Drugs (2018) 78:1289–1296
https://doi.org/10.1007/s40265-018-0965-8

CURRENT OPINION

Fenofibrate and Dyslipidemia: Still a Place in Therapy?

Nicola Tarantino[1] · Francesco Santoro[1,2] · Michele Correale[3] · Luisa De Gennaro[4] · Silvio Romano[5] · Matteo Di Biase[6] · Natale Daniele Brunetti[1]

Published online: 29 August 2018

Abstract
Dyslipidemia is one of the major cardiovascular risk factors, but beyond statin treatment—which represents the cornerstone of therapy—a relevant practical uncertainty regards the use of fibrate derivatives. In the lack of successful results from the main cardiovascular trials, guidelines recommend the use of peroxisome proliferator-activated receptor agonists in selected cases, i.e. patients with true atherogenic dyslipidemia. However, recent observations indicate that fenofibrate treatment may provide a reliable complementary support against residual cardiovascular risk. We therefore summarize current evidence on fenofibrate, seeking to provide an updated interpretation of recent studies in the field.

Key Points

Fenofibrate should be considered a relatively safe and reliable supplemental lipid-lowering agent.

Available trialsof fenofibrate have failed to show major benefit on clinical outcomes.

Extended administration of this drug may reveal beneficial effects inselected patients.

1 Introduction

Cardiovascular disease (CVD) represents and will represent the first cause of morbidity and mortality in Western countries even into the next decades, not even sparing developing countries [1–4]. Dyslipidemia, on the other hand, plays a primary role in mechanisms leading from atherosclerosis to ischemic heart disease [5]. Even after considering genetic causes, dyslipidemia is a potentially modifiable risk condition [6]; however, impressive progress has been made in primary and secondary prevention of CVD, both in terms of lifestyle modifications and drug therapy. Evidence from randomized trials has progressively led international guidelines to recommend a lower and lower threshold for low-density lipoprotein cholesterol (LDL-C) levels, aiming at the consequent reduction of cardiovascular (CV) risk, especially in high-risk populations, including patients with diabetes mellitus (DM) [7, 8]. However, atherogenic dyslipidemia, a laboratory condition characterized by low levels of HDL-C combined with high levels of triglycerides frequently found in DM patients and responsible for what is named the residual cardiovascular risk, [9], is often still under rated and under treated. For all these reasons, in selected patients, lower LDL-C levels do not represent the only target; further risk stratification and an appropriate lipid-lowering agent as add-on therapy are often required.

2 Definition and Epidemiology of Atherogenic Dyslipidemia

Reduction of total cholesterol (TC) and LDL-C generally improves CV risk. However, a full evaluation of lipid profile can show that in 10% of the general population and in 15% of statin-treated patients there are persisting lipid

✉ Natale Daniele Brunetti
natale.brunetti@unifg.it

1 Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy

2 Asklepios Klinik Sankt Georg, Hamburg, Germany

3 Cardiology Department, Ospedali Riuniti University Hospital, Foggia, Italy

4 Ospedale San Paolo, Bari, Italy

5 University of L'Aquila, L'Aquila, Italy

6 Clinica Santa Maria, Gruppo Villa Maria Care and Research, Bari, Italy

abnormalities [10], characterized by elevated triglyceride (TG) levels and decreased levels of high-density lipoprotein cholesterol (HDL-C) regardless of LDL-C value. Beside this qualitative indication, no accepted cut-off level exists because of intrinsic heterogeneity of ranges of normality, age and ethnicity in the studies [11]. In general, the following can be considered as indicative limits: fasting TG > 204 mg/dL or > 2.3 mmol/L, HDL-C < 40 mg/dL or < 1.0 mmol/L for men and < 50 mg/dL or < 1.3 mmol/L for women [12, 13]. This lipid pattern is known as combined or mixed dyslipidemia on the base of higher TG and concomitant lower HDL levels [14], and, although not considered the major component of the vascular plaque, very recent studies show that TG-rich lipoproteins facilitate plaque generation [15]; hence, the name of atherogenic dyslipidemia. Furthermore, since TG levels negatively correlate with LDL particle size, a possible additional explanation of atherogenic potential is mainly attributable to LDL particles of smaller size (the small dense LDL) [16].

This lipid impairment is associated with such dysmetabolic patterns as obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome [17]. Given that worldwide very large number of people feature these phenotypes (almost 200 million patients with T2DM and 300 million are overtly obese), atherogenic dyslipidemia is anything but rare and harmless, even more so if we think that 65% of mortality in patients with T2DM is caused by CVD [18]. The strict interplay of atherogenic dyslipidemia with T2DM accounts for the name of diabetic dyslipidemia. Among all the molecules, fenofibrate seems the best choice against atherogenic dyslipidemia, because of lack of interaction with principal statins compared to gemfibrozil (inhibitor of OATP1B1, enzyme principally involved in simvastatin clearance), along with safety issues (clofibrate was withdrawn from the market for this last reason) [19, 20].

