



## Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: A meta-analysis

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### ABSTRACT

**Background:** Recent data suggest that non-targeted treatment with fibrates modestly reduces the risk of incident cardiovascular events. However the effect of fibrate treatment may be particularly beneficial in patients with guideline-endorsed indications for therapy due to evidence of atherogenic dyslipidemia. We conducted a systematic review and meta-analysis to investigate the influence of fibrates on vascular risk reduction in persons with atherogenic dyslipidemia.

**Methods:** Systematic search of Pubmed, CENTRAL and recent reviews was conducted to identify atherogenic dyslipidemia (serum high density lipoprotein cholesterol [HDL-C] <40 mg/dl or triglycerides >200 mg/dl) cohorts from randomized controlled trials. RR with 95% CI was used as a measure of the association between fibrate therapy and risk of cardiovascular diseases, after pooling data across trials in a random-effects model.

**Results:** Six trials met selection criteria. Compared to placebo, the greatest benefit with fibrate treatment was seen in 7389 subjects with high triglycerides, fibrate therapy reduced risk of vascular events (RR 0.75, 95% CI 0.65 to 0.86,  $P < 0.001$ ); and in 5068 subjects with both high triglycerides and low HDL-C (RR 0.71, 95% CI 0.62 to 0.82,  $P < 0.001$ ). Less benefit was noted in 15,303 subjects selected for low HDL-C (RR 0.84, 95% CI 0.77 to 0.91,  $P < 0.001$ ). Among 9872 subjects with neither high triglycerides nor low HDL-C, fibrate therapy did not reduce subsequent vascular events (RR 0.96, 95% CI 0.85 to 1.09,  $P = 0.53$ ).

**Conclusions:** Fibrate treatment directed at markers of atherogenic dyslipidemia substantially reduce subsequent vascular event risk.

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### 1. Introduction

Hypercholesterolemia is an established major cardiovascular risk factor, and the beneficial effect of lipid modifiers, primarily statins, on global vascular risk reduction is well recognized, and presumed to be largely derived from low density lipoprotein (LDL) cholesterol reduction [1,2]. However, given the high residual risk of cardiovascular events beyond effective LDL-lowering, identification of additional lipid biomarkers independently linked to incident vascular events, and the very modest effect of statins on modifying these other lipid markers, there is mounting interest in optimizing dyslipidemia management via additional therapies.

Atherogenic dyslipidemia is a common form of dyslipidemia characterized by three lipid abnormalities: elevated serum triglycerides, small LDL particles, and reduced serum high-density lipoprotein (HDL) cholesterol [3]. High triglyceride and low HDL cholesterol levels have been shown to singly and collectively boost the risk of cardiovascular events independent of conventional risk factors in large cohort studies [4–6]. Furthermore, guidelines recommend modifying high triglyceride and low HDL as secondary therapeutic targets to provide additional vascular protection [3]. However, the efficacy of using a given therapy to reduce incident vascular risk by achieving recommended therapeutic goals for atherogenic dyslipidemia has not been systematically or comprehensively evaluated.

Fibrates, agonists of the peroxisome proliferator receptors selective for the  $\alpha$  receptors (PPAR- $\alpha$ ), have been demonstrated to be effective at raising HDL cholesterol and lowering triglyceride concentrations [7]. In addition to their lipid-modifying properties, PPAR- $\alpha$  agonists exhibit anti-inflammatory activity (inhibition of aortic smooth-muscle cells activation), which may also confer vas-

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cular protection [8]. A recent meta-analysis of randomized trials showed that fibrate therapy produced a modest relative risk (RR) reduction for major cardiovascular events [9]. However, only a few of the randomized trials included utilized low HDL cholesterol as a criterion for treatment [10,11] and none of them used high triglycerides. Since the issuance of the Adult Treatment Panel III guidelines [3] large randomized trials of fibrate therapy with atherogenic dyslipidemia subgroups have been published [12–14]. To arrive at a robust estimate of the treatment effect of fibrates in persons with atherogenic dyslipidemia, we conducted a systematic review and meta-analysis of atherogenic dyslipidemia cohorts derived from randomized controlled trials comparing fibrates and control groups to date.

## 2. Methods

The study was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement [15].

