Accepted Manuscript

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PII: S1043-6618(16)30153-0
DOI: <http://dx.doi.org/doi:10.1016/j.phrs.2016.06.011>
Reference: YPHRS 3204

To appear in: *Pharmacological Research*

Received date: 28-2-2016
Revised date: 10-6-2016
Accepted date: 10-6-2016

Please cite this article as: Sahebkar Amirhossein, Giua Renato, Pedone Claudio, Ray Kausik K, Vallejo-Vaz Antonio J, Costanzo Luisa. Fibrate Therapy and Flow-Mediated Dilation: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials. *Pharmacological Research* <http://dx.doi.org/10.1016/j.phrs.2016.06.011>

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Fibrate Therapy and Flow-Mediated Dilation:**A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials**

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Graphical abstract

Abstract

Flow-mediated dilation (FMD) of the brachial artery reflects endothelium-dependent vasodilator function; since it correlates with coronary endothelial function, its reduction could predict cardiovascular events. Several studies have investigated the potential impact of fibrates therapy on endothelial function, but clinical findings have not been fully consistent. We aimed to conduct a meta-analysis of randomized placebo-controlled trials in order to clarify whether fibrate therapy could improve endothelial function. A systematic search in PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases was performed to identify randomized placebo-controlled trials investigating the effect of fibrates on endothelial function as estimated by FMD. A random-effects model and generic inverse variance method were used for meta-analysis. Sensitivity analysis, risk of bias evaluation, and publication bias assessment were carried out using standard methods. Random-effects meta-regression was used to evaluate the impact of treatment duration on the estimated effect size. Fifteen trials with a total of 556 subjects met the eligibility criteria. Fibrate

therapy significantly improves FMD (weighted mean difference [WMD]: 1.64%, 95% CI: 1.15, 2.13, $p < 0.001$) and the result was confirmed in both subgroups with treatment durations ≤ 8 weeks (WMD: 1.35%, 95% CI: 0.85, 1.86, $p < 0.001$) and > 8 weeks (WMD: 2.55%, 95% CI: 1.21, 3.89, $p < 0.001$). When the analysis was stratified according to the fibrate type, a significant effect was observed with fenofibrate but not with gemfibrozil, though difference between the two subgroups was not significant. Meta-analysis of data from trials where nitrate mediated dilation (NMD) was available did not suggest a significant change in NMD following treatment with fibrates. The results of this meta-analysis suggest that fibrates may exert beneficial effects on endothelial function, even over a short-term treatment course.

Abbreviations: RCTs: Randomised placebo-controlled trials; FMD: Flow-mediated dilation; NMD: Nitrate mediated dilation; NO: nitric oxide; PPARs: Peroxisome proliferator-activated receptors; hs-CRP: high-sensitivity C-reactive protein; SD: standard deviation; WMD: weighted mean difference; CI: confidence intervals.

Keywords: endothelial function; flow-mediated dilation; pharmacology; cardiovascular risk; meta-analysis.

1. Introduction

Fibrates are a class of drugs characterised by mainly lowering high triglyceride, raising high-density lipoprotein (HDL) cholesterol, and lowering the small dense fraction of low-density lipoprotein (LDL) cholesterol, though there is also evidence on the lipid-independent actions of these drugs [1–3]. Many studies have been done on the potential cardiovascular impact of fibrate therapy, but no univocal data have been found.

A recent meta-analysis showed a protective effect of fibrate for a composite outcome of non-fatal stroke, non-fatal myocardial infarction and vascular death. However, it should be considered that, excluding clofibrate trials, the remaining class of fibrates were no longer effective in preventing the primary composite outcome, remaining effective in preventing myocardial infarction [4].

Even some trials have showed a decreased survival in patients treated with fibrate therapy in primary prevention [5].

Instead of this another meta-analysis showed a reduction in cardiovascular risk related to fibrate therapy if considering patient with hypertriglyceridemia or low HDL-cholesterol [6], and a study on secondary prevention for major adverse cardiovascular events following acute coronary syndrome have observed a significant lower risk in patients treated with statin and fibrate in combination compared to patient treated with only statin [7]. Considering this unclear results of fibrate therapy on cardiovascular events, some studies have investigated the relationship between this therapy and flow-mediated dilation (FMD) of the brachial artery.

Indeed FMD correlates with coronary endothelial function [8], reflecting endothelium-dependent vasodilator function in response to endothelium-dependent nitric oxide (NO) release and its reduction may predict cardiovascular events [9].

It has been shown that lipoproteins, such as low-density lipoproteins, postprandial chylomicron remnants, fasting triglyceride-rich lipoproteins and free fatty acids, affect endothelium-dependent vasodilatation [10,11] through a cytotoxic effect on endothelial cells, which involves generation of free radicals and impairment of nitric oxide synthase gene expression and enzymatic activity [12–

14]. There is evidence suggesting that endothelial function is impaired in patients with elevated levels of plasma triglycerides [15–17], although this finding was not universally confirmed [18].