Safety and efficacy regarding the combination of bezafibrate with statins, even if positive, are based only on the few experiences with smaller samples size and brief follow-up [21, 22]. For this reason, the most important clinical trials investigated fenofibrate in clinical and laboratory outcomes of diabetic patients. Fenofibrate pharmacology and its non-cardiovascular use go beyond the scope of this paper and are discussed elsewhere [11, 23, 24].

3 Fenofibrate: A Trilogy of Success, Disappointment, and Revival

3.1 The DAIS, the FIELD and the ACCORD Lipid Trials: The New Hope

Three large multinational randomized placebo-controlled trials were held between 1996 and 2010: the DAIS, the FIELD and the ACCORD Lipid trials. The DAIS (Diabetes Atherosclerosis Intervention Study) [25] was a randomized multinational angiographic study designed to demonstrate a slower coronary artery disease progression in patients treated with fenofibrate compared to placebo. A smaller decrease in lumen diameter (− 0.06 mm vs − 0.10 mm, $p = 0.029$), and a smaller increase in percentage diameter stenosis, (2.11 vs 3.65%, $p = 0.02$) were shown in fenofibrate recipients after 3 years. Despite significant results, the study was not powered to investigate clinical events, which however were slightly higher in the placebo group. The results were attributed to a substantial change in lipid abnormalities with TG reduction and HDL-C increase, as confirmed by a sub-analysis [26].

The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) [27] was a multinational, randomized controlled trial with 9795 participants aged 50–75 years with well-controlled T2DM, which aimed to evaluate the effect of fenofibrate 200 mg daily. After an average of 5 years' follow-up, the hazard ratio (HR) for the primary composite endpoints for coronary events was not statistically significant [0.89, 95% confidence interval (CI), 0.75–1.05; $p = 0.16$], but a subgroup analysis showed a reduction in nonfatal myocardial infarction (HR = 0.76, 95% CI 0.62–0.94; $p = 0.010$) and also a 21% decrease in coronary revascularization ($p = 0.003$), while total mortality, total stroke and total CVD mortality were similar. In addition more significant effects were observed in terms of less albuminuria progression (2.6% more patients allocated fenofibrate than placebo regressing from or not progressing to albuminuria, $p = 0.002$), and less retinopathy needing laser treatment (5.2 vs 3.6%, $p = 0.0003$), this indicating that the major benefit regarded microvascular complications. This beneficial aspect was also confirmed by a nation-wide Japanese observational analysis, where fenofibrate, as add-on therapy, showed to decreased incidence of diabetic retinopathy [odds ratio (OR), 0.772; 95% CI 0.720–0.827; $p < 0.001$] [28].

However, the lack of significant difference was because a larger number of patients who were treated with placebo were then started on a statin; a post hoc analysis revealed that the efficacy was more notable in patients with higher risk profile (marked dyslipidemia and hypertension) [29].

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid trial determined the effect of daily fenofibrate 200 mg plus simvastatin 20 or 40 mg compared to simvastatin alone in terms of cardiovascular events in a 5-year follow-up [30]. In spite of the expectations and lipidemic improvement, combined therapy was not superior to simple statin treatment in reducing the primary composite endpoint of major CV events (non-fatal myocardial infarction, non-fatal stroke and death from CV cause, HR = 0.92, 95% CI 0.79–1.08, $p = 0.32$). Neither secondary endpoints (primary endpoint plus revascularization or hospitalization,

non-fatal myocardial infarction, stroke, all-cause mortality, fatal or nonfatal congestive heart failure) were significantly different (Table 1); however, beneficial effects were confirmed in microvascular complications (less renal disease and diabetic retinopathy progression) [30, 31]. In a prespecified subgroup analysis, a relative-risk reduction of 31% was observed in patients with more severe atherogenic dyslipidemia (TG > 204 mg/dL, and HDL-C < 34 mg/dL) [32], although this difference was not statistically significant (p for interaction 0.06).

3.2 The SAFARI and the DIACOR Trials: The PPAR-α Strikes Back

The SAFARI trial was another milestone which showed a substantial reduction by 23.6% of TG levels, 5.4% in LDL-C and an 8.8% increase of HDL-C ($p < 0.001$ for all) by administering daily fenofibrate 160 mg combined with simvastatin 20 mg compared to monotherapy [33]. No drug-related serious adverse events were revealed in 4 months of treatment.

