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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 Amirhossein Sahebkar,^{1,2,3} Luis E. Simental-Mendía,⁴ Niki Katsiki,⁵ Željko Reiner,⁶ Maciej Banach,^{7,8}, Matteo Pirro,⁹ Stephen L. Atkin^{10*} ¹Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran ²Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran ³School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran ⁴Biomedical Research Unit, Mexican Social Security Institute, Durango, Mexico ⁵Second Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippocration Hospital, Thessaloniki, Greece ⁶University Hospital Center Zagreb, Department of Internal medicine, Kišpatićeva 12, University of Zagreb, Croatia ⁷Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, Lodz, Poland ⁸Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland ⁹Unit of Internal Medicine, Angiology and Arteriosclerosis Diseases, Department of Medicine, University of Perugia, Perugia, Italy ¹⁰Weill Cornell Medicine Qatar, Education City, PO Box 24144, Doha, Qatar *Corresponding author: Stephen L Atkin. Weill Cornell Medicine Qatar, Education City, PO Box 24144, Doha, Qatar. Tel: +97455635807. Fax +97444928422. Email: sla2002@qatarmed.cornell.edu Word count: 2116 Key words: Fenofibrate; fibrate; apoprotein C; triglyceride; meta-analysis.

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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; I²: 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 \geq 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 (PPAR α) 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 $(SD_{pre-treatment})^2 + (SD_{post-treatment})^2 - (2R \times SD_{pre-treatment} \times SD_{post-treatment})]$, 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 I² 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.

2.

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.
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Auth or	Study design	Target Population	Treatm ent duratio	n	Study group s	Age, years	Fem ale (n,	BMI, (kg/ m ²)	Total cholester ol	LDL cholester ol	HDL choleste rol	Triglycerid es	ApoC- III
							9						

Belfort	Randomi	Metabolic	12									
et al.	zed,	syndrome	weeks									
(2010)	double-	-		16	Fenofibr	46±8	5 (31)	31.6±4	228±72	109±56	34±8	500±284
	blind,				ate 200							
	placebo-			9	mg/day	46±9	3 (33)	31.5±3	219±33	117±30	34±9	343±126
	controlle											
	d				Placebo							
Chan et	Randomi	Type 2	12									
al.	zed,	diabetes	weeks									
(2010)	double-			15	Fenofibr	63±8	2 (13)	28.6±3	143.1±1	73.5±23	44.9±9.	115.1±53
	blind,				ate 145			.4	4.7	.2	3	1
	placebo-			15	mg/day	63±8	2 (13)					
	controlle				6			28.5±3	139.2±1	73.5±23	41.8±1	97.4±70.
	d, cross-				Placebo			.0	4.7	.2	2.0	
	over											
Davids	Randomi	Hypertrigl	8									
on et	zed,	yce-	weeks									
al.	double-	ridemia		96	Fenofibr	56.5±9.	37	30.8±3	245±48.	121±39.	36±9.7	480±186
(2006)	blind,			50	ate 130	7	(38.5)	.9	9	1	25+7.0	470+149
	placebo-			30	mg/day	55 3+7	20	31 5+4	237+42	116+42	35±7.0	4/9±140
	controlle				Placebo	0.55.5±7.	(40.0)	0 0	237±42.	110±42.		
	d				Theebo	Ū	(40.0)		7	т		
Hamilt	Randomi	Type 2	12	15	Overall	63.3±7.	2 (13)	28.4	150.8±2	77.3±15	45.2±6.	124.0
on et	zed,	diabetes	weeks			8		(26.8-	7.1	.5	6	(97.4-
al.	double-			15	Fenofibr		ND	30.1)*				159.4)*
(2010)	blind,			1.5	ate 145	ND			143.1±1	73.5±23	44.5±5.	
	placebo-			15	mg/day	ND	ND	ND	4.7	.2	8	115.1±53
	controlle				Dlaasha	ND		ND	130 2.1	73 5+22	12 7.17	1**
	d, cross-				r idcedo			ND	139.2±1	13.3±23	43./±/.	97 4+70
	over								4.7	.2	5	97.4±70. **
Ishibas	Randomi	Dyslipide	12									
hi et al.	zed,	mia	weeks									
(2016)	double-			36	Fenofibr	51.1±1	3 (8)	26.6±3	232.0±41.	134.2±3	40.2±7.	326.0±20
	blind,				ate 100	1.5		.0	8	5.2	3	4.6
	placebo-			35	mg/day		1 (3)					
	controlle					48.7±9.		26.8±2	225.1±30.	128.4±2	40.2±6.	309.1±1.
					Placebo	0		.6	5	9.4	2	0.2
							10					