The hypolipidemic action of fibrates is mediated by peroxisome proliferator–activated receptor α (PPAR α). PPAR α is a nuclear receptor activated by fatty acids and derivatives and it can stimulate the β -oxidative degradation of fatty acids in tissues, such as the heart, where it is highly expressed. Considering its action, PPAR α can control plasma levels of cholesterol and triglycerides.

Furthermore, some studies have suggested that PPAR α has a direct antiatherogenic action, regulating the expression of key proteins involved in all stages of atherogenesis, including vascular inflammation [19].

Fenofibrate improves brachial artery FMD in subjects with and without type 2 diabetes in the absence of statin therapy [20,21]. Moreover, it can improve brachial artery FMD in statin-treated non-diabetic subjects with dyslipidemia [22]. It has been proposed that fenofibrate significantly improves endothelium-dependent brachial artery FMD without change in endothelium-independent nitrate mediated dilation (NMD), by increasing the release and/or action of NO, thus reducing the cytotoxic effect of hyperlipemia [23].

At the same way some studies have not found any significant effect of fibrate therapy on FMD, even if considering healthy subjects [24], or patients with chronic kidney disease [25].

Globally the results of studies evaluating the impact of fibrate therapy on FMD are unclear. Therefore we aimed to conduct a meta-analysis of data from randomized placebo-controlled trials (RCTs) in order to clarify if fibrate therapy could improve endothelial function, considering its potential impact on cardiovascular events.

2. Methods

2a. Search Strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement(23). SCOPUS and PubMed-Medline

databases were searched using the following free search terms in titles and abstracts: : (fenofibrate OR bezafibrate OR ciprofibrate OR clofibrate OR gemfibrozil) AND (vasodilatation OR vasodilation OR dilation OR dilatation OR endothelial OR endothelium OR "brachial artery" OR FMD OR "vascular reactivity") AND (placebo). The wild-card term "*" was used to increase the sensitivity of the search strategy. The search was limited to studies in humans. The literature was searched from inception to January 12, 2015.

2b. Study Selection

Original studies were included if they met the following inclusion criteria: (i) randomized placebo-controlled trial with either a parallel or cross-over design, (ii) assessment of the impact of fibrate therapy on FMD, (iii) presentation of sufficient information regarding FMD values at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were as follows: (i) non-randomized trials, (ii) lack of placebo control group, (iii) observational studies, (iv) trials that recruited subjects receiving stable fibrate therapy, (v) lack of sufficient information on baseline or follow-up FMD values, and (vi) publication in non-English language.

2c. Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) study location; 4) study design; 5) number of participants in the fibrate and control groups; 5) age, gender and body mass index (BMI) of study participants; 6) baseline levels of total cholesterol, LDL cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, high-sensitivity C-reactive protein (hs-CRP) and glucose; 7) systolic and diastolic blood pressure; and 8) data regarding baseline and follow-up FMD.

2d. Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria(24). The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data),

selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of “yes” indicates low risk of bias, while “no” indicates high risk of bias. Labeling an item as “unclear” indicates an unclear or unknown risk of bias.

2e. Quantitative Data Synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [26]. Net changes in measurements (change scores) were calculated as follows: measurement at end of follow-up minus measurement at baseline. For single-arm cross-over trials, net change in FMD was calculated by subtracting the value after control intervention from that reported after treatment. Standard deviations (SDs) of the mean difference were calculated using the following formula: $SD = \text{square root} [(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$, assuming a correlation coefficient (R) = 0.5. Where standard error of the mean (SEM) was only reported, SD was estimated using the following formula: $SD = SEM \times \text{sqrt}(n)$, where n is the number of subjects.

A random-effects model (using DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of demographic characteristics of the populations studied as well as the differences in study design and type of fibrate [27]. Heterogeneity was quantitatively assessed using the I^2 index. The effect sizes were expressed as weighted mean differences (WMD) and 95% confidence intervals (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using leave-one-out method, i.e. removing one study each time and repeating the analysis [28–30].

2f. Meta-regression

Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the association between calculated WMD and potential confounders including duration of treatment with fibrates and magnitude of triglyceride reduction by statin therapy.

2g. Publication bias

Potential publication bias were explored using visual inspection of Begg's funnel plot asymmetry, fail-safe N test, and Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie "trim and fill" method was used to adjust the analysis for the effects of publication bias [31].

3. Results

3a. *Included studies*

The initial literature search yielded 245 articles. Of these, twenty-nine were selected for full-text assessment. After careful evaluation, fifteen articles met the inclusion criteria. All these studies were eligible for the analysis of FMD, while only twelve studies were eligible for the analysis of NMD. The reasons for rejecting the other fourteen articles were as follows: absence of control group, not measuring FMD and publication in non-English language. A summary of the study selection process is shown in Figure 1.