The DIACOR (Diabetes and Combined Lipid Therapy Regimen) study demonstrated greater reduction of TG in 12 weeks with combination therapy (fenofibrate 160 mg plus simvastatin 20 mg daily) compared with both monotherapies [34]: − 49 versus − 25% (simvastatin subgroup) and − 38% (fenofibrate subgroup) ($p < 0.0001$ and 0.07, respectively). As found in a sub-analysis, dual therapy also lowered small dense-LDL-C (sd-LDL-C) subset [35], and lipid pattern improvement with combination therapy was confirmed in other smaller studies [36, 37]. According to a meta-regression analysis based on these studies [11], fenofibrate 160 mg is the optimal dosage, offering an effective TC reduction (ranging from − 27 to − 43%), regardless of simvastatin dosage, with theoretical minor risk of collateral effects.

Interesting evidence also illustrated that even surrogate biomarkers of cardiovascular risk decreased, and the DIACOR showed that inflammatory molecules such as high-sensitivity C-reactive-protein (hs-CRP) and lipoprotein-phospholipase A2 (LP-PLA2) were reduced in all treated groups [34]. Daily fenofibrate association ameliorated endothelial function measured as flow mediated dilation and insulin sensitivity [38–40], diminishing atherogenic cytokine levels [IL-1b, IL-6, interferon-(IFN)-gamma and tumor necrosis factor (TNF)-α] in high risk patients [41, 42].

Consequently, after disappointing results from the ACCORD Lipid trial, it was only natural to conclude that fenofibrate could likely cause just a cosmetic effect on lipid profile, without any additional significant clinical cardiovascular benefit.

3.3 The ACCORDION and the EFECTL Studies: The Return of the Fenofibrate

In the 2017, the results of the ACCORDION study, a post-trial passive follow-up of the ACCORD Lipid trial, were published. The aim of the study was to verify whether fenofibrate extended add-on treatment reduced CVD risk compared to patients originally treated with placebo [43]. Once again, results showed that the primary composite outcome of fatal and nonfatal myocardial infarction and stroke were similar in the two groups (HR = 0.93, 95% CI 0.83–1.05; $p = 0.25$) after a median follow-up of 9.7 years, although a subgroup analysis further revealed that subjects with severe dyslipidemia (TG > 204 mg/dL and HDL-C < 34 mg/dL) did benefit to a greater extent (HR = 0.73, 95% CI 0.56–0.95, $p = 0.05$). Additionally, reduction in CV mortality almost reached statistical significance (HR = 0.84, 95% CI 0.69–1.01, $p = 0.07$), while an unexpected better response in men compared to women was found (HR = 0.84, 95% CI 0.73–0.96, vs HR = 1.30, 95% CI 1.10–1.68, $p = 0.003$). Given that only 4.3% of patients continued the peroxisome proliferator-activated receptor alpha (PPAR-α) after the original trial end, the authors of the ACCORDION study interpreted the results as a proof of the tardive legacy effect of fenofibrate.

The EFECTL (Effect of Fenofibrate and Ezetimibe Combination Treatment on Lipid) determined that 52 weeks of daily co-administration of ezetimibe 10 mg plus fenofibrate (160 mg or 200 mg in equivalent formulations) effectively reduced LDL-C by 29% and TC by 24% compared to single monotherapies ($p < 0.001$) [44]. TG decrease was significant only when compared to ezetimibe alone (− 45%) ($p < 0.001$), with the greatest percent reduction at week 12. Furthermore, an increase in LDL size (measured in nanometer) was found using fenofibrate in combination or alone compared to ezetimibe (+ 3.4%, $p < 0.001$); side effects were similar in the three groups.

4 Safety: A Phantom Menace

The most common adverse reactions to fenofibrate are hepato- and myotoxicity, either clinically silent or evident. The association with statins can increase the risk of serious adverse reaction for both pharmacodynamic and pharmacokinetic interaction.

Fibrate-related skeletal muscle damage is probably ascribed to reactive oxygen species derived from β-oxidation and mitochondrial dysfunction induced by fibrate, as shown in animal models treated with both potent and weak (fenofibrate) compounds [45, 46]; however, experimental doses are very much higher than those used in humans.

