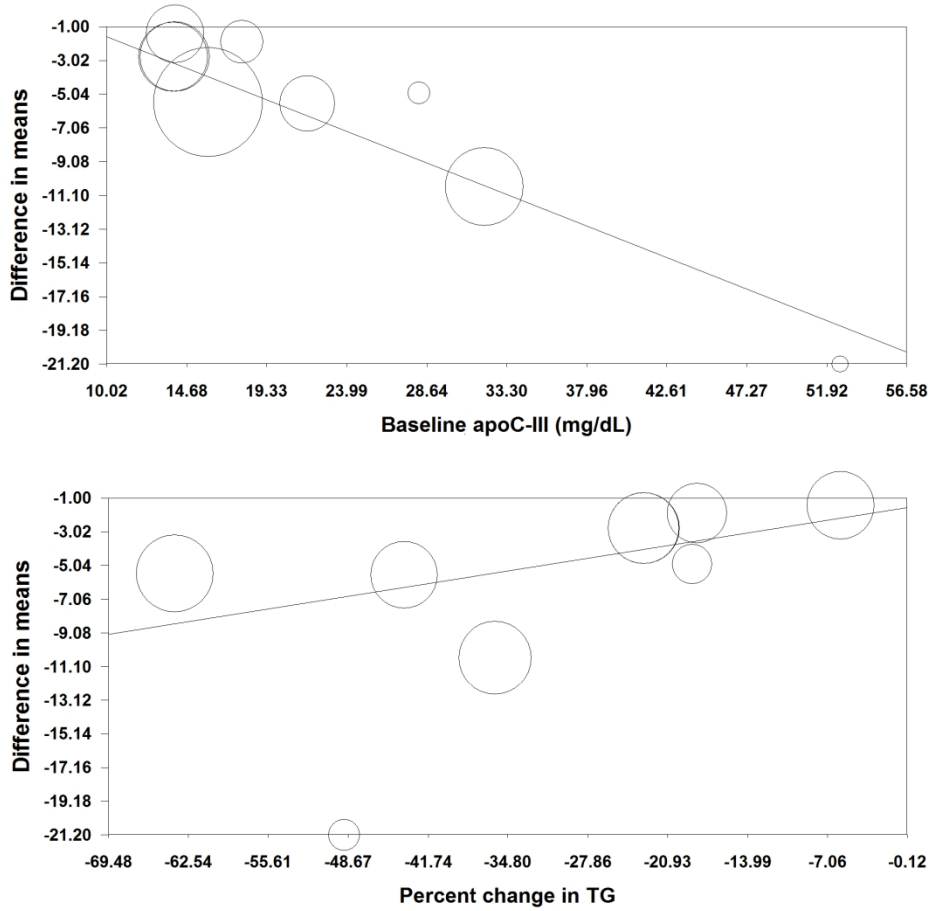

Figure 4. Meta-regression bubble plots of the association between mean changes in plasma apolipoprotein C-III concentrations with baseline apolipoprotein C-III levels and percent change in circulating triglycerides levels. The size of each circle is inversely proportional to the variance of change.

180x174mm (300 x 300 DPI)

