R E V I E W

Simvastatin/fenofibrate combination in the treatment of dyslipidemia: current evidence

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Background: It has been demonstrated that statins can reduce major cardiovascular complications throughout a broad range of patients with dyslipidemia and multiple cardiovascular risk. Despite the impact of statin therapy on cardiovascular morbidity and mortality, a residual cardiovascular risk remains following lowering of low-density lipoprotein cholesterol. In many patients, optimization of the lipid profile cannot be achieved with statin therapy. Therefore, pharmacologic interventions with non-statin therapy can be used.

Aims: The objective of this review was to analyze current clinical evidence of the effects of simvastatin/fenofibrate combination therapy.

Methods: We searched and analyzed the evidence up to June 2014, regarding the effects of statin/fibrate combination therapy for reducing cardiovascular complications.

Results: Forty-nine studies reporting the efficacy and safety of statin/fibrate combination therapy were analyzed. Of the forty-nine, 19 analyzed the simvastatin/fenofibrate combination therapy. This therapy was demonstrated to be safe and superior to the statin monotherapy in modifying atherogenic dyslipidemia, including lipoprotein subclasses. Nevertheless, in randomized clinical trials cardiovascular endpoints were not significantly different when fenofibrate was added to a standard low-density lipoprotein cholesterol reducing therapy. Of note, in the subgroup analysis, positive results were observed in patients with high triglycerides and low high-density lipoproteins. The inclusion of heterogeneous populations in these studies may explain the mixed results of cardiovascular outcomes seen in randomized clinical trials.

Conclusion: Future clinical studies that rigorously address the effects of simvastatin/fenofibrate in patients with triglycerides >2.25 mmol/L and high density lipoprotein cholesterol <0.90 mmol/L, will provide a more accurate conclusion regarding the use of simvastatin/fenofibrate combination therapy. For now, emphasis must be put on non-pharmacological interventions that effectively induce weight loss and strict glycemic control in diabetics. The initiation of simvastatin/fenofibrate combination therapy among patients with residual cardiovascular risk should be employed at the physician's discretion, as this strategy lacks hard cardiovascular end points.

Keywords: dyslipidemia, atherosclerotic cardiovascular disease, residual risk, simvastatin fenofibrate combination therapy

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in adults around the world. In developing countries this condition accounts for 80% of the global cardiovascular disease burden.[1,2] In epidemiological studies, a direct relation of elevated low-density lipoprotein cholesterol (LDL-C) with increased risk for the development of ASCVD was demonstrated; whereas high-density lipoprotein cholesterol (HDL-C)

level was negatively associated.[3–6] The relationship between triglycerides and cardiovascular disease has elicited considerable debate over the years. Various investigators have shown that hypertriglyceridemia is a univariate predictor of cardiovascular disease but not independent in multivariate analysis.[7–15] Postprandial hypertriglyceridemia seems to be a better predictor of ASCVD compared to fasting triglyceride levels.[16,17] The mechanisms associated with increased cardiovascular risk are complex and involve lipid and non-lipid mechanisms.[16–18]

Obesity is increasing worldwide.[19] This leads to an increased prevalence of hypertriglyceridemia, metabolic syndrome (MetS),[20,21] and type 2 diabetes.[22] Of relevance, in South and Central America, the number of people with diabetes will increase by 60% by 2035.[23] In patients with familial forms of dyslipidemia,[24–27] MetS, and diabetes (which is associated with a high incidence of ASCVD), over-nutrition and obesity worsens the lipid profile.[28]

A number of randomized clinical trials (RCTs) have shown that by reducing LDL-C with 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) inhibitors (statins), cardiovascular events are reduced in primary and secondary prevention trials.[29–45] However in these reports, considerable risk for cardiovascular events remains, suggesting that other lipid abnormalities such as hypertriglyceridemia, low HDL-C, high non-HDL-C, apolipoprotein B, and small LDL particles may be implicated in cardiovascular outcomes.[16,46,47]

As of now, recent studies fail to demonstrate therapies that increase HDL-C or those that correct other lipid abnormalities aimed to reduce ASCVD.[48–51]

The Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults (Adult Treatment Panel III) of the National Cholesterol Education Program as well as the 2001 updated version, focused on intensive treatments for patients with coronary artery disease and cardiovascular risk equivalents as assessed with the Framingham algorithm.[52,53] Statements of the American Association of Clinical Endocrinologists, the Canadian Cardiovascular Society, the European Guidelines, and the International Lipid Society are generally in accordance with the National Cholesterol Education Program.[54–57]

The newly published American College of Cardiology/American Heart Association guidelines[58] recommend a risk reduction through moderate to intense statin therapy in:

1. patients with ASCVD;
2. patients with diabetes;
3. patients with primary elevations of LDL-C >4.9 mmol/L;
4. patients without clinical ASCVD who are 40 to 75 years of age with LDL-C 1.8 to 4.88 mmol/L and an estimated 10 year ASCVD risk of ≥7.5% calculated by the Pooled Cohort Equations.

These guidelines presented substantial changes and provoked debates.[59,60] For example, treatment goals for LDL-C and non-HDL-C are no longer recommended. The lack of guidelines provided for treating high triglyceride levels and dyslipidemia after intensive statin therapy, has led to the misunderstanding of which non-statin agents can be recommended.[58] Considering that an ample spectrum of clinical situations must be taken into account to reduce cardiovascular risk, primary care physicians may face difficulties in deciding on the optimal lipid treatment for patients with persistent dyslipidemia, following optimal statin therapy.[16,6–47]

This report focused primarily on the role of triglycerides in cardiovascular disease and reviewed cardiovascular benefits of treatment with statin/fibrate combination in patients with diabetes and mixed dyslipidemia with residual cardiovascular risk.

Methods

For the present review we searched PubMed from 1990 to June 2014 using the key words: randomized cardiovascular clinical trials, safety and efficacy of fibrate, statins and fibrate/statin combination on lipid and lipoprotein profile, adverse effects, morbidity and mortality outcomes.

Results

We reviewed and fully assessed reports and clinical trials regarding the benefits of lipid lowering therapies on cardiovascular disease. We found forty-nine studies that reported the effects of statins and fibrates combination therapy. Of the forty-nine reports, 19 assessed simvastatin/fenofibrate combination therapy and were the source of discussion (results presented in the Tables).

Dyslipidemia and ASCVD

Fasting triglycerides are mainly carried in very low-density lipoprotein (VLDL) and their remnants, while in the postprandial state; triglycerides are transported in chylomicrons and their remnants.[56] As defined by the European Society of Atherosclerosis, triglyceride rich lipoprotein remnants, relate to chylomicron and VLDL particles, which have undergone dynamic remodeling in the plasma after secretion from the intestine or liver.[56]

Under normal conditions these VLDL particles are rapidly cleared from the plasma as they can either be taken via

liver receptors or transformed into LDL-C.[61–63] Dyslipidemic patients, with insulin resistance and MetS, who are at high cardiovascular risk, have reduced chylomicron remnants clearance, increased formation and reduced degradation of VLDL triglycerides resulting in the accumulation of triglyceride rich remnants.[56,64] The mechanisms associated with these lipid alterations are linked to excess apolipoprotein CIII, hepatic lipase, and to postprandial lipemia.[63–68]

It has being demonstrated that LDL-C has a predominant role in atherosclerosis as cholesterol accumulation in the arterial wall is derived primarily from this lipoprotein fraction.[69–74] LDL-C through the interaction with the arterial wall enters the sub endothelial space where it undergoes modifications. It seems that small dense LDL-C enters at a higher rate than buoyant LDL.[75–77] Modifications of LDL in the sub endothelial space activates macrophages, thus promoting the lipid laden macrophage formation and initiating the atherosclerotic process.[69–73]