Table 1 Study characteristics

Trial (population)	Follow-up duration	Study type	Primary outcome/endpoint	Result (*p* value)	Secondary outcome/endpoint	Results (*p* value)
DAIS [25] (731)	3 years	Interventional (randomized, placebo controlled, factorial assignment, double-blinded)	Increase in percentage diameter of coronary stenosis	2.1 (0.02)	Total cholesterol reduction	− 10%
			Decrease in minimum coronary lumen diameter	− 0.06 (0.029)	TG reduction	− 28%
			Decrease in mean coronary segment diameter	− 0.06 (0.17)	LDL reduction	− 6% (0.001 for all)
FIELD [29] (9795)	5 years	Interventional (randomized, placebo controlled, parallel assignment, single-blinded)	CHD death or nonfatal myocardial infarction	[HR] 0.89 (0.16)	CV disease events	[HR] 0.89 (0.035)
					Coronary revascularization	[HR] 0.79 (0.003)
					Total mortality	(0.18)
					Albuminuria	(0.002)
					Retinopathy	(0.0003)
ACCORD [31] (5518)	4.7 years	Interventional (randomized, placebo controlled, factorial assignment, double-blinded)	Major fatal/nonfatal CV event	[HR] 0.92 (0.32)	Primary outcomes plus revascularization/rehospitalization	[HR] 0.94 (0.30)
					Major non-coronary events	[HR] 0.92 (0.26)
					Nonfatal myocardial event	[HR] 0.91 (0.39)
					Any stroke	[HR] 1.05 (0.80)
					Any death	[HR] 0.91 (0.33)
					Any CHF	[HR] 0.8 (0.1)
SAFARI [33] (411)	12 weeks	Interventional (randomized, placebo controlled, parallel assignment, double-blinded)	TG reduction	− 24% (< 0.001)	VLDL reduction	− 25%
			LDL reduction	− 6% (< 0.001)	Total cholesterol reduction	− 6%
					Non-HDL reduction	− 9.2%
					HDL increase	+ 8.8% (< 0.001 for all)
DIACOR[a] [34] (300)	12 weeks	Interventional (randomized, parallel assignment)	TG < 200 mg/dL	− 49.4% (< 0.001)	LDL < 100 mg/dL	− 29.1% $p < 0.0001$ vs simvastatin; $p = 0.07$ vs fenofibrate)
ACCORDION [44] (4644)	9.7 years (5 years of passive follow-up)	Interventional (randomized, factorial assignment, open-label)	Fatal and nonfatal myocardial infarction and stroke	[HR] = 0.93 (0.25)	CV mortality	[HR] = 0.84 (0.07)
EFECTL[a] [44] (236)	52 weeks	Interventional (randomized, parallel assignment, open-label)	LDL reduction	24.2% ± 14.7 (< 0.01)		
			TG reduction	40.0% ± 29.5 (< 0.01)		

ACCORD Action to Control Cardiovascular Risk in Diabetes, ACCORDION Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study, *CV* cardiovascular, *CHD* coronary heart disease, *DIACOR* Diabetes and Combined Lipid Therapy Regimen, *DIAS* Diabetes Atherosclerosis Intervention Study, *EFECTL* Effect of Fenofibrate and Ezetimibe Combination Treatment on Lipid, *FIELD* Fenofibrate Intervention and Event Lowering in Diabetes, *HDL* high-density lipoprotein, *HR* hazard ratio, *LDL* low-density lipoprotein, *SAFARI* Simvastatin plus Fenofibrate for Combined Hyperlipidemia, *TG* triglyceride, *VLDL* very low-density lipoprotein

[a]Comparison between combination therapy with both monotherapies

Similar origin for hepatotoxicity has been speculated, even if recent evidence suggests that PPAR-α agonist can directly increase alanine amino transferase (ALT) and aspartate aminotransferase (AST) gene expression and can also shift hepatic metabolism into a higher ALT/AST ratio [47]. As was observed in FIELD study, fibrates increase cholelithiasis risk, altering cholesterol biliary efflux, and accordingly pancreatitis is significantly more probable (0.5 vs 0.8%, $p = 0.031$) [29]. Indeed, gallbladder disease is a contraindication to the use of fibrates and, it is our opinion, that an abdominal ultrasound should be performed before starting the therapy.

Also, in all the aforementioned trials, serious adverse reactions were isolated cases: for instance, in the SAFARI trial no patient experienced severe abnormalities in liver function and clinical myopathy, and there were no cases of rhabdomyolysis. Asymptomatic creatine kinase (CPK) increased by ten times the upper limit of normality (ULN) in only one patient in the combination therapy group and in none in the simvastatin-only cohort—difference in proportion 0.2 (− 1.6, 1.4, 95% CI). No muscular adverse events (simple myalgia, stiffness, etc.) were associated with abnormal increases in CPK. However, there was a significant difference ($p = 0.03$) between treatment groups for ALT elevation > 3 times the ULN (9 vs 0 patients) without further serious clinical consequences (no case of rhabdomyolysis was recorded) [33]. In the ACCORD Lipid study (the trial with the longest follow-up and the highest number of patients enrolled), the incidence of myotoxicity (myopathy, myositis, and rhabdomyolysis) in the treatment group was equally balanced to placebo plus simvastatin recipients (0.1% for both) [31]. Although nephron-protection resulted in the long term, fibrate co-administration caused transient creatinine elevation (> 1.3 mg/dL for women; > 1.5 mg/dL for men), but no cases of acute renal failure were reported. Despite collateral homocysteine increase, no deep venous thrombosis or pulmonary embolism occurred, in contrast to data recorded in the FIELD study (0.7 vs 1.1%, $p = 0.022$) [29]. Additionally, absolute number of deaths was definitely comparable between the two groups (203 in the fenofibrate plus simvastatin group vs 221 in placebo). Overall risk of myotoxicity was very low in combination therapy, including asymptomatic and occasional CPK increment > 5 or > 10 times the ULN (usually between 0.3 and 2.2%) [31].