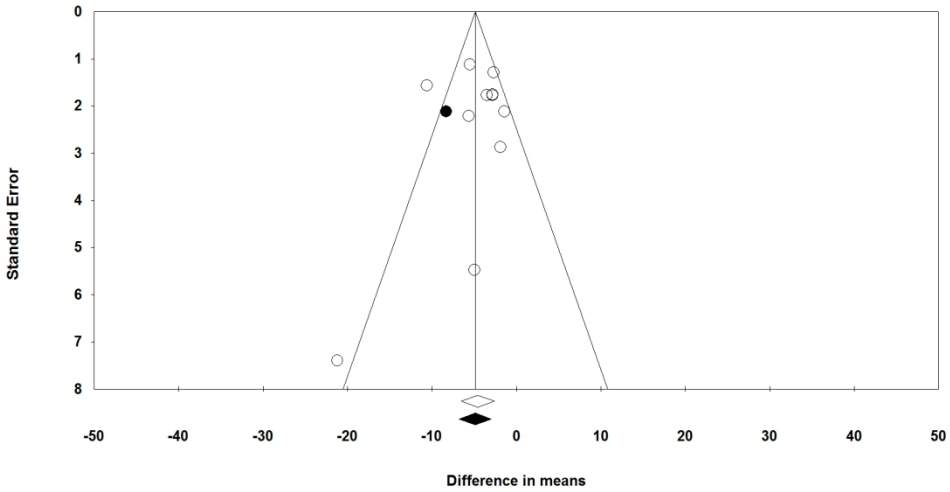

Figure 5. Funnel plot detailing publication bias in the studies reporting the impact of fenofibrate on plasma apo C-III concentrations.

149x78mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 11 and Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1, Figure 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13 and Figure 4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

PRISMA 2009 Checklist

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Effect of Fenofibrate on plasma apolipoprotein C-III levels: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

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Effect of Fenofibrate on plasma apolipoprotein C-III levels: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

Short title. Fenofibrate reduces plasma apoC-III

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Key words: Fenofibrate; fibrate; apoprotein C; triglyceride; meta-analysis.

ABSTRACT

Objectives. This meta-analysis of randomized 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. Randomized 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 August 18, 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 glycemic 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% confidence interval (CI): -6.95, -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.

Keywords: fenofibrate; glucose; apolipoprotein C-III; meta-analysis.

Strengths and limitations

- This was the first systematic review to determine the effect of fenofibrate on plasma apo C-III.
- The strength of this study was the use of the meta-analysis that utilized 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 hyperapolipoproteinemia C-III and lack of presenting gender-stratified results by individual studies.

INTRODUCTION

Elevated triglycerides have been shown to be an independent marker of coronary artery disease (CAD) [1 2 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 ApoC-III messenger RNA and a reduction of apoC-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 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 EPIC-Norfolk prospective population study [7]. It has been suggested that apoC-III may exert atherogenic properties by both direct (via enhancing inflammation) and indirect (*via* promoting hypertriglyceridemia) mechanisms [8].

Fibrates are a therapeutic class of drugs that are used primarily for the treatment of hypertriglyceridemia, but are also for combined dyslipidemias in which both triglycerides and LDL-cholesterol are elevated [9 10 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 (PPARα) through modulation of genes expression related to fatty acid and lipoprotein metabolism [22 23 24].

This meta-analysis of randomized 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-analysis (PRISMA) 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 Supplementary File 1. The search was limited to articles published in English language. The literature was searched from inception to August 18, 2017.

Study Selection

Original studies were included if they met the following inclusion criteria: (i) being a randomized placebo-controlled clinical trial with either parallel or cross-over design, (ii) investigating the impact of fenofibrate versus placebo on total circulating concentrations of apoC-III, and, (iii) presentation of sufficient information on apoC-III concentrations at baseline and at study end in both intervention and placebo groups or providing the net change values. Exclusion criteria were: (i) non-clinical studies, (ii) uncontrolled OR non-placebo-controlled studies, (iii) observational studies with case-control, cross-sectional or cohort design, (iv) reporting postprandial plasma apoC-III levels, and (v) lack of sufficient information on baseline or follow-up total circulating apoC-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 apoC-III. When apoC-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 (CMA) V2 software (Biostat, NJ). 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. Standard deviations (SDs) of $(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: SD = SEM × 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 standardized mean difference (WMD) and 95% confidence interval (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 (i.e., 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 apoC-III concentrations were entered into a random-effects meta-regression model to explore their association with the estimated effect size on plasma apoC-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 multi-database search. After screening of titles and abstracts, 22 articles were assessed in full text. Of these 5 articles were excluded because of lack of reporting serum/plasma total apo C-III concentrations, 4 because of duplicate reporting of data from the same population, 2 because of reporting postprandial apo C-III levels, and 1 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**).

Study characteristics

Data were pooled from 10 randomized 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 cross-over 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 [38 34] and 2016. Treatment duration ranged from 2 weeks [36 40] up to 12 weeks [30 31 31 33 34]. Study designs of included trials were parallel [30 41 34 36] and cross-over [31 33 35 37 38 39 40]. Selected studies enrolled subjects with metabolic syndrome [30], type 2 diabetes [31 33], hypertriglyceridemia [32 35 38], dyslipidemia [34 36] and nondiabetic subjects [40]. Characteristics of the included clinical trials are presented in **Table 1**.