As stated above, LDL-C is considered the main atherogenic lipoprotein particle, but other apolipoprotein B-containing lipoproteins such as triglyceride rich remnants and lipoprotein(a) also contribute to sub endothelial cholesterol accumulation. Triglyceride rich remnants accumulate in plasma, penetrate the arterial intima, and are retained by connective tissue matrix.[78–92] These particles can be taken up by arterial macrophages leading to foam cell formation, participating in atherogenesis as seen in atherosclerotic lesions. Moreover, triglyceride rich particles have been associated with the progression of coronary artery disease and increased cardiovascular risk.[84,85] Another line of evidence came from studies which demonstrated that triglyceride rich remnants are associated with impaired vasodilation, enhanced inflammatory responses, cytokine formation, and linked to a pro-thrombotic state.[93–95]

High triglyceride levels are inversely related to low HDL-C, which becomes smaller and triglyceride enriched; these changes have been associated with defective function of HDL.[96–98] Thus, HDL may lose its putative protective role against atherosclerosis, as normal HDL particles maintain normal endothelial vasoreactivity, reduce oxidative stress and the expression of adhesion molecules and cytokines, among other anti-atherogenic mechanisms.[96–98]

Supporting the notion of the role of triglycerides on cardiovascular disease, a recent study demonstrated that mutations in the coding sequence of particular genes have the ability to alter plasma triglyceride levels.[99] Specifically, carriers of the apolipoprotein C 3 (APOC3) mutation had plasma triglyceride concentrations of up to 40% lower than those without it.

Correspondingly, carriers of these mutations were found to have a reduced risk of coronary heart disease.[99]

Thus, the role of triglycerides in atherogenesis may be related to direct and indirect mechanisms.[56] Some are linked to lipoprotein metabolism, including postprandial hypertriglycemia associated with elevation of triglyceride rich remnants in plasma and promoting cholesterol accumulation in the arterial wall and; generating dysfunctional HDL, that adversely affects cholesterol efflux from macrophages.[78–92] Indirectly, hypertriglyceridemia, leads to endothelial dysfunction creating favorable conditions for atherogenesis.[93–95]

Clinical management of hypertriglyceridemia and mixed dyslipidemia

In order to manage hypertriglyceridemia and mixed dyslipidemia, correction of secondary causes of dyslipidemia, and lifestyle changes must be implemented.[54–58] Adherence to lifestyle modifications and strict glycemic control in diabetics is mandatory. In general, it is recommended that patients should focus on the reduction of saturated fats, trans fats, cholesterol, alcohol, and sugar (sucrose and fructose).[100] A reduced calorie diet consisting of at least five servings of fruit and vegetables has been known to be beneficial. Furthermore, consuming about 2 g/day of plant sterols as well as 10–25 g/day of soluble fiber can aid in lowering LDL-C.[54–58] If the patient is a smoker, every effort should be made to help the patient quit. Physical activity improves lipid profile, increases strength and flexibility, and reduces insulin resistance. Aerobic exercise programs should include at least 30 minutes of moderate to intense activity four to six times a week. Some examples of aerobic exercise could include walking, riding a stationary bicycle, water aerobics, and sporting activities. Additionally, muscle-strengthening activity is recommended at least 2 days a week.[101]

If non-pharmacologic treatment fails to optimize lipid abnormalities, targeting abnormal lipid levels with statins alone or in combination with non-statin drugs can be employed.[54–58]

Fibrates

Fibrates are agonists of the peroxisome proliferator-activated receptors and lower serum triglycerides by 35%–50%. They also increase serum HDL-C by 5%–20%. Fibrates diminish hepatic secretion of VLDL while inducing clearance of both chylomicrons and VLDL particles through the activation of LPL and downregulation of apolipoprotein C-III gene expression.[102–107]

The lipid lowering effects of gemfibrozil and fenofibrate are comparable.[104,105] Additionally, some studies state that fibrates reduce lipoprotein(a),[106] but this concept is controversial. Fenofibrate reduces fibrinogen levels, whereas gemfibrozil has no effect on this parameter.[103]

Fibrates have been associated with increased creatinine and homocysteine levels.[107] However, this effect is reversible once the discontinuation of the medication has taken place.[51,103–105]