Minor drug adverse reactions, such as allergy, cataract, and interstitial lung disease, have been described in sporadic cases.

Finally, despite overall rarity of serious adverse events and the net beneficial effect of lipid-lowering medications in terms of primary and secondary cardiovascular prevention, physicians should be aware of safety aspects and frequently monitor patients on high dosage of statins and other drugs whose interferences may be harmful (almost exclusively for simvastatin) or with preexisting risk factors (chronic kidney disease, hepatic insufficiency, muscular disease, age, and hypothyroidism) [11, 48]. It is generally recommended to measure ALT and CPK at baseline and after some weeks of treatment or at the first suspected symptoms in healthy subjects. Food and Drug Administration (FDA) suggests testing renal function periodically in elderly patients or those with renal insufficiency [49]. Transaminases and CPK should be monitored periodically in any case; however, bilirubin is a more reliable indicator of damage, as National Lipid Association's Liver Expert Panel states [50].

5 Commentary

Paradoxically, fenofibrate is a well-tolerated and safe molecule, able to effectively correct lipid abnormalities, improve endothelial function and balance systemic inflammation, but poor cardiovascular benefit was shown in randomized trials. Current European guidelines recommend the use of fenofibrate in cases of hypertriglyceridemia (> 200 mg/dL) (class IIb, level of evidence C) [7], while American recommendation is more supportive (grade A, best evidence level 1) [8], especially if HDL-C is < 40 mg/dL. Only post hoc subgroup analysis indicated that fenofibrate in association with other lipid-lowering agents reduces clinical events, but no effect was reported in terms of CV mortality. Nevertheless, a decrease by 16% of the residual risk of death due to CV disease, heart attack, or stroke in patients with established CVD was found in a Cochrane meta-analysis, which included both fenofibrate in monotherapy and on top of another lipid-modifying agent. A very scant effect was achieved in primary prevention [51], yet fenofibrate highly reduces microvascular complications, with lower diabetic nephropathy, retinopathy and limb amputation rates.

Where is the solution of the rebus? Perhaps, the most plausible answer is that we inappropriately tested the right drug in the wrong patients as the model of the precision medicine would instead recommend [52]. It is noteworthy that the FIELD study was conducted in a pre-guidelines age, when statin was not mandatory as it is nowadays, and furthermore the necessity of lipid-lowering therapy was even an exclusion criterion. Maybe combination therapy in selected patients is right way to use the right drug.

Moreover, in the ACCORDL study the vast majority of enrolled subjects did not suffer from atherogenic dyslipidemia (median TG levels 162 mg/dL), and fenofibrate was associated with a moderate-intensity statin. Thus, it now appears clear why the best results were observed in subpopulation with true atherogenic dyslipidemia and elevated residual risk, that is the persisting risk despite the evidence-based standard of care.

Finally, despite the fact that improvement in lipid patterns occurs within a few months, the ACCORDION study showed that primary endpoint did not change after an additional 5 years of follow-up, and statistical significance was almost reached for cardiovascular mortality after less than ten years. Therefore, another consideration to be drawn is that, besides a more appropriate study population, maybe fenofibrate requires a longer period of time to produce its clinical effects.

Interesting, although not definitive, results from pharmacogenomics reinforce this concept [53–55]. In fact, sequencing the PPAR-α gene in 300 patients from the GOLDN study (Genetics of Lipid Lowering Drugs and Diet Network), 13 single nucleotide polymorphisms (SNPs)—as for instance rs4253793 and rs41332048—were associated with a very poor response after three weeks of treatment with fenofibrate (odds ratio = 6.46 for carriers of > 1 SNP; 95% CI 1.4–30.8, $p = 0.02$) [53]. In particular, lipoprotein lipase (LPL) mutation with gain-of-function (p.S447*) either in homo- and heterozygosis, was found to negatively correlate with the use of fenofibrate compared to placebo in terms of the cardiovascular events in 4414 participants of the ACCORD (RR 1.56, 95% CI 0.98–2.47, $p = 0.01$) [56].

Taken together, these results indicate that fenofibrate could still play a pivotal role in cardiovascular secondary prevention when used as add-on therapy, but perhaps, the more appropriate is the selected population—probably subjects with true atherogenic dyslipidemia—the more effective is the drug. Further studies with longer-term outcomes, stricter clinical inclusion criteria, hopefully with the benefit of genetic innovations, are warranted to confirm this hypothesis.