Table 1. Demographic characteristics of the included studies.

Author	Study design	Target Population	Treatment durati	Total population	Study grou	Age, years	Female/ male (n)	BMI, (kg/	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides	ApoC-III

			on	(n)	ps			m^2)	(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)
Belfort et al. (2010)	Randomized, double-blind, placebo-controlled	Metabolic syndrome	12 weeks	16 9	Fenofibrate 200 mg/day Placebo	46±8 46±9	5/11 3/6	31.6±4 31.5±3	228±72 219±33	109±56 117±30	34±8 34±9	500±284 343±126	52.7±23.2 35.5±12.3
Chan et al. (2010)	Randomized, double-blind, placebo-controlled, cross-over	Type 2 diabetes	12 weeks	15 15	Fenofibrate 145 mg/day Placebo	63±8 63±8	213 2/13	28.6±3.4 28.5±3.0	143.1±14.7 139.2±14.7	73.5±23.2 73.5±23.2	44.9±9.3 41.8±12.0	115.1±53.1 97.4±70.9	14.0±4.6 13.8±5.4
Davidson et al. (2006)	Randomized, double-blind, placebo-controlled	Hypertriglyceridemia	8 weeks	96 50	Fenofibrate 130 mg/day Placebo	56.5±9.7 55.3±7.0	37/59 20/30	30.8±3.9 31.5±4.9	245±48.9 237±42.4	121±39.1 116±42.4	36±9.7 35±7.0	480±186 479±148	32±9.7 30±7.0
Ishibashi et al. (2016)	Randomized, double-blind, placebo-controlled	Dyslipidemia	12 weeks	36 35	Fenofibrate 100 mg/day Placebo	51.1±11.5 48.7±9.0	3/33 1/34	26.6±3.0 26.8±2.6	232.0±41.8 225.1±30.5	134.2±35.2 128.4±29.4	40.2±7.3 40.2±6.2	326.0±204.6 309.1±130.2	15.9±4.8 14.9±4.5
Kazumi et al. (2003)	Randomized, double-blind, placebo-controlled, cross-	Hypertriglyceridemia	8 weeks	43 21 22	Overall Fenofibrate 300 mg/day	57.1±9.1 ND ND	5/38 ND ND	24.3±2.6 ND ND	238±45.8 245±51	ND ND	40.0±10.0 49.4±	352±274 342±30	17.9±8.2 20.0±

	over				Placebo				.5		23.9	4	11.7
Kosoglou et al. (2004)	Randomized, single-blind, placebo-controlled	Dyslipidemia	2 weeks	8 8	Fenofibrate 200 mg/day Placebo	ND ND	ND ND	ND ND	239.8±10.8 266.8±32.5	197.2±32.8 177.9±32.8	50.3±21.7 46.4±10.8	132.9±50.0 186.0±35.4	28.2±4.8 32.5±14.7
Ooi et al. (2012)	Randomized, double-blind, placebo-controlled, cross-over	Metabolic syndrome	5 weeks	11 11 11	Overall Fenofibrate 200 mg/day Placebo	46.3±6.9	0/11	30.5±2.6	211.9±21.7 227.4±18.9	143.1±22.8 152.4±27.8	40.2±8.9 36.3±5.0	147.0±78.8 216.1±90.3	12.0±1.4 15.5±1.0
Sasaki et al. (2002)	Randomized, double-blind, placebo-controlled, cross-over	Hypertriglyceridemia	8 weeks	50 40 40	Overall Fenofibrate 300 mg/day Placebo	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
Vega et al. (2003)	Randomized, placebo-controlled, cross-over	Metabolic syndrome	8 weeks	13 13 13	Overall Fenofibrate 200 mg/day Placebo	56.5±8.9	0/13	30.5±4.2	ND	ND	ND	ND	ND
Wagner et al. (2005)	Randomized, open-label, placebo-controlled, cross-	Nondiabetic subjects	2 weeks	12 9 9	Overall Fenofibrate 201 mg/day Placebo	24† ND ND	0/12 0/9 0/9	27 (21-34)** ND ND	ND 170.1±30.9 150.8±30.9	ND 100.5±23.2 88.9±27.1	ND 34.8±11.6 38.7±7.7	ND 186.0±106.3 132.9±62.0	ND 14.0±5.7 10.5±2.7

over

Values are expressed as mean ± SD
*Geometric mean (95% CI)
**Median (IQR)
†Mean only
Abbreviations: ND, no data; BMI, body mass index; IQR; interquartile range.