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Kazum	Randomi	Hypertrigl	8	43	Overall	57.1±9.	5 (11)	24.3±2				
i et al.	zed,	yce-	weeks			1		.6				
(2003)	double-	ridemia		21	Fenofibr		ND		238±45.	ND	40.0±1	352±2
	blind,				ate 300	ND		ND	8		0.0	
	placebo-			22	mg/day		ND			ND		342±3
	controlle					ND		ND	245±51.		49.4±2	
	d, cross-				Placebo				5		3.9	
	over											
Kosogl	Randomi	Dyslipide	2									
ou et	zed.	mia	weeks									
al.	single-			8	Fenofibr	ND	ND	ND	239.8±1	197.2±3	50.3±2	132.9±
(2004)	blind,				ate 200				0.8	2.8	1.7	0
	placebo-			8	mg/day	ND	ND	ND				
	controlle								266.8±3	177.9±3	46.4±1	186.0±
	d				Placebo				2.5	2.8	0.8	4
Ooi et	Randomi	Metabolic	5	11	Overall	46.3±6.	0 (0.0)	30.5±2				
al.	zed,	syndrome	weeks			9	. ()	.6				
(2012)	double-	5		11	Fenofibr				211.9±2	143.1±2	40.2±8.	147.0±
. ,	blind,				ate 200				1.7	2.8	9	8
	placebo-			11	mg/day							
	controlle								227.4±1	152.4±2	36.3±5.	216.1±
	d, cross-				Placebo				8.9	7.8	0	3
	over											
Sasaki	Randomi	Hypertrigl	8	50	Overall	54.6±1	19	ND	241.0±6	119.2±4	39.9±1	431.8±
et al.	zed,	yce-	weeks			2.7	(38)		5.7	9.9	1.6	5.5
(2002)	double-	ridemia		40	Fenofibr							
	blind,				ate 300							
	placebo-			40	mg/day							
	controlle											
	d, cross-				Placebo							
	over											
Vega et	Randomi	Metabolic	8	13	Overall	56.5±8.	0 (0.0)	30.5±4	ND	ND	ND	ND
al.	zed,	syndrome	weeks			9		.2				
(2003)	placebo-			13	Fenofibr							
	controlle			12	ate 200							
	d, cross-			13	mg/day							
	over											
							11					

					Placebo								
Wagne	Randomi	Nondiabet	2	12	Overall	24 [†]	0 (0.0)	27 (21-	ND	ND	ND	ND	ND
r et al.	zed,	ic subjects	weeks					34)**					
(2005)	open-			9	Fenofibr	ND	0 (0.0)		170.1±3	100.5±2	34.8±1	186.0±10	14.0±5.
	label,				ate 201			ND	0.9	3.2	1.6	6.3	7
	placebo-			9	mg/day	ND	0 (0.0)						
	controlle							ND	150.8±3	88.9±27	38.7±7.	132.9±62.	10.5±2.
	d, cross-				Placebo				0.9	.1	7	0	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.

	Sequence	Allocation	Blinding of	Incomplete	Selective	Other
			participants,		outcome	sources of
	generation	concealment	personnel	outcome	reporting	bias
			and outcome	data		
Study			assessors			
Belfort et al. (2010)	L	U	U	L	L	U

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

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

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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; I²: 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; I²: 70.74%) or \geq 12 weeks (WMD: -4.73 mg/dL, 95% CI: -8.29, -1.18, p=0.009; I²: 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; I²: 80.23%) and \geq 200 mg/day (WMD: -3.70 mg/dL, 95% CI: -6.35, -1.05, p=0.006; I²: 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.

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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. E.C.

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. \geq 200 mg/day) and durations (< 12 weeks vs. \geq 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.

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

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Study name		5	Statistics f			Difference	Difference in means and 95% C				
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value				
Belfort 2010	-21.200	7.397	54.708	-35.697	-6.703	-2.866	0.004	I —		- 1	
Chan 2010	-2.800	1.756	3.083	-6.241	0.641	-1.595	0.111				
Davidson 2006	-10.580	1.564	2.445	-13.644	-7.516	-6.767	0.000				
Hamilton 2010	-2.800	1.772	3.141	-6.274	0.674	-1.580	0.114			-∎∔	
Ishibashi 2016	-5.520	1.123	1.260	-7.720	-3.320	-4.917	0.000				
Kazumi 2003	-1.900	2.866	8.216	-7.518	3.718	-0.663	0.507				
Kosoglou 2004	-4.960	5.467	29.891	-15.676	5.756	-0.907	0.364				
Ooi 2012	-3.500	1.762	3.103	-6.952	-0.048	-1.987	0.047			-==-	
Sasaki 2002	-5.600	2.206	4.866	-9.923	-1.277	-2.539	0.011				
Vega 2003	-2.700	1.290	1.665	-5.229	-0.171	-2.092	0.036				
Wagner 2005	-1.440	2.114	4.469	-5.583	2.703	-0.681	0.496			-	
	-4.559	1.007	1.015	-6.533	-2.585	-4.526	0.000			•	
								-40.00	-20.00	0.00	20.00

Favours fenofibrate Favours placebo

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Study name		5	Statistics w	ith study	remove	d			Differen	ce in mea	ns (95%	
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value		Cl) wit	h study re	moved	
Belfort 2010	-4.298	0.939	0.882	-6.139	-2.457	-4.576	0.000		┼╋	-		
Vega 2003	-4.837	1.123	1.261	-7.038	-2.637	-4.308	0.000		_+∎	-		
Wagner 2005	-4.884	1.061	1.125	-6.963	-2.805	-4.604	0.000			.		
Chan 2010	-4.783	1.108	1.228	-6.955	-2.611	-4.316	0.000		_+∎	-		
Davidson 2006	6-3.705	0.704	0.496	-5.085	-2.324	-5.260	0.000		-	-		
Hamilton 2010	0-4.781	1.107	1.226	-6.952	-2.611	-4.318	0.000		_+∎	-		
Ishibashi 2016	6-4.449	1.186	1.407	-6.774	-2.124	-3.751	0.000		_+∎-	-		
Kazumi 2003	-4.766	1.063	1.130	-6.849	-2.683	-4.484	0.000		-+	-		
Kosoglou 2004	4-4.553	1.045	1.091	-6.600	-2.505	-4.358	0.000		+-	-		
Ooi 2012	-4.702	1.123	1.260	-6.902	-2.501	-4.188	0.000		_+∎	-		
Sasaki 2002	-4.465	1.101	1.211	-6.623	-2.308	-4.057	0.000		-+	-		
	-4.559	1.007	1.015	-6.533	-2.585	-4.526	0.000		-	•		
								-12.00	-6.00	0.00	6.00	12.00

Favours fenofibrate Favours placebo

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-oneout sensitivity analysis.