Pemafibrate, a promising third-generation molecule (named SPPARM, selective-PPAR-modulator-α), appears non-inferior and significantly safer compared to fenofibrate 200 mg daily [57, 58]. The PROMINENT trial (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) will test whether or not PPAR-α agonists are beneficial, exclusively enrolling patients with overt atherogenic dyslipidemia treated with pemafibrate [59].

6 Conclusions

Fenofibrate therapeutic efficacy is limited to specific populations, which should be actively pursued by clinicians as a prescription target. Future and better-designed trials are warranted to more definitely identify the place of fenofibrate in the pharmacological armamentarium.

Compliance with Ethical Standards

Funding No external funding was used in the preparation of this manuscript.

Conflict of interest Nicola Tarantino, Francesco Santoro, Michele Correale, Luisa De Gennaro, Silvia Romano, Matteo Di Biase and Natale Daniele Brunetti declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

References

1. Global Burden of Disease Study. Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2013;2015(386):743–800.
2. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. Comparative Risk Assessment Collaborating Group. Lancet. 2002;360:1347–60.
3. Sharma M, Ganguly NK. Premature coronary artery disease in Indians and its associated risk factors. Vasc Health Risk Manag. 2005;1:217–25.
4. Hossain P, Kawar B, El NM. Obesity and diabetes in the developing world—a growing challenge. N Engl J Med. 2007;356:213–5.
5. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937–52.
6. Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. Prim Care. 2013;40:195–211.
7. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL, Authors/Task Force Members; Additional Contributor. 2016 ESC/EAS guidelines for the management of dyslipidaemias. EurHeart J. 2016;37:2999–3058.
8. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia And Prevention of Cardiovascular Disease. Endocr Pract. 2017;23(Suppl 2):1–87.
9. Vanuzzo D. The epidemiological concept of residual risk. Intern Emerg Med. 2011;6(Suppl 1):45–51.
10. Halcox J, Misra A. Type 2 diabetes mellitus, metabolic syndrome, and mixed dyslipidemia: how similar, how different, and how to treat? Metab Syndr Relat Disord. 2015;13:1–21.
11. Tarantino N, Santoro F, De Gennaro L, Correale M, Guastafierro F, Gaglione A, Di Biase M, Brunetti ND. Fenofibrate/simvastatin fixed-dose combination in the treatment of mixed dyslipidemia: safety, efficacy, and place in therapy. Vasc Health Risk Manag. 2017;13:29–41.
12. Okopień B, Buldak L, Bołdys A. Fibrates in the management of atherogenic dyslipidemia. Expert Rev Cardiovasc Ther. 2017;15:913–21.
13. Ferrari R, Aguiar C, Alegria E, Bonadonna RC, Cosentino F, Elisaf M, Farnier M, Ferrières J, Filardi PP9, Hancu N, Kayikcioglu M, Mello E Silva A, Millan J, Reiner Ž, Tokgozoglu L, Valensi P17, Viigimaa M, Vrablik M, Zambon A, Zamorano JL,