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 characterized 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**.

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. (2010)	L	U	U	L	L	U
Chan et al. (2010)	U	U	U	L	L	U
Davidson et al. (2006)	U	U	U	L	L	U

Ishibashi et al. (2016)	L	U	U	L	L	U
Kazumi et al. (2003)	U	U	U	L	L	U
Kosoglou et al. (2004)	U	U	H	L	L	U
Ooi et al. (2012)	U	U	U	L	L	U
Sasaki et al. (2002)	U	L	U	L	L	U
Vega et al. (2003)	U	U	H	L	L	U
Wagner et al. (2005)	U	U	H	L	L	U

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

Quantitative data synthesis

The present meta-analysis of data from 11 randomized 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, -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, -1.64, p=0.002; I^2: 70.74%) or ≥ 12 weeks (WMD: -5.66 mg/dL, 95% CI: -10.15, -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, -2.27, p=0.002; I^2: 83.26%) and ≥ 200 mg/day (WMD: -3.47 mg/dL, 95% CI: -5.51, -1.42, p=0.001; I^2: 27.51%). Again, there was no 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, -0.22; p<0.001) and baseline triglyceride (slope: -0.02; 95% CI: -0.03, -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,

0.27; p=0.185) nor were there any association with baseline LDL-C (slope: -0.02; 95% CI: -0.12, 0.08; p=0.677), HDL-C (slope: 0.35; 95% CI: -0.29, 0.98; p=0.284) and BMI (slope: -0.75; 95% CI: -2.08, 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, -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 randomized 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 hyperapolipoproteinemia C-III hypertriglyceridemia. 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 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] [44] [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 [48] [49] [50] [7]. 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 stabilizing and regressing effects of fenofibrate[53] [54]on the atherosclerotic plaque. It has been shown that elevated triglycerides and low HDL-cholesterol 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] [56] [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 anti-sense 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 apoC-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 apoC-III. Of note, the reduction of apoC-III levels was also observed with fenofibrate doses < 200 mg/day, but it is unclear whether a reduction in apoC-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 characterized by a small population size and a limited number of individuals. However, the pooled population analyzed 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 hyperapolipoproteinemia 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 apoC-III levels, even with short-term treatment and doses < 200mg daily.

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Conflict of interest. NK has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra Zeneca, Boehringer Ingelheim, Elpen, MSD, Novartis, NovoNordisk, Sanofi and WinMedica. MB has served on speaker's bureau and as an advisory board member for Amgen, Sanofi-Aventis and Lilly. Dr. Majeed is the Founder & Chairman of Sabinsa Corporation and Sami Labs Limited.

Author Contribution statement.

AS and LES contributed to the literature search, article screening, data acquisition and abstraction. AS contributed to the statistical analysis. SLA, AS and LES contributed to interpretation of the results and drafting of the manuscript. NK, ZR, MB and MP contributed to critical revision of the manuscript. All authors approved the final version of the manuscript for submission.

Data sharing statement

All data is shown in the manuscript

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FIGURE LEGENDS

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals 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% confidence intervals 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.

Figure 4. Random-effects funnel plot detailing publication bias in the studies reporting the impact of fenofibrate on plasma apo C-III concentrations.