128x118mm (300 x 300 DPI)

Group by	-			Statistics	for each	study				Differenc	e in means an	id 95% CI	
Dose category		Difference	Standard	Varian	Lowe	Upper	7.Value	n.Value					
< 200 mg/day	Chan 2010	-2 800	1 756	3.0	83 -6 24	0.641	-1.595	0 111	1	1		1	- i
< 200 mg/day	Davidson 2006	-10 580	1.564	2.4	15-13.64	-7.516	-6 767	0.000					
< 200 mg/day	Hamilton 2010	-2.800	1 772	3.1	11 -6 27	0.674	-1.580	0.114					
< 200 mg/day	Ichibachi 2016	5.520	1 100	1.0	80 7 7 20	2 2 2 2 0	4.017	0.000					
< 200 mg/day	ISINDASIN 2010	-5.409	1.123	2.0	16 -9.96	-3.320	-4.917	0.000			二		
>= 200 mg/day	Belfort 2010	-21 200	7 307	54.7	10 -0.007	-6 703	-2.866	0.001					
>= 200 mg/day	Kerumi 2002	-21.200	0.000	0.0	16 7 51	-0.703	-2.000	0.607		_			
>= 200 mg/day	Kazumi 2003	-1.900	2.000 E.467	20.0	10 -7.510	5.710	-0.003	0.307					
>= 200 mg/day	Rosogiou 2004	-4.900	0.407	29.0	91-15.070	0 0.700	-0.907	0.011					
>= 200 mg/day	Sasaki 2002	-5.000	2.200	4.0	00 -9.92	-1.211	-2.539	0.011		· · ·			
>= 200 mg/day	Wagner 2005	-1.440	2.114	4.4	09 -5.58	2.703	-0.681	0.496					
>= 200 mg/day	001 2012	-3.500	1.762	3.1	03 -6.95	-0.048	-1.987	0.047					
>= 200 mg/day	Vega 2003	-2.700	1.290	1.6	55 -5.229	-0.171	-2.092	0.036					
>= 200 mg/day		-3.466	1.043	1.0	88 -5.51	-1.422	-3.323	0.001			•		
Overall		-4.014	0.891	0.7	95 -5.76	-2.267	-4.503	0.000	1		• 1		
									-40.00	-20.00	0.00	20.00	40.00
									Favo	urs fenofil	brate Fav	ours plac	ebo
Group by	Stud			61-1	istics for .	ach study			Favo	urs fenofil	brate Fav	ours plac	ebo
Group by Treatment duration cate	egory Stud	y name		Stat	istics for	each study			Favo	urs fenofil	brate Fav	ours plac	ebo
Group by Treatment duration cate	egory Stud	y name Dif	ference Sta means	Stat ndard error V:	istics for e	each study wer Uppe mit limi	er t Z-Value	p-Value	Favo	urs fenofil	brate Fav	rours plac	ebo
Group by Treatment duration cate < 12 weeks	egory Stud	y name Dif in ison 2006	ference Sta means of -10.580	Stat ndard error Va 1.564	istics for e ariance 1 2.445 -13	ach stud y wer Uppe mit limi 3.644 -7.51	r t Z-Value 16 -6.767	p-Value 0.000	Favo	urs fenofil D <u>ifferenc</u>	brate Fav e in means and	rours plac	ebo
Group by Treatment duration cate < 12 weeks < 12 weeks	<mark>agory Stud</mark> Davii Kazu	y name Dif in ison 2006 mi 2003	ference Sta means (-10.580 -1.900	Stat ndard rror Va 1.564 2.866	istics for (triance 1 2.445 - 1: 8.216 - 1	ach study wer Uppe mit limi 1.644 -7.51 1.518 3.71	r t Z-Value 16 -6.767 18 -0.663	p-Value 0.000 0.507	Favo	Difference	brate Fav	rours plac	ebo
Group by Treatment duration cate < 12 weeks < 12 weeks < 12 weeks	<mark>egory Stud</mark> Davis Kazu Kosc	y name Dif in Ison 2006 mi 2003 glou 2004	ference Sta means (-10.580 -1.900 -4.960	Stat ndard error V: 1.564 2.866 5.467	istics for 4 triance 1 2.445 -11 8.216 -1 29.891 -1	ach study wer Uppe mit limi .644 -7.51 .518 3.71 .676 5.75	r Z-Value 6 -6.767 18 -0.663 56 -0.907	p-Value 0.000 0.507 0.364	Favo	Difference	brate Fav	rours plac	ebo
Group by Treatment duration cate < 12 weeks < 12 weeks < 12 weeks < 12 weeks	egory Stud Davi Kazu Kosc Sasa	y name Dif in dson 2006 mi 2003 glou 2004 ki 2002	ference Sta means (-10.580 -1.900 -4.960 -5.600	Stat ndard Pror V3 1.564 2.866 5.467 2.206	istics for 4 triance 1 2.445 -11 8.216 -1 29.891 -11 4.866 -4	ach study wer Uppe mit limit 518 3.71 .518 3.71 .518 3.71 .518 1.75 .923 -1.27	r Z-Value 6 -6.767 8 -0.663 -0.907 7 -2.539	p-Value 0.000 0.507 0.364 0.011	Favo	Difference	brate Fav	rours plac	ebo