A total of 556 subjects were included in the analysis of FMD. Considering that seven studies had a crossover design [22–24,32–35], globally 380 subjects were in the fibrate group and 387 subjects in the control group. Excluding the studies that did not perform NMD [32,36,37], we selected a total of 462 subjects (328 subjects in the study group and 335 in the control group) for the analysis of NMD. Two studies did not plan a wash-out period [33,35], while the other five included different wash-out periods ranging from 10 days to 2 months [22–24,32,34].

Included studies were published during the period of 2001–2012, and they were conducted in Italy [32], Australia [21,23,25,38], Wales [39], South Korea [22,33–35,37,40], Japan [36], USA [41], and the Netherlands [24].

Ten trials used fenofibrate, including 145 mg [23,41], 160 mg [37,40] or 200 mg dosages [21,22,33–35,38], three trials used gemfibrozil (600 mg twice daily [25,32] or 900 mg once daily dosage [24]), one trial used ciprofibrate 100 mg [39], and another trial used bezafibrate 400 mg

[36]. The duration of fibrate therapy ranged between seven days and six months. Finally, the selected studies were performed in subjects with obesity [38], type 2 diabetes [21,23,32,38,39], hyperlipidemia [21,22,33,34,36–38,40] (including hypercholesterolemia, hypertriglyceridemia or combined hyperlipidemia), chronic kidney disease [25] and coronary artery disease [36]. Two trials were performed on healthy subjects [24,41]. Demographic and baseline biochemical parameters of the included studies are shown in Table 1.

3b. Risk of bias assessment

Most of the selected studies did not provide sufficient data about random sequence generation and allocation concealment. Nevertheless, other potential sources of bias were sufficiently addressed by most of the included trials. Twelve studies were double-blind [21–25,32–34,37–39,41] while the other three studies were single-blind [36,37,40]. Financial support was not reported in four studies [22,35,36,39]. Details on the risk of bias in the included trials are summarized in Supplementary Materials (Table 1).

3c. Effect of fibrate therapy on FMD

A significant improvement of FMD was found after combining the results of the 15 RCTs (WMD: 1.64%, 95% CI: 1.15, 2.13, $p < 0.001$; I^2 : 74.82%) (Figure 2). Sensitivity analysis using one-study remove approach confirmed the robustness of this effect (Figure 2).

The positive impact of fibrates on FMD was observed in both subgroups with treatment durations ≤ 8 weeks (WMD: 1.35%, 95% CI: 0.85, 1.86, $p < 0.001$; I^2 : 65.26%) and > 8 weeks (WMD: 2.55%, 95% CI: 1.21, 3.89, $p < 0.001$; I^2 : 84.63%); yet the effect was numerically greater in the latter subgroup (Figure 3).

When the analysis was stratified according to the fibrate type, there was a significant effect with fenofibrate (WMD: 1.58%, 95% CI: 1.28, 1.88, $p < 0.001$; I^2 : 35.88%) but not with gemfibrozil (WMD: 1.98%, 95% CI: -2.98, 6.94, $p = 0.434$; I^2 : 94.20%), however the difference between the two subgroups was not significant (Figure 4).

3d. Effect of fibrate therapy on NMD

The meta-analysis of the data from 12 RCTs did not suggest a significant change in NMD following treatment with fibrates (WMD: -0.28%, 95% CI: -0.76, 0.19, $p = 0.247$; I^2 : 0%) (Figure 5). This effect was robust in sensitivity analysis and removing of no single study did significantly change the significance of pooled estimate (Figure 5).

In subgroup analysis, no significant effect was observed with either fenofibrate (WMD: -0.42%, 95% CI: -0.96, 0.13, $p = 0.136$; I^2 : 1.89%) or gemfibrozil (WMD: 0.77%, 95% CI: -2.19, 3.73, $p = 0.611$; I^2 : 0%) (Figure 6), or with RCTs lasting either ≤ 8 weeks (WMD: 0.11%, 95% CI: -0.57, 0.79, $p = 0.748$; I^2 : 0%) or > 8 weeks (WMD: -0.71%, 95% CI: -1.71, 0.29, $p = 0.166$; I^2 : 49.79%) (Figure 7).

3e. Meta-regression

Random-effects meta-regression analysis was performed to evaluate whether changes in FMD and NMD values are dependent on the duration of treatment with fibrates, baseline values, or the magnitude of the reduction in plasma triglyceride concentrations following treatment. With respect to FMD, there was a positive association with treatment duration (slope: 0.15; 95% CI: 0.02, 0.27; $p = 0.020$) but not with baseline FMD values (slope: 0.35; 95% CI: -0.23, 0.92; $p = 0.240$) or plasma triglyceride changes (slope: -0.01; 95% CI: -0.02, 0.01; $p = 0.351$) (Figure 8).