Supplementary File 1. An example of search strategy in PubMed-Medline

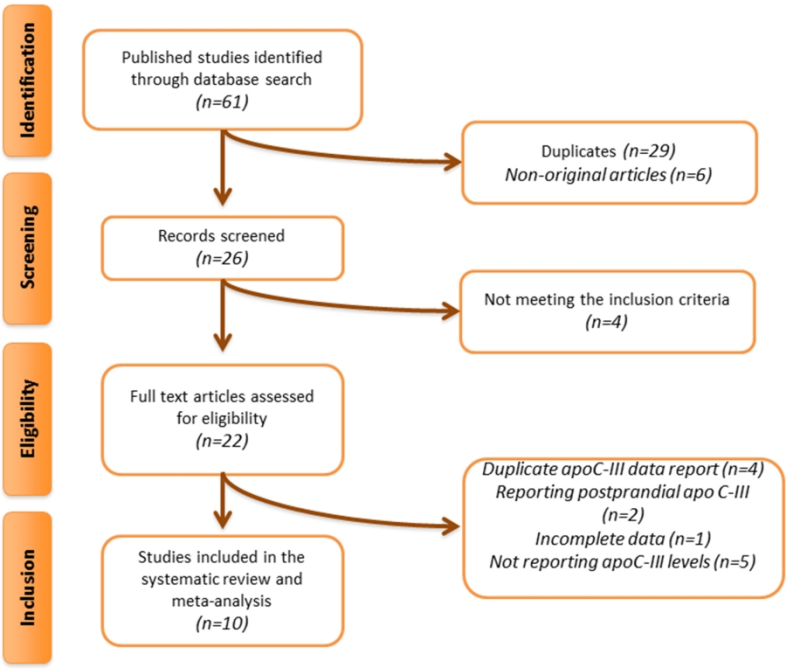

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

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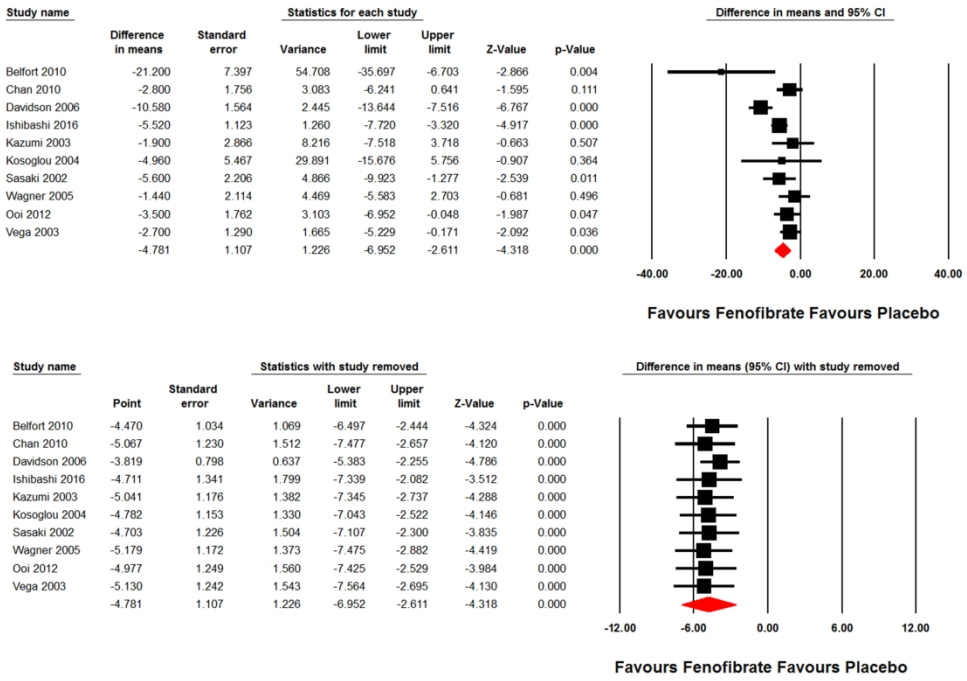

Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the effects of fenofibrate on circulating apolipoprotein C-III concentrations. The lower plot shows the results of leave-one-out sensitivity analysis. Analyses were performed using a random-effects model.