Catapano AL. Current practice in identifying and treating cardiovascular risk, with a focus on residual risk associated with atherogenic dyslipidaemia. Eur Heart J Suppl. 2016;18(Suppl C):C2–C12.
14. Cannon CP. Combination therapy in mixed dyslipidemia. J Intern Med. 2008;263:35365.
15. Goldberg IJ. Fat in the blood, fat in the artery, fat in the heart: triglyceride in physiology and disease. Arterioscler Thromb Vasc Biol. 2018;38:700–6.
16. Kondo A, Muranaka Y, Ohta I, Notsu K, Manabe M, Kotani K, Saito K, Maekawa M, Kanno T. Relationship between triglyceride concentrations and LDL size evaluated by malondialdehyde-modified LDL. Clin Chem. 2001;47:893–900.
17. Ginsberg Henry N, MacCallum Paul R. The Obesity, Metabolic Syndrome, and Type 2 Diabetes Mellitus Pandemic: part I. Increased cardiovascular disease risk and the importance of atherogenic dyslipidemia in persons with the metabolic syndrome and type 2 diabetes mellitus. J Cardiometab Syndr. 2009;4:113–9.
18. Cecilia C, Wang L, Hess CN, Hiatt WR, Goldfine AB. Atherosclerotic cardiovascular disease and heart failure in type 2 diabetes—mechanisms, management, and clinical considerations. Circulation. 2016;133:2459–502.
19. Remick J, Weintraub H, Setton R, Offenbacher J, Fisher E, Schwartzbard A. Fibrate therapy: an update. Cardiol Rev. 2008;16:129–41.
20. Davidson MH, Armani A, McKenney JM, Jacobson TA. Safety considerations with fibrate therapy. Am J Cardiol. 2007;99(6A):3C–18C.
21. Teramoto T, Abe K, Taneyama T. Safety and efficacy of long-term combination therapy with bezafibrate and ezetimibe in patients with dyslipidemia in the prospective, observational J-COMPATIBLE study. Cardiovasc Diabetol. 2013;12:163.
22. Koopal C, Marais AD, Westerink J, van der Graaf Y, Visseren FLJ. Effect of adding bezafibrate to standard lipid-lowering therapy on post-fat load lipid levels in patients with familial dysbetalipoproteinemia. A randomized placebo-controlled crossover trial. J Lipid Res. 2017;58:2180–2187.
23. Grundy SM, Vega GL. Fibric acids: effects on lipids and lipoprotein metabolism. Am J Med. 1987;83(5B):9–20.
24. Fernández-Miranda C, Pérez-Carreras M, Colina F, López-Alonso G, Vargas C, Solís-Herruzo JA. A pilot trial of fenofibrate for the treatment of non-alcoholic fatty liver disease. Dig Liver Dis. 2008;40:200–5.
25. Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the diabetes atherosclerosis intervention study, a randomised study. Lancet. 2001;357(9260):905–10.
26. Tsunoda F, Asztalos IB, Horvath KV, Steiner G, Schaefer EJ, Asztalos BF. Fenofibrate, HDL, and Cardiovascular Disease in Type-2 Diabetes: the DAIS Trial. Atherosclerosis. 2016;247:35–9.
27. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C. Laakso M; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366(9500):1849–61.
28. Kawasaki R, Konta T, Nishida K. Lipid-lowering medication is associated with decreased risk of diabetic retinopathy and the need for treatment in patients with type 2 diabetes: A real-world observational analysis of a health claims database. Diabetes Obes Metab. 2018. https://doi.org/10.1111/dom.13372.
29. Scott R, O'Brien R, Fulcher G, Pardy C, D'Emden M, Tse D, Taskinen MR, Ehnholm C. Keech A; Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study Investigators. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetes Care. 2009;32:493–8.
30. Ginsberg HN, Elam MB, Lovato LC, et al. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–74.
31. The ACCORD Study Group and ACCORD Eye Study. Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363:233–44.
32. Elam M, Lovato LC, Ginsberg H. Role of fibrates in cardiovascular disease prevention, the ACCORD-Lipid perspective. Curr Opin Lipidol. 2011;22:55–61.
33. Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol. 2005;95:462–8.
34. Muhlestein JB, May HT, Jensen JR, et al. The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. J Am Coll Cardiol. 2006;48:396–401.
35. May HT, Anderson JL, Pearson RR, et al. Comparison of effects of simvastatin alone versus fenofibrate alone versus simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study). Am J Cardiol. 2008;101:486–9.
36. Mohiuddin SM, Pepine CJ, Kelly MT, Buttler SM, Setze CM, Sleep DJ, Stolzenbach JC. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J. 2009;157:195–203.
37. Stefanutti C, Bucci A, Di Giacomo S, et al. Efficacy, safety and tolerability of combined low-dose simvastatin-fenofibrate treatment in primary mixed hyperlipidaemia. Clin Drug Investig. 2004;24:465–77.
38. Ghani RA, Bin Yaakob I, Wahab NA, Zainudin S, Mustafa N, Sukor N, Wan Mohamud WN, Kadir KA, Kamaruddin NA. The influence of fenofibrate on lipid profile, endothelial dysfunction, and inflammatory markers in type 2 diabetes mellitus patients with typical and mixed dyslipidemia. J Clin Lipidol. 2013;7:446–53.
39. Harmer JA, Keech AC, Veillard AS, Skilton MR, Marwick TH, Watts GF, Meredith IT, Celermajer DS, FIELD Vascular Study Investigators. Fenofibrate effects on arterial endothelial function in adults with type 2 diabetes mellitus: a FIELD substudy. Atherosclerosis. 2015;242:295–302.
40. Koh KK, Quon MJ, Lim S, Lee Y, Sakuma I, Lee YH, Han SH, Shin EK. Effects of fenofibrate therapy on circulating adipocytokines in patients with primary hypertriglyceridemia. Atherosclerosis. 2011;214:144–7.
41. Belfort R, Berria R, Cornell J, Cusi K. Fenofibrate reduces systemic inflammation markers independent of its effects on lipid and glucose metabolism in patients with the metabolic syndrome. J Clin Endocrinol Metab. 2010;95:829–36.
42. Krysiak R, Gdula-Dymek A, Okopien B. The effect of fenofibrate on lymphocyte release of proinflammatory cytokines and systemic inflammation in simvastatin-treated patients with atherosclerosis and early glucose metabolism disturbances. Basic Clin Pharmacol Toxicol. 2013;112:198–202.
43. Elam MB, Ginsberg HN, Lovato LC, Corson M, Largay J, Leiter LA, Lopez C, O'Connor PJ, Sweeney ME, Weiss D, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm R, Ismail-Beigi F, Goff DC Jr, Fleg JL, Rosenberg Y, Byington RP; ACCORDION Study Investigators. Association of fenofibrate therapy with long-term cardiovascular risk in statin-treated patients with type 2 diabetes. JAMA Cardiol. 2017;2:370–380.