With respect to NMD, no significant association was found with either treatment duration (slope: -0.17; 95% CI: -0.38, 0.04; $p = 0.103$), baseline NMD values (slope: -0.09; 95% CI: -0.33, 0.15; $p = 0.467$), or the magnitude of the reduction in plasma triglyceride concentrations (slope: -0.01; 95% CI: -0.02, 0.005; $p = 0.288$) (Figure 9).

3f. Publication bias

The funnel plot of the study precision (inverse standard error) by effect size (mean difference) was slightly asymmetrical for the meta-analysis of fibrates' effects on FMD. This asymmetry was addressed by imputation of two potentially missing studies on the right side of funnel plot using "trim and fill" correction, yielding a corrected effect size of 1.86% (95% CI: 1.35, 2.38) (Figure 10). The fail-safe N test suggested 650 missing studies would be required to make the calculated effect size to non-significant. There was no sign of publication bias in the analysis of FMD according to the results of Begg's rank correlation (Kendall's Tau with continuity correction = 0.15, $z = 0.79$, two-tailed p -value = 0.428) and Egger's linear regression (intercept = 0.70, standard error = 1.04; 95% CI = -1.54, 2.94, $t = 0.67$, $df = 13$, two-tailed $p = 0.512$) tests.

For NMD, although Begg's rank correlation (Kendall's Tau with continuity correction = 0.08, $z = 0.34$, two-tailed p -value = 0.732) and Egger's linear regression (intercept = 0.67, standard error = 0.68; 95% CI = -0.85, 2.18, $t = 0.98$, $df = 10$, two-tailed $p = 0.349$) were non-significant, an asymmetric distribution of studies was observed in the funnel plot. Trim and fill correction led to the imputation of 4 potentially missing studies on the left side of funnel plot yielding a corrected effect size of -0.40% (95% CI: -0.85, 0.05) (Figure 10).

4. Discussion

The present meta-analysis including 15 RCTs and 556 individuals shows an improvement in endothelial function measured by FMD in patients treated with fibrates compared with placebo. This effect appears to be influenced by the duration of treatment, but to be independent of the triglyceride-lowering effect of fibrates. Conversely, our meta-analysis found no significant change in endothelium-independent NMD, a marker of vascular smooth muscle function.

All of the studies have used a lower cuff occlusion in order to evaluate the FMD. This is particularly important because with upper cuff occlusion the vasodilation obtained is less NO dependent [42].

Fibrates may improve endothelial function through activation of different pathways. Fibrates act as PPAR α agonists, inducing the transcription of target genes with PPAR response elements in their promoter regions. After binding with its ligands, PPAR α increases the transcription of lipoprotein lipase (involved in the hydrolysis of triglyceride-rich lipoproteins), reduces the synthesis of apolipoprotein B and very low density lipoprotein (VLDL) particles and enhances transcription of the major HDL apolipoproteins apoA-I and apoA-II [43,44]. Fibrates thus influence both synthesis and catabolism of triglyceride-rich lipoproteins, and these have been shown to be strongly associated with an atherogenic lipid profile and coronary artery disease [45]. Attenuating the magnitude and duration of the exposure of the endothelium to atherogenic lipoproteins may be of benefit, leading to an improvement in FMD together with reduction in triglyceride-rich VLDL particles [23,32,34,39].

PPAR α activation regulates also expression of key proteins involved in vascular inflammation and atherogenesis. Vascular endothelial cells, vascular smooth muscle cells and monocyte/macrophages express PPAR α . It has been shown both *in vitro* [46] and *in vivo* [47] that fibrates modulate monocyte recruitment by limiting the expression of leucocyte adhesion molecules on the surface of both endothelial cells and infiltrating mononuclear cells. Moreover, PPAR α agonists reduce the release of matrix metalloproteinases by monocyte/macrophages [48]. Direct anti-atherogenic actions of PPAR α agonists at the vascular wall [49] seem to be mediated by a reduction in the expression of inflammatory genes regulated by NF- κ B[50–52]. Finally, treatment with fibrates can improve FMD via regulating the balance between vasodilation and vasoconstriction. Endothelial NO synthase is responsible for NO production in the vascular endothelium in healthy adults. Endothelial cell expression of this enzyme is increased in humans on fenofibrate treatment [41,53]. Moreover, fenofibrate has been reported to decrease expression of endothelin-1 [54], an

endothelium-derived potent vasoconstrictor. Finally, treatment with fibrates is associated with an increase in the levels of adiponectin [22,33,36,37,50,55], an adipose-derived factor that may improve endothelial function by multiple mechanisms. It mimics the metabolic actions of insulin [56], which exerts many cardioprotective effects and may also directly increase production of NO in the vascular wall [57]. Furthermore, adiponectin is directly involved in endothelium protection through inhibition of adhesion molecules and proinflammatory cytokine production [50,58], and by stimulation of NO production from endothelium via activation of AMP-activated protein kinase [59].