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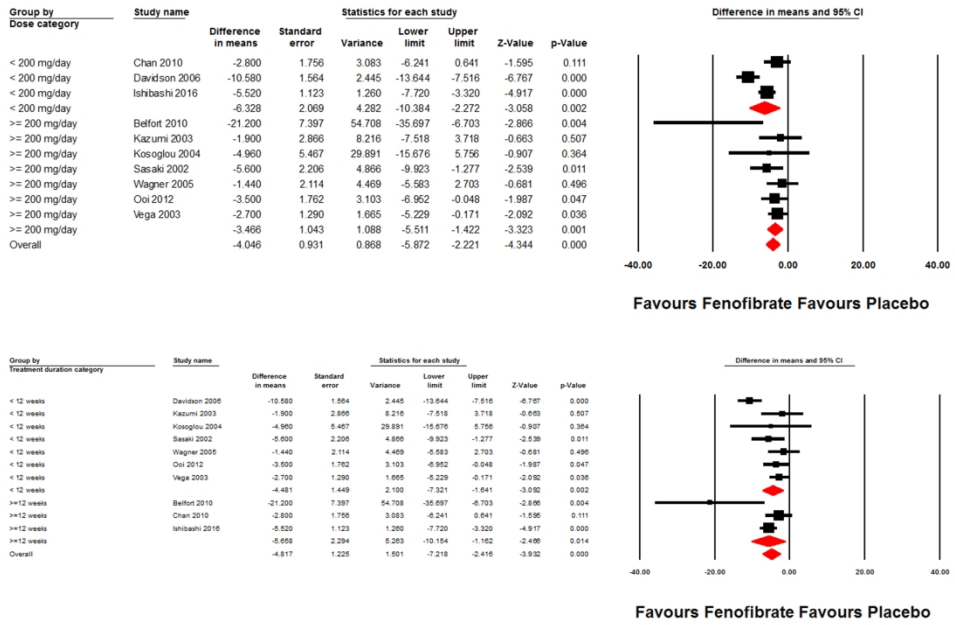

Figure 3. Forest plot displaying weighted mean difference and 95% confidence intervals for the effects of different doses (< 200 mg/day vs. ≥ 200 mg/day) and durations (< 12 weeks vs. ≥ 12 weeks) of treatment with fenofibrate on circulating apolipoprotein C-III concentrations. Analyses were performed using a random-effects model.

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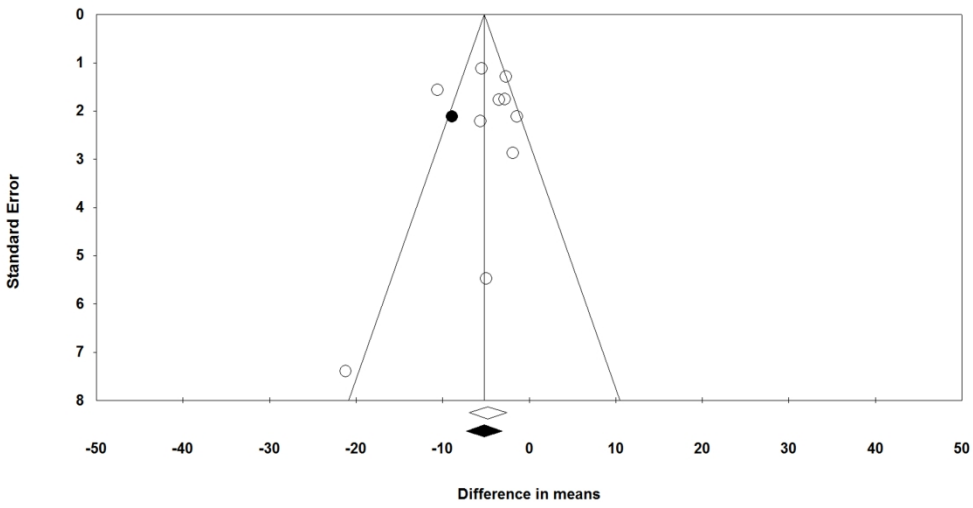

Figure 4. Random-effects funnel plot detailing publication bias in the studies reporting the impact of fenofibrate on plasma apo C-III concentrations.