Group by Treatment duration cate < 12 weeks < 12 weeks < 12 weeks < 12 weeks < 12 weeks < 12 weeks	egory Stud David Kazu Kosc Sase Wag	y name Dif Ison 2006 mi 2003 glou 2003 ki 2002 ner 2005	ference Sta means (-10.580 -1.900 -4.960 -5.600 -1.440	Stat rror V: 1.564 2.866 5.467 2.206 2.114	istics for 4 triance 1 2.445 -11 8.216 -1 29.891 -12 4.866 -4 4.866 -4	ach study wer Uppe mit limi .644 -7.5 .518 3.71 .676 5.75 .923 -1.22 .583 2.70	r Z-Value 66 -6.767 18 -0.663 56 -0.907 7 -2.539 13 -0.681	p-Value 0.000 0.507 0.364 0.011 0.496	Favo	Difference	brate Fav	rours plac	ebo
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Group by Treatment duration cate < 12 weeks < 12 weeks	egory Stud Davia Kazu Koso Sasa Wag Oʻa'i Vega	y name Dif in Ison 2006 mi 2003 glou 2004 ki 2002 ner 2005 i012 2003	ference Sta means (-10,580 -1,900 -5,600 -1,440 -3,500 -3,500	Stat ndard trror V: 1.564 2.866 5.467 2.206 2.114 1.762 1.290	istics for (triance 1 2.445 - 11 8.216 - 1 29.891 - 18 4.866 - 4 4.469 - 3 3.103 - (1.665 - 4	study wer Upper imit limit i.644 -7.5/ 5.75 3.71 i.676 5.75 9.23 -1.21 5.583 2.70 9.52 -0.02 9.52 -0.01	r Z-Value 6 -6.767 8 -0.663 56 -0.907 7 -2.539 3 -0.681 8 -1.967 71 -2.092	p-Value 0.000 0.507 0.364 0.011 0.496 0.047 0.036	Favor	Difference	brate Fav	rours plac	ebo
Group by Treatment duration cate < 12 weeks < 12 weeks	agory Stud Davi Kazı Kosc Sass Wag Oci 2 Vega	y name Dif Ison 2006 mi 2003 glou 2004 ki 2002 her 2005 012 2003	ference Sta means 4 -10.580 -1.900 -4.960 -5.600 -1.440 -3.500 -2.700 -2.700	Stat mdard V 1.564 2.886 5.467 2.206 2.114 1.762 1.290 1.290 1.449	istics for e riance i 2.445 -13 8.216 -1 29.891 -19 4.866 -4 4.469 -4 3.103 -6 1.665 -4 2.100 -1	wer Upper imit limit :644 -7.5 :676 5.77 :676 5.72 :583 2.70 :592 -0.04 :229 -0.01 :321 -1.64	r Z-Value 6 -6.767 8 -0.683 56 -0.907 7 -2.539 3 -0.681 18 -1.987 1 -2.092 11 -3.092	p-Value 0.000 0.507 0.364 0.011 0.496 0.047 0.036	Favo	Difference	e in means and	rours plac	ebo
Group by Treatment duration cate < 12 weeks < 12 weeks	egory Stud Davis Kazu Kasu Sasa Sasa Vag Belto Belto	y name Dif Ison 2006 mi 2003 glou 2004 ki 2002 ner 2005 i012 2003 rt 2010	ference Sta means 1 -10.580 -4.960 -5.600 -3.500 -2.700 -4.481 -2.1200	Stat ndard V 1.564 2.866 2.114 1.762 1.290 1.290 1.290 7.397	istics for 4 riance 1 2.445 -13 8.216 -1 29.891 -14 4.866 -4 4.469 -4 3.103 -6 1.665 -4 2.100 -3 54.708 -33	ach study wer mit Uppe limit 1644 -7.51 1.518 3.7' 1.676 5.75 9.22 -1.22 1.583 2.70 9.923 -1.22 3.21 -1.67 3.21 -1.67	r Z-Value 6 -6.767 8 -0.663 6 -0.907 7 -2.539 3 -0.681 8 -1.967 71 -2.092 11 -3.092 33 -2.866	p-Value 0.000 0.507 0.364 0.049 0.047 0.036 0.004	Favor	Urs fenofil	brate Fav	rours plac	ebo
Group by Treatment duration cate < 12 weeks < 12 weeks > 12 weeks > 12 weeks > 12 weeks	egory Stud Davis Kazı Kosc Sasa Sasa Ooi Vega Belfio Char	y name Dif ison 2006 mi 2003 glou 2004 ki 2002 ner 2005 012 2003 rt 2010 .2010	ference Sta means (-10.580 -1.900 -4.960 -5.600 -5.600 -2.700 -2.700 -4.481 -21.200	Stat ndard rror V3 1.564 2.866 5.467 2.206 2.114 1.762 1.290 1.490 1.497 7.397 1.756	istics for a riance 1 2.445 -11 8.216 -1 29.891 -18 4.866 -4 4.469 -4 3.103 -4 1.665 -4 2.100 -1 54.708 -3 3.083 -6 3.083 -6	sach study wer Upper limit -7.51 3.616 5.75 9.23 -1.21 5.68 3.71 9.952 -0.04 2.229 -0.17 3.21 -1.64 6.697 -6.67 2.241 0.64	r Z-Value 16 -6.767 8 -0.663 36 -0.907 7 -2.539 33 -0.681 8 -1.987 71 -2.092 11 -3.092 33 -2.866 11 -1.555	p-Value 0.000 0.364 0.011 0.496 0.036 0.036 0.002 0.002	Favor	Urfference	brate Fav	ours plac	ebo