A recent meta-analysis showed a pooled overall cardiovascular risk of 0.92 (95% CI 0.88-0.95) per 1% increase in FMD [43]. Considering these data, the pooled increase in FMD that we have found in the present study (+1.64%) seems to be of clinical relevance for the reduction of cardiovascular risk. Despite our results disclose a possible link between fibrates and improvement in vascular health, current literature data concerning the ability of this treatment of preventing cardiovascular events are contrasting. According to the results of a meta-analysis published in 2010 [60], fibrate therapy produces a 10% RR reduction (95% CI 0-18) for major cardiovascular events and a 13% RR reduction (95% CI 7-19) for coronary events but has no effect on the risk of stroke and mortality. A recent Cochrane systematic review including 13 trials and 16,112 participants [4] demonstrates that fibrates exerts protective effects over the primary composite outcome (non-fatal stroke, non.fatal myocardial infarction and vascular death); however, after excluding clofibrate trials, the remaining class of fibrates were no longer effective in preventing the primary composite outcome but remained effective in preventing myocardial infarction. Furthermore, large-scale trials demonstrated that fenofibrate therapy reduces the rate of cardiovascular events only in patients at high risk, such as those with diabetes mellitus and atherogenic dyslipidemia (low levels of HDL-C and increased triglycerides) [58,58,61]. It is conceivable that trial results may considerably differ according to the background cardiovascular risk of participants. Findings from our meta-analysis may be influenced by participants in the studies testing fenofibrate [21–23,33,35,37,38]: they were

obese and/or dyslipidemic and all had endothelial dysfunction at baseline (basal FMD < 6%, range 3.1-5%), representing a high-risk category, where improvement in the lipid profile is expected to exert beneficial effects on vascular health. Taking into account that low HDL-C and high triglycerides levels have been associated with reduced post-ischemic endothelial vasodilation, as shown in a cohort of patients with metabolic syndrome [58], findings of the present meta-analysis might contribute to the interpretation of results of FIELD and ACCORD trials [58,58,61].

According to the results of this meta-analysis, the positive effect on FMD was significant for fenofibrate but not for gemfibrozil. This finding should be interpreted with caution. Firstly, since a small number of patients treated with gemfibrozil were included in this meta-analysis, our results are not conclusive. Secondly, we should take into account the characteristics of the patients treated with gemfibrozil. Three studies testing gemfibrozil were included in this meta-analysis. Dogra et al [25] studied patients with chronic kidney disease (stages 3 to 5), reporting that both atorvastatin and gemfibrozil treatments have no effect on endothelial function. Indeed, as previously shown in other studies [58,62], in this population dyslipidemia seems not to be a primary contributor to arterial dysfunction. The other two studies administering gemfibrozil enrolled a small number of patients at low metabolic risk, in contrast to studies testing fenofibrate. Avogaro et al. [32] studied 10 diabetic patients without dyslipidemia (baseline FMD: 7.8%) and Wilmink et al. [24] enrolled 15 healthy young volunteers (baseline FMD: 9%).

Some limitations should be taken into account in the interpretation of our findings. The meta-analysis included studies with a small sample size, from 10 to 97 patients, for a total of 556 participants. Moreover, the studied cohorts differed for baseline characteristics and included both people with comorbidities (diabetes, hyperlipidemia, chronic renal failure) and healthy subjects. The included studies diverged also for the type of fibrate administered, dosage and duration of treatment, as shown in Table 1. Notably, since number of patients treated with gemfibrozil and ciprofibrate was relatively small, it is not possible to gather any definitive conclusion. We tried to

minimize the impact of such an inter-study heterogeneity by applying a random-effects model and also performing subgroup and meta-regression analyses.

5. Conclusions

In conclusion, the results of the present meta-analysis, being the first of its kind, point out that fibrates may exert positive effects on endothelial function, even over a short-term treatment course. The magnitude of this pleiotropic action of fibrates in comparison to other conventional and novel lipid-modifying treatments [63–68], including selective PPAR modulators [69,70], needs to be determined. More data from longitudinal studies are needed to assess whether the improvement in FMD may reflect a true reduction in the cardiovascular risk and if this positive effects are restricted to some particular categories of patients.

Funding: no sponsor contributed to this research.

Acknowledgments: none.

Conflict of interest: none declared.

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FIGURE LEGENDS

Figure 1. Flow chart of study selection.

Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of fibrate therapy on FMD. Lower plot shows leave-one-out sensitivity analysis.