### 2.1. Data sources and searches

We searched Pubmed, the Cochrane Central Register of Controlled Trials (CENTRAL), the clinical trial registry maintained at clinicaltrials.gov, the World Health Organization international clinical trials registry, and Internet Stroke Center stroke trials, with the terms “fibrate” or “fibric acid” or “fenofibrate” or “bezafibrate” or “ciprofibrate” or “clofibrate” or “gemfibrozil” crossed with “cardiovascular disease” or “myocardial ischemia” or “myocardial infarct” or “ischemic heart disease” or “coronary heart disease” or “coronary artery disease” or “angina” or “stroke” or “cerebrovascular disease” or “cerebrovascular attack” or “cerebral ischemia” or “brain ischemia” or “intracranial hemorrhage”. We restricted our search to human beings and clinical trials from 1966 to April 2010. There were no language restrictions. We also reviewed the Introduction and Discussion sections of retrieved trials and of prior meta-analyses to identify additional trials [7,9,16].

### 2.2. Study selection and data extraction

Studies were selected when they met the following entry criteria: (1) cohort was derived from a randomized controlled trial; (2) the participants and the number of incident cardiovascular disease or coronary heart disease events were reported separately for active treatment and control groups in persons with triglyceride level > 200 mg/dl and/or HDL cholesterol level < 40 mg/dl; (3) comparison of fibrates with placebo; and (4) the intervention duration was at least 6 months. Studies that used slightly varying cutoff point of triglyceride and HDL cholesterol were included. Studies were excluded when (1) sample size < 100 in cohorts or (2) either the control or the active therapy group received an additional treatment that the other group did not receive. All data from eligible studies were abstracted by 2 independent investigators (M.L. and A.T.) according to a standard protocol. Discrepancies were resolved by discussion with a third investigator (B.O.) and by referencing the original report.

### 2.3. Statistical analysis

Data were analyzed according to the intention-to-treat principle. Relative risk with 95% confidence interval (CI) was used as a measure of the association between fibrate therapy and risk of subsequent vascular events in different atherogenic dyslipidemia status (elevated triglyceride with HDL status not specified vs. reduced HDL cholesterol with triglyceride status not specified

vs. both elevated triglycerides and reduced HDL cholesterol vs. neither elevated triglycerides nor reduced HDL cholesterol). When cardiovascular disease events were not available, coronary heart disease events were employed in primary analysis. Heterogeneity was assessed by the probability value of chi square statistics and  $I^2$ , which describes the percentage of variability in the effect estimates that is due to heterogeneity rather than chance [17,18]. Heterogeneity was considered significant when the probability value of chi square statistics was <0.05. We regarded an  $I^2$  value of <40% as “heterogeneity might not be important” and >75% as “considerable heterogeneity” based on the suggestion of the Cochrane Handbook for Systematic Reviews of Interventions [19]. We pooled data across trials by using the random-effects model based on Mantel–Haenszel methods and compared the results with those obtained from a fixed-effects model [20,21]. Publication bias was estimated visually by funnel plots displaying standard error as the measure of sample size and RR as the measure of treatment effect [22].

The primary endpoint of this study was cardiovascular events, defined as the composite of nonfatal myocardial infarct, nonfatal stroke, and vascular death. When cardiovascular events were not available but coronary events (defined as the composite of fatal myocardial infarction, nonfatal myocardial infarction, and sudden death) were available, the latter was used for analysis. Although mortality would have been a useful endpoint, we did not use it as an endpoint because it was not available in subgroups of atherogenic dyslipidemia in most studies.

Subgroup analyses were conducted according to baseline vascular risk condition (diabetes mellitus vs. non-diabetes), primary vs. secondary prevention, treatment regimen (gemfibrozil vs. bezafibrate vs. fenofibrate), mono-therapy vs. combination therapy (fibrates alone vs. fibrate + statin), and end point for analysis (cardiovascular disease vs. coronary heart disease). To identify any study, that may have exerted a disproportionate influence on the summary treatment effect, we removed each individual study from the meta-analysis one at a time. For all analyses,  $P < 0.05$  was considered statistically significant. The Cochrane Collaboration's Review Manager Software Package (RevMan 5) was used for the meta-analysis.