Group by Treatment duration cate < 12 weeks < 12 weeks > 12 weeks > 12 weeks > 12 weeks > 12 weeks > 12 weeks	egory David David Kazı Kosc Sasa Vega Ooi 2 Vega Belfo Chara Ham	y name Dif ison 2006 mi 2003 glou 2004 ki 2002 her 2005 i012 2003 rt 2010 i 2010 ton 2010	ference Sta means of -10,580 -1,900 -4,960 -5,600 -1,440 -3,500 -2,700 -4,481 -21,200 -2,800	Stat ndard rror V 1.564 2.866 5.467 2.206 2.114 1.762 1.290 1.449 7.397 1.756 1.772	istics for e triance 1 2.445 -11 8.216 -1 29.891 -11 4.866 -4 4.469 -4 3.103 -4 1.065 -4 2.100 -1 54.708 -33 3.083 -4 3.103 -4 3.103 -4 1.065 -4 2.100 -1 54.708 -3 3.083 -4 3.101 -4 3.103	ach study wer Upper Iimi Iimi .644 -7.51 .518 3.71 .676 5.75 .923 -1.27 .583 2.70 .321 -1.66 .697 -6.77 .224 0.01 .224 0.61 .274 0.61	r Z-Value 6 -6.767 18 -0.663 6 -0.907 77 -2.539 13 -0.881 18 -1.987 11 -2.082 11 -3.092 13 -2.866 11 -1.555 74 -1.555	p-Value 0.000 0.507 0.364 0.011 0.496 0.047 0.002 0.002 0.004 0.111	Favor	Difference	brate Fav	199%, CI	ebo
Group by Treatment duration cate < 12 weeks < 12 weeks > 12 weeks	egory Davis Kazu Kosc Sasa Sasa Visa Ooi 2 Vega Belfo Char Ishib	y name Dif Ison 2006 mi 2003 glou 2004 ki 2002 ner 2005 012 2003 rt 2010 izo10 izo10 izo10 izo10	ference Sta means - -10.580 -1.900 -5.600 -1.440 -2.700 -2.700 -2.700 -2.800 -2.800 -2.800 -2.5520	Stat rror V: 1.564 2.866 2.114 1.720 1.290 1.449 7.397 1.752 1.772 1.723	istics for 4 triance 1 2.445 -12 8.216 -2 2.9891 -12 9.981 -12 9.981 -12 4.866 -4 4.469 -4 3.103 -4 2.100 -2 54.708 -3 3.083 -4 3.083 -4 1.260 -2 3.141 -4 1.260 -2	ach study wer Imit Uppe Imit 0.44 -7.51 5.15 3.71 6.87 5.75 9.923 -1.27 5.83 2.77 9.952 -0.04 3.21 -1.64 6.897 -6.70 2.241 0.64 7.274 0.63 7.274 0.33	r z-Value 6 -6.767 18 -0.663 6 -0.907 7 -2.539 3 -0.681 1.987 11 -3.092 11 -3.092 13 -2.866 11 -1.595 14 -1.585 20 -4.917 -2.921 -2.922 -2.92 -2.922	p-Value 0.000 0.507 0.364 0.047 0.036 0.004 0.004 0.111 0.111 0.111	Favor	Difference	brate Fav	995% CI	ebo
Group by Treatment duration cate < 12 weeks < 12 weeks > 12 weeks	egory Davi Davi Kazı Koso Sasa Wag Ooi Vega Bello Char Bello Char Ishib	y name Dif ison 2006 mi 2003 glou 2004 ki 2002 ner 2005 i012 2003 rt 2010 i2010 i2010 ashi 2016	ference Sta means (1.900 -5.600 -5.600 -3.500 -2.700 -4.481 -2.200 -2.800 -2.800 -2.800 -5.520	Stat ndard rror V 2.886 5.467 2.206 2.114 1.762 1.290 1.490 1.490 1.490 1.490 1.490 1.495 1.756 1.772 1.123	istics for 4 riance 1 2.445 -13 8.216 -1 29.891 -19 4.866 -4 3.103 -4 1.865 -4 2.100 -1 5.4708 -3 3.083 -4 3.083 -4 3.083 -4 1.260 -1 2.500 -1	wer Uppe 1844 -7.51 1518 3.71 1676 5.72 923 -1.21 583 2.70 952 -0.04 1321 -1.64 6897 -6.77 7.20 -3.33 6.88 -1.48	r Z-Value 16 -6.767 18 -0.663 6 -0.907 7 -2.539 13 -0.681 8 -1.967 14 -2.092 14 -3.092 13 -2.866 14 -1.580 20 -4.917 1 -2.897 2 - 4.917 1 -2.897 2 - 4.917 2 - 4.917 2 - 4.917 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.897 -2.992 -2.997 -2.992 -2.997 -2.992 -2.997 -2.997 -2.992 -2.997 -2.97	p-Value 0.000 0.507 0.364 0.011 0.036 0.002 0.004 0.002 0.002 0.011 0.111 0.114 0.000	Favor	Difference	brate Fav	99% CI	ebo