HMG CoA reductase inhibitors

Statins are competitive inhibitors of HMG CoA reductase, the rate-limiting enzyme required for cholesterol biosynthesis. This reduces the intracellular cholesterol pool and up-regulates the LDL receptor. Consequently, this increases the LDL-C uptake and degradation particularly in the liver and reduces plasma LDL-C levels.[108] Moreover, statins affect VLDL synthesis and moderately reduce plasma triglyceride levels, as well as increase plasma HDL-C.[109–111]

Adverse effects have been reported, such as myopathy, liver dysfunction, and rarely rabdomyolisis.[112] Recently, an increased risk of developing diabetes has been observed.[113–117] This increased risk is higher with intensive rather than moderate statin therapy.[117] However, the beneficial effects of statins on cardiovascular events and mortality outweigh the possibilities of an increased risk of developing diabetes.[116]

Evidence of fibrates for the prevention of cardiovascular complications

Clinical intervention studies, in which diabetic and non-diabetic patients received fibrates, showed a reduction in cardiovascular events in primary and secondary prevention trials. The Helsinki Heart Study showed benefits from gemfibrozil therapy in patients with high triglyceride levels (>2.25 mmol/L) and LDL-C/HDL-C ratio >5.0.[118] The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study (VA-HIT) evaluated the effect of gemfibrozil therapy in patients with a history of cardiovascular disease, low HDL-C, relatively low LDL-C, and triglyceride levels ≤ 3.38 mmol/L.[119] Fibrate therapy in patients with type 2 diabetes reduced the rate of coronary heart disease events.[120] The Bezafibrate Infarction Prevention (BIP) study showed a favorable effect on lipid parameters but no reduction in coronary events.[121] In The Diabetes Atherosclerosis Intervention Study, fenofibrate showed a reduction in LDL particle size and a decreased progression of coronary heart disease, but no differences in cardiovascular outcomes for type

2 diabetics.[122] The Field study was performed among more than 9,000 type 2 diabetics and used micronized fenofibrate. While there was no significant change in the rates of coronary outcomes, there was however, a slight increase in mortality rates.[123,124] A meta-analysis of RCTs comparing fibrate with placebo illustrated a reduction of major cardiovascular and coronary events by 10% and 13%, respectively. Additionally, a significant reduction in revascularizations was demonstrated, but no effect on all-cause mortality was noted.[124]

Evidence of statins for the prevention of cardiovascular complications

Angiographic studies with statins have shown slow progression and induced regression of coronary lesions.[31] RCTs were performed among patients with low, moderate, and high LDL-C, as well as among patients with the presence and absence of cardiovascular disease and diabetes.[29–44,125]

In patients at low risk of vascular events, a meta-analysis showed that a 1 mmol/L reduction in LDL-C resulted in the absolute reduction of major vascular events of approximately eleven per 1,000 over 5 years.[42,43] In 2010, data from a meta-analysis of 170,000 participants in 26 RCTs demonstrated that by reducing LDL-C by 2–3 mmol/L, a 40%–50% reduction in cardiovascular risk would be obtained.[42]

Based on this evidence, the American College of Cardiology/American Heart Association guidelines recommended intensive statin doses for cardiovascular risk reduction.[58] However, not all the patients tolerate this regimen and alternative therapeutic approaches are needed.[52–57] Recent studies in hypercholesterolemic and diabetic patients have shown that the combination of ezetimibe/simvastatin was more effective than atorvastatin or rosuvastatin monotherapy in lowering LDL-C compared to statin therapy.[126] Furthermore, a recent report showed that in diabetic patients who received the ezetimibe/atorvastatin therapy, a greater regression of plaque volume was present in comparison to atorvastatin alone.[127] Ongoing studies will determine if this combination therapy will reduce cardiovascular mortality.

Evidence of statin/fibrate combination for the prevention of cardiovascular complications

In many patients at risk of ASCVD, a residual cardiovascular risk remains after statin therapy has been implemented and LDL-C targets achieved.[16,45–47] Such patients typically display high triglycerides and low HDL-C

levels. Thus, as reported recently,[128–130] managing residual cardiovascular risk needs to be addressed in patients on optimal statin therapy. Statin/fibrate combination therapy could be considered as a logical approach to optimize lipid and lipoprotein levels in such patients.