## 3. Results

The literature review yielded 1548 articles, among which 25 were reviewed in full text (Fig. 1). Of these studies, six studies met the entry criteria [10–12,14,23,24]. The characteristics of these atherogenic dyslipidemia cohorts with their original trials are presented in Table 1 [10–14,23–25]. Although the formal assessment of vascular endpoints in these subgroups across trials is important, it must be clearly noted that these results were derived from post hoc analyses of these trials [10–14,23–25]. Also, the HDL-cholesterol and triglyceride cutpoints used in these analyses differed from trial to trial as shown in Table 1. Since we only used atherogenic dyslipidemia subgroups, which were somewhat but not substantially different in cutoff points, of each trial for analyses, the between-study differences in the lipid entry criteria was not likely to largely influence the results. Three trials reported associations of fibrate therapy and cardiovascular disease risk [11,12,14] while three reported associations of fibrate therapy and coronary heart disease risk [10,23,24]. Three dyslipidemic cohorts assessed the effect of gemfibrozil [10,11,24] two assessed fenofibrate [12,14] and one assessed bezafibrate [23]. One dyslipidemic cohort compared fenofibrate plus simvastatin vs. simvastatin [12] while others compared fibrate vs. placebo. The study duration ranged from 2.7 years [10] to 6.3 years [23].