Favours fenofibrate Favours placebo

124x100mm (300 x 300 DPI)

Figure 3. Forest plot displaying weighted mean difference and 95% confidence intervals for the effects of

different doses (< 200 mg/day vs. \geq 200 mg/day) and durations (< 12 weeks vs. \geq 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.

180x174mm (300 x 300 DPI)





PRISMA 2009 Checklist

4 5 Section/topic 6	#	Checklist item	Reported on page #
7 TITLE	-		
⁸ Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
12 12 13 14	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
16 17 Rationale	3	Describe the rationale for the review in the context of what is already known.	4
18 Objectives 19	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
21 METHODS			
22 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
24 Eligibility criteria 25 26	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
27 Information sources 28	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
²⁹ Search 30 31	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
32 Study selection 33	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
³⁴ Data collection process 35 36	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
37 Data items 38	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
 ³⁹ Risk of bias in individual ⁴⁰ 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
42 Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
⁴³ Synthesis of results 44 45	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. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6

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1 2	PRISMA 20)09	Checklist	
3 4 -		-	Page 1 of 2	
5 6 7	Section/topic	#	Checklist item	Reported on page #
/ 8 9	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
10	Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
13	RESULTS			
14	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
16 17 18	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
19 20 21 22	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
23 24 25 26	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
27 28	Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2 and 3
29 30	Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14

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33 DISCUSSION 34 35 36 37 38

31 Additional analysis

Summary of evidence 24 Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to 14 key groups (e.g., healthcare providers, users, and policy makers). Limitations 25 Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of 14 identified research, reporting bias). Conclusions 26 Provide a general interpretation of the results in the context of other evidence, and implications for future research. 14 FUNDING Funding Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the 27 17 systematic review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).

13 and

Figure 4

4 46 47

44

32

39 40

4

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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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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Primary Subject Heading :	Cardiovascular medicine
Secondary Subject Heading:	Research methods
Keywords:	fenofibrate, fibrate, apolipoprotein C, meta-analysis



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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 Amirhossein Sahebkar,^{1,2,3} Luis E. Simental-Mendía,⁴ Niki Katsiki,⁵ Željko Reiner,⁶ Maciej Banach,^{7,8}, Matteo Pirro,⁹ Stephen L. Atkin^{10*} ¹Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran ²Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran ³School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran ⁴Biomedical Research Unit, Mexican Social Security Institute, Durango, Mexico ⁵Second Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippocration Hospital, Thessaloniki, Greece ⁶University Hospital Center Zagreb, Department of Internal medicine, Kišpatićeva 12, University of Zagreb, Croatia ⁷Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, Lodz, Poland ⁸Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland ⁹Unit of Internal Medicine, Angiology and Arteriosclerosis Diseases, Department of Medicine, University of Perugia, Perugia, Italy ¹⁰Weill Cornell Medicine Qatar, Education City, PO Box 24144, Doha, Qatar *Corresponding author: Stephen L Atkin. Weill Cornell Medicine Qatar, Education City, PO Box 24144, Doha, Qatar. Tel: +97455635807. Fax +97444928422. Email: sla2002@qatarmed.cornell.edu 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; I²: 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 \geq 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.

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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 (PPAR α) 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) statement²⁵. 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 $(SD_{pre-treatment})^2 + (SD_{post-treatment})^2 - (2R \times SD_{pre-treatment} \times SD_{post-treatment})]$, 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). OPP,

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, 3hypertriglyceridemia ^{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.

Auth	Study	Target	Treat	Total	Stud	Age,	Female/	BMI	Total	LDL	HDL	Triglycer	ApoC-
or	design	Populatio	ment	popula	у	years	male (n)	,	choleste	choleste	cholest	ides	III
		n	durati	tion	grou			(kg/	rol	rol	erol		

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			on	(n)	ps			m ²)	(mg/dl)	(mg/dl)	(mg/dl)	(mg/d
Belfort	Random	Metaboli	12									
et al.	ized,	с	weeks									
(2010)	double-	syndrome		16	Fenofibr	46±8	5/11	31.6±	228±72	109±56	34±8	500±
	blind,				ate 200			4				4
	placebo-			9	mg/day	46±9	3/6		219±33	117±30	34±9	
	controlle							31.5±				343±
	d				Placebo			3				6
Chan	Random	Type 2	12									
et al.	ized,	diabetes	weeks									
(2010)	double-			15	Fenofibr	63±8	213	28.6±	$143.1\pm$	73.5±2	44.9±	115.1
	blind,				ate 145			3.4	14.7	3.2	9.3	3.1
	placebo-			15	mg/day	63±8	2/13					
	controlle							28.5±	139.2±	73.5±2	41.8±	97.4±
	d, cross-				Placebo			3.0	14.7	3.2	12.0	.9
	over											
Davids	Random	Hypertrig	8									
on et	ized,	lyce-	weeks									
al.	double-	ridemia		96	Fenofibr	56.5±9	37/59	30.8±	245±48	121±39	36±9.	480±
(2006)	blind,				ate 130	.7		3.9	.9	.1	7	6
	placebo-			50	mg/day		20/30					
	controlle					55.3±7		31.5±	237±42	116±42	35±7.	479±
	d				Placebo	.0		4.9	.4	.4	0	8
								4				
Ishibas	Random	Dyslipide	12									
hi et	ized,	mia	weeks									
al.	double-			36	Fenofibr	51.1±1	3/33	26.6±	232.0±4	134.2±	40.2±	326.0
(2016)	blind,				ate 100	1.5		3.0	1.8	35.2	7.3	04.
	placebo-			35	mg/day		1/34					
	controlle					48.7±9		26.8±	225.1±3	128.4±	40.2±	309.1
	d				Placebo	.0		2.6	0.5	29.4	6.2	30.
Kazu	Random	Hypertrig	8	43	Overall	57.1±9	5/38	24.3±				
mi et	ized,	lyce-	weeks			.1		2.6				
al.	double-	ridemia		21	Fenofibr		ND		238±45	ND	40.0±	352±
(2003)	blind,				ate 300	ND		ND	.8		10.0	4
	placebo-			22	mg/day		ND			ND		
	controlle					ND		ND	245±51		49.4±	342±