Figure 3. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of fibrate therapy on FMD in trials with treatment durations of ≤ 8 weeks (upper plot) and > 8 weeks (lower plot).

Figure 4. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of fibrate therapy on FMD in trials fenofibrate (upper plot) and gemfibrozil (lower plot).

Figure 5. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of fibrate therapy on NMD. Lower plot shows leave-one-out sensitivity analysis.

Figure 6. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of fibrate therapy on NMD in trials fenofibrate (upper plot) and gemfibrozil (lower plot).

Figure 7. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of fibrate therapy on NMD in trials with treatment durations of ≤ 8 weeks (upper plot) and > 8 weeks (lower plot).

Figure 8. Meta-regression plots of the association between mean changes FMD with duration of fibrate therapy (upper plot) and magnitude of reduction in plasma triglycerides (lower plot).

Figure 9. Meta-regression plots of the association between mean changes NMD with duration of fibrate therapy (upper plot) and magnitude of reduction in plasma triglycerides (lower plot).

Figure 10. Funnel plot detailing publication bias in the studies reporting the impact of fibrate therapy on FMD (upper plot) and NMD (lower plot). Open diamond represents observed effect size; closed diamond represents imputed effect size.

TABLES

Table 1. Panel A and B. Demographic characteristics of the included studies.

Study	Avogaro 2001	Chan 2012	Dogra 2007	Evans 2000	Hamilton 2010	Koh 2004	Koh 2005 Diab Care	Koh 2005 JACC
Location	Italy	Australia	Australia	Wales	Australia	Korea	Korea	Korea
Design	Double blind trial	Double blind trial	Double blind trial	Double blind trial	Double blind trial	Double blind trial	Double blind trial	Double blind trial
Duration of trial	12 weeks	12 weeks	6 weeks	12 weeks	12 weeks	8 weeks	8 weeks	8 weeks
Inclusion criteria	Type 2 diabetic patients	Obese, dislipidemic, type 2 diabetic patients	Patients with chronic kidney disease	Type 2 diabetic patients	Type 2 diabetic patients	Hypertriglyceridemic patients	Hypertriglyceridemic patients	Dislipidemic patients
Drug used	Gemfibrozil 600 mg bid	Fenofibrate 200 mg	Gemfibrozil 600 mg bid	Ciprofibrate 100 mg	Fenofibrate 145 mg	Fenofibrate 200 mg	Fenofibrate 200 mg	Fenofibrate 200 mg
Participants	10	28	59	20	15	25	46	56
Study group	10 ^s	13	27	10	15 ^s	25 ^s	46 ^s	56 ^s
Placebo	10 ^s	15	32	10	15 ^s	25 ^s	46 ^s	56 ^s
Age (years)	63 ± 5	51 ± 7			63 ± 8	51 ± 2	58 ± 2	56 ± 1
Study group			58 ± 13	49 ± 4				
Placebo			62 ± 11	49 ± 5				
Female (%)	N/A	N/A			13.3	40	61	59
Study group				40				
Placebo				50				
Smokers (%)	N/A	0		0	0	0	0	21
Study group			25.9					
Placebo			15.6					
BMI (kg/m ²)	28 ± 5	34 ± 3			28.4	24.9 ± 0.6	25.8 ± 0.4	25.5 ± 0.3
Study group			26.2 ± 4.7	32.7 ± 4.2				
Placebo			27.9 ± 6.4	31.3 ± 6.7				
Diabetes (%)	100	100		100	100	0	0	16
Study group			22.2					
Placebo			21.9					
CKD (%)	0	0	100	N/A	0	0	0	0
Study group								
Placebo								
Cardiovascular disease (%)	0	0		N/A	33	0	0	21
Study group			18.5					
Placebo			21.9					
Hypertension (%)	50	0		0	67	N/A	21.7	68
Study group			63.0					