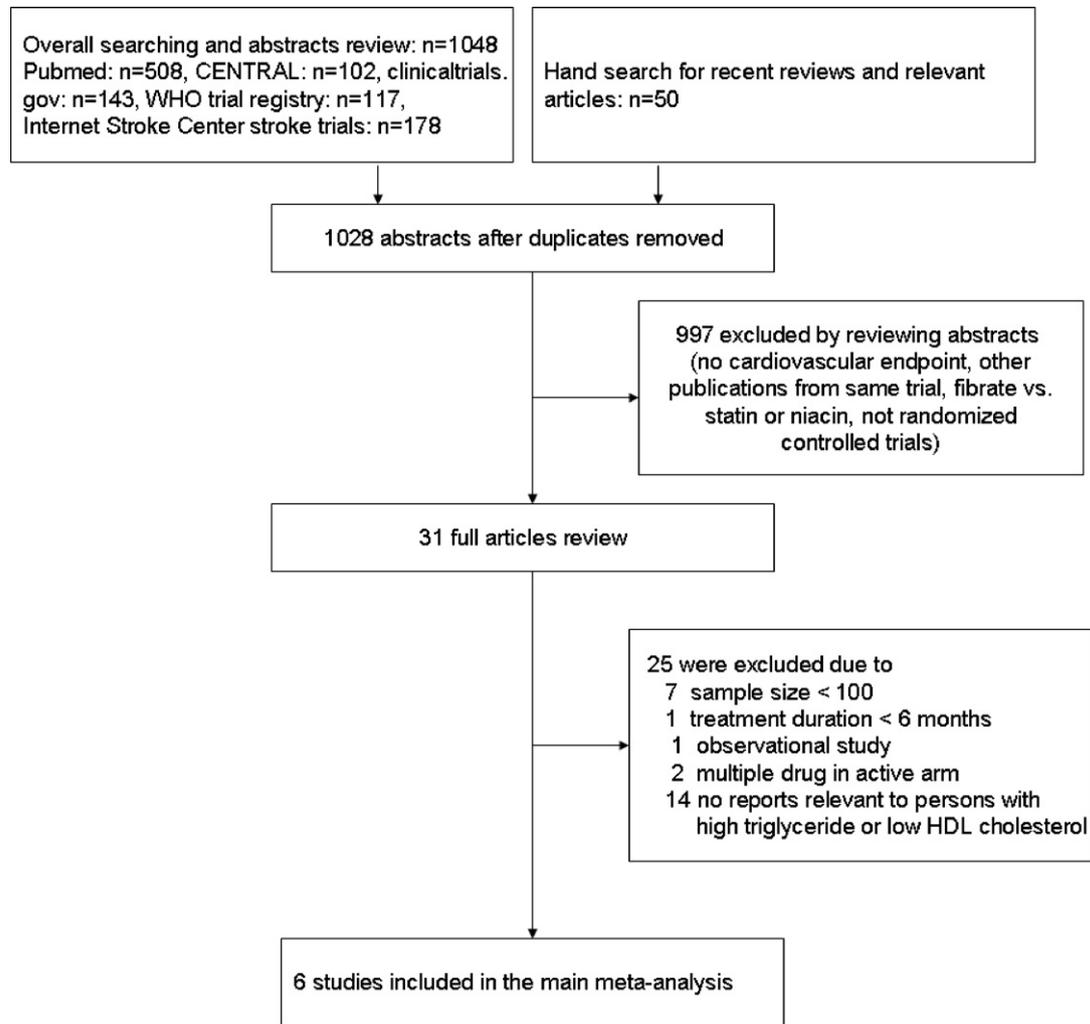
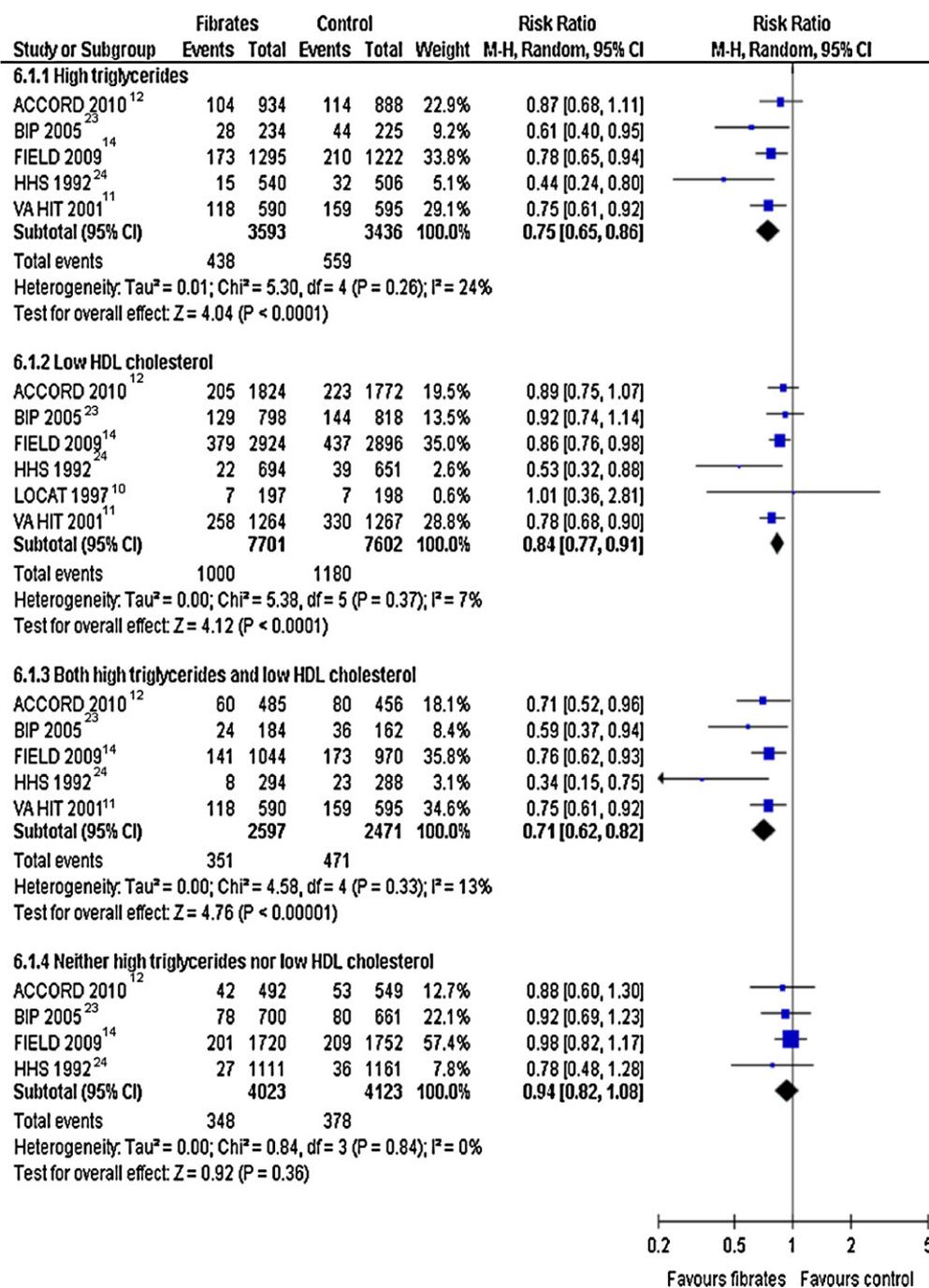


Fig. 1. Study selection process.