44. Oikawa S, Yamashita S, Nakaya N, Sasaki J. Kono S; Effect of Fenofibrate and Ezetimibe Combination Treatment on Lipid (EFECTL) Study Investigators. Efficacy and Safety of Long-term Coadministration of Fenofibrate and Ezetimibe in Patients with Combined Hyperlipidemia: results of the EFECTL Study. J Atheroscler Thromb. 2017;24:77–94.
45. Pettersen JC, Pruimboom-Brees I, Francone OL, Amacher DE, Boldt SE, Kerlin RL, Ballinger WE. The PPARα agonists fenofibrate and CP-778875 cause increased β-oxidation, leading to oxidative injury in skeletal and cardiac muscle in the rat. Toxicol Pathol. 2012;40:435–47.
46. Balfour JA, McTavish D, Heel RC. Fenofibrate. A review of its pharmacodynamics and pharmacokinetic properties and therapeutic use in dyslipidaemia. Drugs. 1990;40:260–90.
47. Kobayashi A, Suzuki Y, Kuno H, Sugai S, Sakakibara H, Shimoi K. Effects of fenofibrate on plasma and hepatic transaminase activities and hepatic transaminase gene expression in rats. J Toxicol Sci. 2009;34:377–87.
48. Guo J, Meng F, Ma N, et al. Meta-analysis of safety of the coadministration of statin with fenofibrate in patients with combined hyperlipidemia. Am J Cardiol. 2012;110:1296–301.
49. Food and Drug Administration. FDA drug safety communication: review update of Trilipix (fenofibric acid) and the ACCORD Lipid trial. 2011.
50. Cohen DE, Anania FA, Chalasani N. An assessment of statin safety by hepatologists. Am J Cardiol. 2006;97:77C–81C.
51. Wang D, Liu B, Tao W, Hao Z, Liu M. Fibrates for secondary prevention of cardiovascular disease and stroke. Cochrane Database Syst Rev. 2015;10:CD009580. https://doi.org/10.1002/14651858.cd009580.pub2.
52. Hodson R. Precision medicine. Nature. 2016;537(7619):S49.
53. Irvin MR, Zhang Q, Kabagambe EK, Perry RT, Straka RJ, Tiwari HK, Borecki IB, Shimmin LC, Stuart C, Zhong Y, Hixson JE, Arnett DK. Rare PPARA variants and extreme response to fenofibrate in the genetics of lipid-lowering drugs and diet network study. Pharmacogenet Genom. 2012;22:367–72.
54. Smith JA, Arnett DK, Kelly RJ, Ordovas JM, Sun YV, Hopkins PN, Hixson JE, Straka RJ, Peacock JM, Kardia SL. The genetic architecture of fasting plasma triglyceride response to fenofibrate treatment. Eur J Hum Genet. 2008;16:603–13.
55. Rotroff DM, Pijut SS, Marvel SW, Jack JR, Havener TM, Pujol A, Schluter A, Graf GA, Ginsberg HN9, Shah HS, Gao H, Morieri ML, Doria A, Mychaleckyi JC, McLeod HL, Buse JB, Wagner M, Motsinger-Reif AA; ACCORD/ACCORDion Investigators. Genetic variants in HSD17B3, SMAD3, and IPO11 impact circulating lipids in response to fenofibrate in individuals with type 2 diabetes. Clin Pharmacol Ther. 2018;103:712–721.
56. Morieri ML, Shah H, Doria A, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Genetic Study Group. Variants in ANGPTL4 and the risk of coronary artery disease. N Engl J Med. 2016;375:2304–5.
57. Arai H, Yamashita S, Yokote K, Araki E, Suganami H, Ishibashi S, K-877 Study Group. Efficacy and safety of pemafibrate versus fenofibrate in patients with high triglyceride and low HDL cholesterol levels: a multicenter, placebo-controlled, double-blind, randomized trial. J Atheroscler Thromb. 2018;25:521–38.
58. Botta M, Audano M, Sahebkar A, Sirtori CR, Mitro N, Ruscica M. PPAR agonists and metabolic syndrome: an established role? Int J Mol Sci. 2018;19(4):1197.
59. Anon. Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT). https://clinicaltrials.gov/ct2/show/NCT03071692. Accessed 18 June 2018.