Placebo			75.0					
Fasting Glucose (mg/dL)	250.2 ± 61.2	154.8 ± 70.2			135 ± 23.4	N/A	N/A	
<u>Study group</u>			86	199.8 ± 59.4				91 ± 4
Placebo			92	181.8 ± 72.0				92 ± 3
LDL-C (mg/dL)	112.1 ± 52.2	127.6 ± 30.9			77.4 ± 15.5	161 ± 6	133 ± 8	
<u>Study group</u>			131 ± 34	138.0 ± 23.2				128 ± 6
Placebo			112 ± 43	133.8 ± 34.8				134 ± 7
HDL-C (mg/dL)	42.5 ± 5.8	34.8 ± 3.9			45.2 ± 6.6	43 ± 2	44 ± 1	
<u>Study group</u>			49.9	39.8 ± 7.7				46 ± 1
Placebo			46.0	42.2 ± 7.7				46 ± 1
Total cholesterol (mg/dL)	222.4 ± 49.1	205.0 ± 30.9			150.8 ± 27.1	201 ± 6	236 ± 8	
<u>Study group</u>			217 ± 35	228.2 ± 42.5				240 ± 6
Placebo			197 ± 49	216.6 ± 54.1				243 ± 7
Tryglicerides (mg/dL)	348.1 ± 83.3	194.9 ± 53.1			124	346 ± 11	293 ± 15	
<u>Study group</u>			153	248 ± 186				322 ± 19
Placebo			148	248 ± 150				301 ± 23
SBP (mmHg)	149 ± 11	131 ± 16			128 ± 4	N/A	N/A	N/A
<u>Study group</u>			134 ± 26	139 ± 24				
Placebo			135 ± 24	144 ± 32				
DBP (mmHg)	91 ± 7	75 ± 9			73 ± 9	N/A	N/A	N/A
<u>Study group</u>			75 ± 12	76 ± 10				
Placebo			72 ± 12	73 ± 6				
CRP (mg/dL)	N/A	N/A	N/A	N/A	N/A		N/A	N/A
<u>Study group</u>						0.11*		
Placebo						0.17*		
hs-CRP (mg/L)	N/A	3.6 ± 2.9		N/A	N/A	N/A		
<u>Study group</u>			3.1				0.70*	1.2
Placebo			5.3				0.80*	1.2
Adiponectin (mcg/mL)*	N/A			N/A	N/A	N/A	N/A	
<u>Study group</u>		3.9 ± 0.8						3.4
Placebo		4.0 ± 0.7						3.4
HbA1c (%)	9.6 ± 2.3	6.9 ± 1.5	N/A		7.0 ± 0.2	N/A	N/A	N/A
<u>Study group</u>				8.3 ± 1.3				

<u>Placebo</u>				8.0 ± 1.5				
Baseline FMD (%)	7.9	3.6 ± 2.0				Not shown	Not shown	
<u>Study group</u>			4.1 ± 3.5		3.2 ± 0.4			4.56 ± 0.19
<u>Placebo</u>			3.5 ± 2.3		3.1 ± 0.6			4.70 ± 0.18
Baseline NMD (%)	N/A	16 ± 6				Not shown	Not shown	
<u>Study group</u>			15.4 ± 8.5		17.2 ± 1.5			14.16 ± 0.55
<u>Placebo</u>			16.0 ± 9.2		16.9 ± 1.6			13.76 ± 0.50

Table 1. Panel B. Demographic characteristics of the included studies.

Study	Koh 2006	Koh 2011	Koh 2012	Nakamura 2007	Playford 2002	Walker 2012	Wilmink 2001
Location	Korea	Korea	Korea	Japan	Australia	USA	Netherlands
Design	Double blind trial	Single blind trial	Single blind trial	Single blind trial	Double blind trial	Double blind trial	Double blind trial
Duration of trial	8 weeks	8 weeks	8 weeks	6 months	12 weeks	7 days	3 weeks
Inclusion criteria	Hypertriglyceridemic hypertensive patients	Hypertriglyceridemic patients	Hypertriglyceridemic patients	Hyperlipemic and coronary artery disease patients	Type 2 diabetes, dislipidemic patients	Healthy subjects	Healthy subjects
Drug used	Fenofibrate 200 mg	Fenofibrate 160 mg	Fenofibrate 160 mg	Bezafibrate 400 mg	Fenofibrate 200 mg	Fenofibrate 145 mg	Gemfibrozil 900 mg
Participants	44	53	97	31	35	22	15 ^s
<u>Study group</u>	44 ^s	26	48	16	17	12	15
<u>Placebo</u>	44 ^s	27	49	15	18	10	15
Age (years)	44 ^s	54 ± 1			Not shown		25 ± 4
<u>Study group</u>			55 ± 1	61 ± 8		63 ± 2	
<u>Placebo</u>			54 ± 1	59 ± 8		63 ± 2	
Female (%)	41	41			N/A		0
<u>Study group</u>			38	31		42	
<u>Placebo</u>			41	33		50	
Smokers (%)	32	8			0	0	0
<u>Study group</u>			19	50			
<u>Placebo</u>			16	47			
BMI (kg/m²)	26.0 ± 0.5	25.4 ± 0.3			N/A		
<u>Study group</u>			25.5 ± 0.36	26.2		24 ± 1	22.9 ± 2.6
<u>Placebo</u>			25.2 ± 0.33	26.2		27 ± 1	23.1 ± 2.7