**Table 1**  
Characteristics of included trials with their atherogenic dyslipidemia cohorts.

	ACCORD[12]	BIP[23]	FIELD[13,14]	HSS[24,25]	LOCAT[10]	VA HIT[11]
Pre-existing condition	Diabetes mellitus	CHD	Diabetes mellitus	Dyslipidemia, non-HDL-C $\geq 202$ mg/dl	CHD (post-coronary bypass surgery), HDL-C $\leq 42.5$ mg/dl	CHD, HDL-C $\leq 38.3$ mg/dl
Patient number in original trials	5518	3090	9795	4081	395	2531
Countries	USA and Canada	Israel	Australia, New Zealand, and Finland	Finland	Finland	USA
Active treatment	Fenofibrate + Simvastatin	Bezafibrate	Fenofibrate	Gemfibrozil	Gemfibrozil	Gemfibrozil
Control	Simvastatin	Placebo	Placebo	Placebo	Placebo	Placebo
Duration	4.7 years	6.3 years	5 years	5 years	2.7 years	5.1 years
End point for analysis	CVD	CHD	CVD	CHD	CHD	CVD
Definition of hypertriglyceridemia and low HDL-C for analysis						
Hypertriglyceridemia definition	$\geq 204$ mg/dl	$\geq 200$ mg/dl	$\geq 204$ mg/dl	$\geq 204$ mg/dl	NA	$>150$ mg/dl
Low HDL cholesterol definition	$<41$ mg/dl	$<35$ mg/dl	Men $< 40$ mg/dl and women $< 50$ mg/dl	$<41.9$ mg/dl	$\leq 42.5$ mg/dl	$\leq 40$ mg/dl

CVD: cardiovascular diseases, CHD: coronary heart diseases, HDL-C: high density lipoprotein cholesterol, NA: not available.



**Fig. 2.** Study level forest plot of effect of fibrates on risk of cardiovascular diseases in persons with triglycerides > 200 mg/dl or nearest equivalent; HDL-cholesterol < 40 mg/dl or nearest equivalent; triglycerides > 200 mg/dl and HDL-cholesterol < 40 mg/dl or nearest equivalent; and persons with neither high triglycerides nor low HDL cholesterol in the included trials.

Fig. 2 shows the association between different status of atherogenic dyslipidemia at study entry and subsequent vascular risk. Among patients with hypertriglyceridemia, data from five trials, comprising 7389 participants, showed fibrate therapy reduced the risk of vascular events compared to placebo (RR 0.75, 95% CI 0.65–0.86,  $P < 0.001$ , number needed to treat [NNT] = 24). Among patients with reduced HDL-cholesterol, data from six trials, comprising 15,303 participants, showed fibrate therapy reduced the risk of vascular events compared to placebo (RR 0.84, 95% CI 0.77–0.91,  $P < 0.001$ , NNT = 40). Among patients with both hypertriglyceridemia and reduced HDL-cholesterol, data from five cohorts comprising 5068 participants showed fibrate therapy reduced the risk of vascular events compared to placebo (RR 0.71,

95% CI 0.62–0.82,  $P < 0.001$ , NNT = 19). When 9872 participants in the four included trials who did not have identified atherogenic dyslipidemia (i.e. neither elevated triglycerides nor reduced HDL cholesterol) were analyzed, fibrates did not significantly reduce risk of vascular events compared to placebo (RR 0.96, 95% CI 0.85–1.09,  $P = 0.53$ ). There was no substantial heterogeneity within each group but there was substantial heterogeneity across the 4 atherogenic dyslipidemia status groups. The estimates from the fixed-effect model were similar to the estimate from random-effect model. Excluding individual trials yielded pooled results that were not significantly different from the overall pooled estimates. Although one particular trial met our inclusion criteria (LOCAT), it was a relatively small angiographic trial that had very few vascular events. Analysis