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Kosog	Random	Dyslipide	2										
lou et	ized,	mia	weeks										
al.	single-			8	Fenofibr	ND	ND	ND	239.8±	197.2±	50.3±	132.9±5	
(2004)	blind,				ate 200				10.8	32.8	21.7	0.0	
	placebo-			8	mg/day	ND	ND	ND					
	controlle								266.8±	177.9±	46.4±	186.0±3	
	d				Placebo				32.5	32.8	10.8	5.4	
Ooi et	Random	Metaboli	5	11	Overall	46.3±6	0/11	30.5±					
al.	ized,	с	weeks			.9		2.6					
(2012)	double-	syndrome		11	Fenofibr				211.9±	143.1±	40.2±	147.0±7	
	blind,				ate 200				21.7	22.8	8.9	8.8	
	placebo-			11	mg/day								
	controlle								227.4±	152.4±	36.3±	216.1±9	
	d, cross-				Placebo				18.9	27.8	5.0	0.3	
	over												
Sasaki	Random	Hypertrig	8	50	Overall	54.6±1	19/31	ND	241.0±	119.2±	39.9±	431.8±3	
et al.	ized,	lyce-	weeks			2.7			65.7	49.9	11.6	05.5	
(2002)	double-	ridemia		40	Fenofibr								
	blind,				ate 300								
	placebo-			40	mg/day								
	controlle				DL 1								
	d, cross-				Placebo								
	over												
Vega	Random	Metaboli	8	13	Overall	56.5±8	0/13	30.5±	ND	ND	ND	ND	
et al.	ized,	с	weeks			.9		4.2					
(2003)	placebo-	syndrome		13	Fenofibr								
	controlle				ate 200								
	d, cross-			13	mg/day								
	over				Placebo								
Wagne	Pandom	Nondisha	2	12	Overall	24†	0/12	77	ND	ND	ND	ND	
vv agne	ized	tic	ے weeks	12	Overall	24	0/12	(21	ND	IND	ND	ND	
1 Ct dl.	oper	uu subiests	WEEKS	9	Fenofibr	ND	0/9	(21- 34)**	170 1+	100 5+	34 8+	186 0+1	
(2003)	open-	subjects		,	ate 201		019	54)***	30.9	23.2	11.6	06 3	
	nlaget -			9	mg/day	ND	0/9	ND	50.7	22.2	11.0	00.5	
	placebo-				ing/uay		-		150.8±	88.9±2	38.7±	132.9±6	
	controlle				Placebo			ND	30.9	7.1	7.7	2.0	
									/				

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**.

Гable 2.	Quality	of bias	assessment	of the	inclu	ded	studies	according	to the	Cochrane	guidelines	
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Study	Sequence	Allocation	Blinding of participants, personnel and outcome	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
		11				

3 4 5 6	Ishibashi et al. (2016)	L	U	U	L	L	U
7 8 9 10 11	Kazumi et al. (2003)	U	U	U	L	L	U
12 13 14 15 16	Kosoglou et al. (2004)	U	U	Н	L	L	U
17 18 19 20	Ooi et al. (2012)	U	U	U	L	L	U
21 22 23 24 25	Sasaki et al. (2002)	U	L	U	L	L	U
25 26 27 28 29	Vega et al. (2003)	U	U	Н	L	L	U
30 31 32 33	Wagner et al. (2005)	U	U	н	L	L	U
35 36 37 38 39 40 41 42 43 44	L, low risk of bias; H, high ris	sk of bias; I	U, unclear ris	k of bias.	31		
45 46 47 48 49 50 51 52 53 54			12				
55 56 57 58 59 60	For peer review	only - http://	bmjopen.bmj.c	om/site/about/	'guidelines.xh	tml	

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; I²: 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; I²: 70.74%) or \geq 12 weeks (WMD: -5.66 mg/dL, 95% CI: -10.15, -1.16, p=0.014; I²: 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; I²: 83.26%) and \geq 200 mg/day (WMD: -3.47 mg/dL, 95% CI: -5.51, -1.42, p=0.001; I²: 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-IIIlowering 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 elie. 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

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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 CAD⁵¹; 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. \geq 200 mg/day) and durations (< 12 weeks vs. \geq 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

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For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



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

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Study name			Statistic	s for each st	udy					Differer	ice in mean	s and 95%	сі
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	e p-Va	lue					
Belfort 2010	-21.200	7.397	54.708	-35.697	-6.703	-2.86	6 0.	.004	I —	-			I I
Chan 2010	-2.800	1.756	3.083	-6.241	0.641	-1.59	5 0	.111					1 1
Davidson 2006	-10.580	1.564	2.445	-13.644	-7.516	-6.76	7 0.	.000		14			1 1
Ishibashi 2016	-5.520	1.123	1.260	-7.720	-3.320	-4.91	7 0.	.000			_∎		1 1
Kazumi 2003	-1.900	2.866	8.216	-7.518	3.718	-0.66	3 0.	.507			───		1 1
Kosoglou 2004	-4.960	5.467	29.891	-15.676	5.756	-0.90	7 0.	.364				-	1 1
Sasaki 2002	-5.600	2.206	4.866	-9.923	-1.277	-2.53	9 0	.011					1 1
Wagner 2005	-1.440	2.114	4.469	-5.583	2.703	-0.68	1 0.	496			_		1 1
Ooi 2012	-3.500	1.762	3.103	-6.952	-0.048	-1.98	7 0.	.047					1 1
Vega 2003	-2.700	1.290	1.665	-5.229	-0.171	-2.09	2 0.	.036					1 1
	-4.781	1.107	1.226	-6.952	-2.611	-4.31	8 0.	.000			•		1 1
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Study name			Statistics wit	h study reme	oved			Di	Favour	s Feno	fibrate F	avours	Placebo
	Point	Standard error	Varianc e	Lower L limit	lpper limit Z	-Value	p-Value						
Belfort 2010	-4.470	1.034	1.069	-6.497	-2.444	-4.324	0.000	1	+	-	í.	1	1
Chan 2010	-5.067	1,230	1.512	-7.477	-2.657	-4.120	0.000						
Davidson 2006	-3.819	0.798	0.637	-5.383	-2.255	-4.786	0.000)				
Ishibashi 2016	-4.711	1.341	1.799	-7.339	-2.082	-3.512	0.000		-				
Kazumi 2003	-5.041	1.176	1.382	-7.345	-2.737	-4.288	0.000						
Kosoglou 2004	-4.782	1.153	1.330	-7.043	-2.522	-4.146	0.000						
Sasaki 2002	-4.703	1.226	1.504	-7.107	-2.300	-3.835	0.000		-				
Wagner 2005	-5.179	1.172	1.373	-7.475	-2.882	-4.419	0.000			Ē.,			
Ooi 2012	-4.977	1,249	1,560	-7.425	-2.529	-3.984	0.000						
Vega 2003	-5.130	1.242	1.543	-7.564	-2.695	-4.130	0.000		i				
	-4.781	1.107	1.226	-6.952	-2.611	-4.318	0.000		-				
								-12.00	-6.0	0	0.00	6.00	12.00
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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-oneout sensitivity analysis. Analyses were performed using a random-effects model.