Diabetes (%)	0	8			100	0	0
<u>Study group</u>			8	50			
<u>Placebo</u>			8	47			
CKD (%)	N/A	N/A	N/A	N/A	0	0	0
<u>Study group</u>							
<u>Placebo</u>							
Cardiovascular disease (%)	N/A	0	0	100	0	0	0
<u>Study group</u>							
<u>Placebo</u>							
Hypertension (%)	100	19			0	0	0
<u>Study group</u>			27	44			
<u>Placebo</u>			24	40			
Fasting Glucose (mg/dL)		N/A					N/A
<u>Study group</u>	89 ± 2		106 ± 2	117 ± 20	156.7 ± 21.6	94 ± 2	
<u>Placebo</u>	92 ± 2		105 ± 3	118 ± 31	122.5 ± 10.8	92 ± 3	
LDL-C (mg/dL)		93 ± 4					N/A
<u>Study group</u>	112 ± 6		119 ± 5	135 ± 24	119.9 ± 7.7	128 ± 9	
<u>Placebo</u>	108 ± 6		109 ± 4	130 ± 23	119.9 ± 7.7	126 ± 5	
HDL-C (mg/dL)		40 ± 2					N/A
<u>Study group</u>	45 ± 1		44 ± 2	44 ± 7	37.1 ± 1.5	57 ± 3	
<u>Placebo</u>	45 ± 2		43 ± 2	44 ± 6	38.7 ± 1.2	58 ± 8	
Total cholesterol (mg/dL)		195 ± 4		N/A			N/A
<u>Study group</u>	208 ± 5		208 ± 4		212.8 ± 7.7	207 ± 10	
<u>Placebo</u>	198 ± 5		208 ± 4		205.0 ± 3.9	205 ± 9	
Tryglicerides (mg/dL)		308 ± 12		N/A			N/A
<u>Study group</u>	255 ± 21		274 ± 19		230	108 ± 10	
<u>Placebo</u>	226 ± 23		267 ± 13		213	105 ± 11	
SBP (mmHg)	N/A	N/A	N/A	N/A			N/A
<u>Study group</u>					131 ± 5	119 ± 3	
<u>Placebo</u>					137 ± 4	122 ± 3	
DBP (mmHg)	N/A	N/A	N/A	N/A			N/A
<u>Study group</u>					74 ± 2	76 ± 3	
<u>Placebo</u>					78 ± 2	77 ± 1	
CRP (mg/dL)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
<u>Study group</u>							
<u>Placebo</u>							
hs-CRP (mg/L)		N/A		N/A	N/A		N/A
<u>Study group</u>	1.00		1			0.8 ± 0.2	
<u>Placebo</u>	0.90		1.10			1.0 ±	

						0.2	
Adiponectin (mcg/mL)*				N/A	N/A	N/A	N/A
<u>Study group</u>	3.0 ± 0.3	2.41	2.57				
<u>Placebo</u>	3.4 ± 0.3	1.78	2.42				
HbA1c (%)	N/A			N/A		N/A	N/A
<u>Study group</u>		5.7*	5.95 ± 0.1		7.0 ± 0.4		
<u>Placebo</u>		5.9*	5.97 ± 0.1		6.3 ± 0.3		
Baseline FMD (%)		Not shown				Not shown	
<u>Study group</u>	4.17 ± 0.24		4.63 ± 0.26	4.3 ± 2.2	3.34 ± 0.85		9.0 ± 3.8
<u>Placebo</u>	4.19 ± 0.32		4.67 ± 0.28	4.1 ± 2.5	4.98 ± 0.75		9.1 ± 3.4
Baseline NMD (%)	N/A [§]	Not shown		N/A		Not shown	
<u>Study group</u>			16.62 ± 0.59		16.15 ± 1.7		16.8 ± 5.5
<u>Placebo</u>			16.44 ± 0.69		16.82 ± 1.6		16.6 ± 5.9

\$ crossover design

§ differences are not significant, before and after treatment. Data not shown in the original paper

* after treatment data

Table 2. Risk of bias assessment in included studies (based on Cochrane Risk of Bias Criteria)

Study	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data
Avogaro 2001	U	U	L	H	L	U	L
Chan 2012	U	U	L	L	L	U	L
Dogra 2007	L	L	L	L	L	U	L
Evans 2000	U	U	H	L	L	U	H
Hamilton 2010	U	U	L	H	L	L	L
Koh 2004	U	L	L	H	L	U	L
Koh 2005 Diab Care	U	U	L	H	L	U	L
Koh et al., 2005 JACC	U	U	L	H	L	U	L
Koh 2006	L	U	L	H	L	U	L
Koh 2011	L	U	L	H	H	U	L
Koh 2012	L	L	L	H	H	U	L
Nakamura 2007	L	U	L	H	H	U	L
Playford 2002	U	U	L	H	L	U	H
Walker 2012	L	U	L	H	L	U	H
Wilmink 2001	L	U	L	H	L	U	L

Abbreviations: H, high risk of bias; L, low risk of bias; U, unclear risk of bias