**Table 2**  
Effect of fibrate on vascular risk in persons with atherogenic dyslipidemia in subgroup analyses.

	Triglyceride > 200 mg/dl or nearest equivalent, RR (95% CI)	HDL cholesterol < 40 mg/dl or nearest equivalent, RR (95% CI)	Triglyceride > 200 mg/dl and HDL cholesterol < 40 mg/dl or nearest equivalent, RR (95% CI)
Population			
Diabetes mellitus as an entry criteria	0.81 (0.70–0.94)	0.87 (0.78–0.97)	0.74 (0.62–0.88)
Diabetes mellitus not as an entry criteria	0.65 (0.50–0.85)	0.80 (0.68–0.95)	0.61 (0.42–0.88)
Prevention			
Primary (< 50% people with CVD at entry)	0.75 (0.59–0.96)	0.84 (0.71–0.98)	0.68 (0.52–0.89)
Secondary	0.72 (0.60–0.87)	0.82 (0.73–0.93)	0.72 (0.59–0.87)
Treatment regimen			
Gemfibrozile	0.62 (0.37–1.02)	0.74 (0.59–0.93)	0.55 (0.26–1.18)
Bezafibrate	0.61 (0.40–0.95)	0.92 (0.74–1.14)	0.59 (0.37–0.94)
Fenofibrate	0.81 (0.70–0.94)	0.87 (0.78–0.97)	0.74 (0.62–0.88)
Mono-therapy vs. combination therapy			
Fibrate alone	0.72 (0.61–0.84)	0.83 (0.75–0.92)	0.70 (0.57–0.84)
Fibrate + statin	0.87 (0.68–1.11)	0.89 (0.75–1.07)	0.71 (0.52–0.96)
End point used for analysis			
CVD	0.79 (0.70–0.89)	0.84 (0.77–0.91)	0.74 (0.65–0.85)
CHD	0.55 (0.38–0.78)	0.78 (0.52–1.16)	0.49 (0.30–0.81)

CVD: cardiovascular diseases, CHD: coronary heart diseases, RR: relative risk, CI: confidence interval.

excluding this trial showed evidence of similar benefit, for example, among patients with reduced HDL-cholesterol, data excluding LOCAT, showed fibrate therapy reduced the risk of vascular events compared to placebo (RR 0.84, 95% CI 0.76–0.92,  $P < 0.001$ ).

There was asymmetric appearance on funnel plots noted in persons with high triglycerides and persons with both high triglycerides and low HDL cholesterol. The slight under representation of small studies showing neutral or unexpected harmful effects of fibrate therapy suggested a mild degree of publication bias (Supplement Fig. 1). Estimates from the fixed-effects model in these outcomes were similar to the random-effects model suggesting that any small-study effects had little effect on the overall effect estimate [19].

Table 2 shows that fibrate therapy in persons with high serum triglycerides and/or low HDL-cholesterol reduced the risk of subsequent vascular events in all subgroups over a broad range of conditions (different coexisting vascular risk factors, treatment regimen, mono-therapy or combination therapy, and different end point events).

#### 4. Discussion

Our systematic review of more than 15,000 persons with atherogenic dyslipidemia from six randomized controlled trials found that fibrate therapy was associated with a 16–29% subsequent vascular risk reduction. The effect was most pronounced in persons with presence of both elevated serum triglycerides and reduced HDL cholesterol levels. When elevated serum triglyceride level was used as the treatment target criterion, fibrates (vs. placebo) showed 25% risk reduction; when reduced HDL cholesterol level was used as the treatment target criterion, fibrates (vs. placebo) showed 16% risk reduction. Of note, in persons with neither elevated triglycerides nor reduced HDL cholesterol, fibrate therapy did not reduce the risk of subsequent vascular events. Our results further reinforce the Adult Treatment Panel III guidelines which stress the importance of incorporating targeted modification of elevated serum triglycerides and low HDL cholesterol levels as part of an optimal vascular risk reduction strategy [3].

There are some plausible explanations for the larger effect of fibrate therapy on serum elevated triglyceride levels compared to low serum HDL cholesterol levels. First, although detailed, patient-level data of lipid change under fibrate therapy was not available for the subgroups of subjects with atherogenic dyslipidemia in these

trials, evidence from their overall cohorts indicated that fibrate therapy lowered serum triglyceride level by 15–40% triglycerides but only raised serum HDL cholesterol levels by 0.4–6%. Fibrates, especially fenofibrate, raise serum homocysteine levels, which can in turn lower HDL cholesterol levels and offset HDL level increasing actions [13,26]. For instance, in two trials of fenofibrate, serum HDL cholesterol increments were <1% by the end of the studies [12,13]. The greater effect of fibrate treatment on triglyceride reduction compared to HDL cholesterol elevation likely translated to greater vascular event reduction when patients with elevated triglycerides levels were targeted. However, it should also be pointed out that available data suggest that simply raising HDL cholesterol does not necessarily reduce risk of coronary heart disease events and coronary heart disease death [27].