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Search query

(fenofibrate[Title/Abstract] AND (placeb[Title/Abstract] OR placeba[Title/Abstract] OR placebased[Title/Abstract] OR placebcxontrolled[Title/Abstract] OR placebe[Title/Abstract] OR placebic[Title/Abstract] OR placebic'[Title/Abstract] OR placebo[Title/Abstract] OR placebo'[Title/Abstract] OR placebo''[Title/Abstract] OR placebo's[Title/Abstract] OR placebo1[Title/Abstract] OR placebo2[Title/Abstract] OR placebo3[Title/Abstract] OR placebo4[Title/Abstract] OR placebo88[Title/Abstract] OR placeboaluminum[Title/Abstract] OR placeboamong[Title/Abstract] OR placeboand[Title/Abstract] OR placebobased[Title/Abstract] OR placebobisphosphonates[Title/Abstract] OR placeboch[Title/Abstract] OR placebocompared[Title/Abstract] OR placebocontrol[Title/Abstract] OR placebocontrolled[Title/Abstract] OR placebocorrected[Title/Abstract] OR placebodata[Title/Abstract] OR placeboduration[Title/Abstract] OR placeboeffect[Title/Abstract] OR placeboes[Title/Abstract] OR placebofor[Title/Abstract] OR placebogained[Title/Abstract] OR placebogenic[Title/Abstract] OR placebogenics[Title/Abstract] OR placebogroup[Title/Abstract] OR placebohbt[Title/Abstract] OR placeboimplanted[Title/Abstract] OR placeboin[Title/Abstract] OR placebokontrollierte[Title/Abstract] OR placebokontrollierten[Title/Abstract] OR placebolike[Title/Abstract] OR placebology[Title/Abstract] OR placebolotherapy[Title/Abstract] OR placebome[Title/Abstract] OR placebome'[Title/Abstract] OR placebomental[Title/Abstract] OR placebomore[Title/Abstract] OR placebomovement[Title/Abstract] OR placebon[Title/Abstract] OR placebonone[Title/Abstract] OR placebonor[Title/Abstract] OR placeboone[Title/Abstract] OR placeboor[Title/Abstract] OR placeboour[Title/Abstract] OR placebopdt[Title/Abstract] OR placebopemetrexed[Title/Abstract] OR placeboper[Title/Abstract] OR placeboperiode[Title/Abstract] OR placebophenomenon[Title/Abstract] OR placebophenytoin[Title/Abstract] OR placebopost1[Title/Abstract] OR placebopost10[Title/Abstract] OR placebopost19[Title/Abstract] OR placebopre[Title/Abstract] OR placebopre1[Title/Abstract] OR placebopre10[Title/Abstract] OR placebopre18[Title/Abstract] OR placebor[Title/Abstract] OR placeborange[Title/Abstract] OR placeboresults[Title/Abstract] OR placebos[Title/Abstract] OR placebos'[Title/Abstract] OR placeboscored[Title/Abstract] OR placebostimulation[Title/Abstract] OR placebothe[Title/Abstract] OR placebotherapy[Title/Abstract] OR placebothere[Title/Abstract] OR placebothis[Title/Abstract] OR placebotreated[Title/Abstract] OR placebotwo[Title/Abstract] OR placebovmc[Title/Abstract] OR placebow[Title/Abstract] OR placebowe[Title/Abstract] OR placebowhen[Title/Abstract] OR placebowirkung[Title/Abstract] OR placebowomen[Title/Abstract] OR placeboxetine[Title/Abstract])) AND (("apolipoprotein c-iii"[MeSH Terms] OR ("apolipoprotein"[All Fields] AND "c-iii"[All Fields]) OR "apolipoprotein c-iii"[All Fields] OR ("apoc"[All Fields] AND "iii"[All Fields]) OR "apoc iii"[All Fields]) OR apociii[All Fields] OR "APO C-III"[All Fields] OR "APO CIII"[All Fields] OR apoc3[All Fields] OR "APO C3"[All Fields] OR "apolipoprotein CIII"[All Fields] OR "apolipoprotein C-III"[All Fields] OR "apolipoproteinCIII"[All Fields] OR "apolipoproteinC-III"[All Fields])

Notes:

All terms searched in title and abstract (here marked with Title/Abstract) and in MeSH (here marked with [Mesh]) when available.

No Filters or limitations applied

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 11 and Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1, Figure 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13 and Figure 4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

PRISMA 2009 Checklist

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