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Group by	Study name			Statistics	for each s	tudy				Differen	ce in means an	d 95% CI	
Dose category		Difference in means	Standard error	Variance	Lower	Upper limit	Z-Value	p-Value					
< 200 mg/day	Chan 2010	-2.800	1.756	3.083	-6.241	0.641	-1.595	0.111	1	1		1	1
< 200 mg/day	Davidson 2006	-10.580	1.564	2.445	-13.644	-7.516	-6.767	0.000		_	F I		
< 200 mg/day	Ishibashi 2016	-5.520	1,123	1.260	-7.720	-3.320	-4.917	0.000			-		
< 200 mg/day		-6.328	2.069	4.282	-10.384	-2.272	-3.058	0.002			<u>– I</u>		
>= 200 mg/day	Belfort 2010	-21.200	7.397	54,708	-35.697	-6.703	-2.866	0.004			_		
>= 200 mg/day	Kazumi 2003	-1.900	2.866	8.216	-7.518	3.718	-0.663	0.507					
>= 200 mg/day	Kosoglou 2004	-4.960	5 467	29 891	-15 676	5 756	-0.907	0.364					
>= 200 mg/day	Sasaki 2002	-5.600	2 206	4 866	-9.923	-1 277	-2 539	0.011		·			
>= 200 mg/day	Wagner 2005	-1 440	2 114	4 469	-5 583	2 703	-0.681	0.496					
>= 200 mg/day	Oni 2012	-3 500	1 762	3 102	6 952	-0.048	-1.987	0.047					
>= 200 mg/day	Vega 2003	-2 700	1 200	1.665	-5 220	-0.171	-2.092	0.036			-		
>= 200 mg/day	vega 2005	2.100	1.042	1.000	5 511	1 422	2 2 2 2 2 2	0.000			-		
Cuesell		-0.400	0.021	0.000	5.072	2 224	4.244	0.001					
Overall		-4.040	0.931	0.000	-0.072	-2.221	-4.344	0.000	1	1	•	1	1
									-40.00	-20.00	0.00	20.00	40.00
									Favoi	ırs Fenofi	brate Fav	ours Plac	ebo
Group by Treatment duration category	Study nar	ne		St	atistics for eac	h study				Diffe	rence in means and 9	5% CI	
		Diffe	rence Stan heans er	dard ror Varia	Lov Ince lin	ver Upper nit limit	Z-Value	p-Value					
< 12 weeks	Davidson	2008	-10.580	1.564	2.445 -13	644 -7.51	6 -6.767	0.000	1	- I -	-		
< 12 weeks	Kazumi 2	003	-1.900	2.868	8.216 -7.	518 3.71	8 -0.663	0.507					
< 12 weeks	Kosoglou	2004	-4.960	5.467 2	9.891 -15.	676 5.75	6 -0.907	0.364					
< 12 weeks	Sasaki 20	02	-5.600	2.200	4.000 -0.	523 -1.2/1 583 3.70	-2.030	0.011					
< 12 weeks	Oni 2012		-3.500	1.762	3.103 .0	952 -0.04	8 -1.987	0.047					
< 12 weeks	Vega 200	3	-2.700	1.290	1.005 -5.	229 -0.17	1 -2.092	0.038			-		
< 12 weeks			-4.481	1.449	2.100 -7.	321 -1.64	1 -3.092	0.002			•		
>=12 weeks	Belfort 20	110	-21.200	7.397 5	4.708 -35.	697 -6.70	3 -2.800	0.004			_		
>=12 weeks	Chan 201	0	-2.800	1.758	3.083 -8.	241 0.64	1 -1.595	0.111	1				
>=12 weeks	Ishibashi .	2018	-5.520	1.123	1.260 -7.	720 -3.32	0 -4.917	0.000	1		=		
>=12 weeks			-5.658	2.294	5.263 -10.	154 -1.163	2 -2.466	0.014	1				
Overall			-9.617	1.225	1.001 -7.	218 -2.41	o -3.932	0.000	1	1	-	1	1
									-40.00	-20.00	0.00	20.00	40.00
									Favo	urs Fenof	ibrate Fav	ours Plac	ebo

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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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
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

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PRISMA 2009 Checklist

		Page 1 01 2	
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 only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	17



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