Our study is consistent with previous studies that highlighted the important effect of triglyceride levels on cardiovascular risk. A study based on Third National Health and Nutrition Examination Survey data showed that among metabolic syndrome components, elevated serum triglyceride level has the strongest relation to prevalent myocardial infarction and stroke in patients with metabolic syndrome [28]. Another study showed that elevated serum triglyceride level, among metabolic syndrome components, had the highest hazard ratios to independently predict coronary atheroma progression [29]. An additional study among patients receiving statin therapy after acute coronary syndrome, demonstrated that patients with triglyceride levels less than 150 mg/dl had a lower risk of recurrent coronary heart disease events independent of the level of LDL cholesterol [30]. This finding that elevated serum triglyceride levels predict cardiovascular risk, even in patients with LDL cholesterol levels considered to be normal, may result from both the atherogenicity of triglyceride-rich remnant particles and effects on the relative functionality of circulating LDL cholesterol and HDL cholesterol particles [29,31,32].

Potential publication bias was noted with a slight under representation of small studies showing neutral or unexpected harmful effects of fibrate therapy. When the analysis was redone excluding two small cohorts, [23,24] the benefit of fibrate therapy became slightly smaller in high triglycerides cohorts (RR 0.79, 95% CI 0.70–0.89,  $P < 0.001$ ) and high triglycerides and low HDL cholesterol cohorts (RR 0.74, 95% CI 0.65–0.85,  $P < 0.001$ ).

Subgroup analyses were conducted based on various cohort characteristics. In general, we found diverse forms of fibrate therapy to be consistently effective in reducing subsequent cardio-

vascular events in diverse persons and distinct settings. However, given the limited number of trials, rather than indicating relative efficacy of the differing fibrates, our results may simply reflect the characteristics of the individual trials, for example gemfibrozil was used in HHS and VA-HIT both studies that showed an overall impact and enrolled a population of males with high prevalence of dyslipidemia whereas FIELD and ACCORD-Lipid enrolled significant numbers of women and minorities.

This study has some limitations. First, the relation described by the current study is based on analysis of subgroups in randomized controlled trials who were not the basis of the prespecified trial hypotheses. Further randomized controlled trials focusing on the effect of fibrate therapy in solely persons with atherogenic dyslipidemia are therefore warranted. Second, the end-point definitions varied across the included cohorts. While three cohorts reported efficacy of fibrates on both coronary and cerebrovascular events, three reported efficacy of fibrates on coronary events alone. In our main analysis, we combined these to estimate vascular risk then analyzed the data separately in subgroup analyses. Third, since this is a study-level meta-analysis and individual data is not available, we were unable to further clarify which subgroup (e.g. prior or post cardiovascular disease) will receive the most benefits from the fibrate intervention in these individual large-scale trials, such as FIELD and ACCORD. Finally, about 85% participants included in this study had a history of coronary heart disease or diabetes mellitus in addition to atherogenic dyslipidemia, so the study's findings are potentially more generalizable to these populations.

In conclusion, the current meta-analysis demonstrated that fibrate treatment directed at markers of atherogenic dyslipidemia, especially hypertriglyceridemia, substantially reduced subsequent vascular event risk. Although LDL cholesterol lowering, preferably with a statin, remains the primary lipid target for vascular risk reduction, it may not be unreasonable to consider fibrate therapy as a next step, probably in combination with statin, in optimizing vascular risk reduction among persons with atherogenic dyslipidemia, pending confirmation of efficacy in specifically designed future randomized controlled trials.

### Conflict of interest and financial interest

None.

### Author contributions

Study concept and design: Lee, Saver, Chow, Towfighi, Ovbiagele. Acquisition of data: Lee, Towfighi. Analysis and interpretation of data: Lee, Saver, Chow, Towfighi, Ovbiagele. Drafting of the manuscript: Lee. Critical revision of the manuscript for important intellectual content: Lee, Saver, Chow, Towfighi, Ovbiagele. Study supervision: Saver and Ovbiagele. Final approval of the version to be published: Lee, Saver, Chow, Towfighi, Ovbiagele.

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2011.04.020.

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