Because gemfibrozil has been shown to inhibit statin acid glucuronidation and increases the area under the curve when both drugs are consumed, this agent is generally not recommended to be used with statins.[131] In contrast, co-administration of statins and fenofibrate does not affect the pharmacokinetics of statins. Thus, statin/fenofibrate combination therapy is an attractive alternative for patients with mixed dyslipidemia and for those in whom lipid abnormalities persisted after initial statin therapy.[131–133]

Numerous studies specifically evaluated the effects of simvastatin/fenofibrate combination therapy.[132–165] Additional reductions in lipid and lipoprotein concentrations were observed in statin/fenofibrate combination therapy, in comparison to statin monotherapy.[149–163] Also, the combination therapy reduced inflammatory markers including fibrinogen, high-sensitivity C reactive protein, and plasminogen activator inhibitor-1 levels;[156,158] and improved postprandial endothelial dysfunction.[145]

As seen in Table 1, eight randomized double-blind efficacy studies using simvastatin/fenofibrate combination therapy were compared to statins alone.[144,153,155–160] These studies were performed in diabetics and non-diabetics with mixed dyslipidemia, as well as patients with and without cardiovascular disease.

The effect of simvastatin/fenofibrate combination therapy was not restricted to reductions in total-cholesterol, triglycerides, and increments of HDL-C. In patients with mixed dyslipidemia, the addition of statin/fenofibrate statins caused a further reduction of VLDL plus intermediate density lipoprotein and VLDL plus intermediate density lipoprotein apolipoprotein B of 36% and 34%, respectively and changes in the pattern of LDL particles.[152,154] Likewise, other investigators,[157] showed a shift from LDL pattern B to the more buoyant LDL pattern. This was specifically noted in diabetic patients with mixed dyslipidemia who were treated with simvastatin 20 mg plus fenofibrate 160 mg.[160]

Outcome of clinical trials

Due to the positive effects of statin/fibrate combination, additional studies were developed in patients with diabetes and high cardiovascular risk to assess the benefits on cardiovascular outcomes.

Of the studies, three RCTs presented cardiovascular outcomes.[51,163,164] As seen in Table 2, the effectiveness of the combination therapy in patients with ischemic heart disease, was measured by echocardiographic and exercise tests. Improved myocardial function, as well as a significant improvement in left ventricular ejection fraction, resulted in favorable changes in exercise performance.[163] Similarly, in the FIRST study,[164] the simvastatin/fenofibrate combination therapy induced changes in carotid intima media thickness (cIMT) – a surrogate marker of cardiovascular disease – in subgroups of patients including those ≥60 years, with a history of coronary artery disease, cIMT >0.795 mm, with baseline triglycerides in the middle tertile, and statin use at entry to study. Nonetheless, both of these studies were relatively small, of short duration, and no effect on mortality was demonstrated.

In The Action to Control Cardiovascular Risk in Diabetes (ACCORD lipid trial),[51] the only cardiovascular outcome study, the addition of fenofibrate (160 or 54 mg/day) to simvastatin therapy (20–40 mg/day) did not demonstrate total population mortality effects. In this study, the dyslipidemic patients had an elevated relative cardiovascular risk compared to those without dyslipidemia despite the fact that median LDL-C achieved optimal levels. In the whole group the primary outcome occurred at a rate of 2.4%/year for placebo and 2.2%/year for combination therapy, results that were not significantly different (P=0.32).[51] In the prespecified subgroup analysis, men showed a lower primary event with the combination therapy and the dyslipidemic patients had 31% lower outcomes compared to the rest of the participants (P-value not reported), suggesting that in such patients the combination therapy could offer additional benefits in reducing ASCVD risk.[51] Interestingly, when the postprandial triglyceride and intestinal lipoprotein remnants excursion was examined in dyslipidemic patients from the ACCORD lipid trial,[166] the statin/fenofibrate combination therapy significantly reduced apolipoprotein B 48 remnants' lipoprotein particles. Since these particles have atherogenic potential, the effects of such therapy could benefit diabetic dyslipidemic patients.[166]

Side effects of statin/fibrate combination therapy include muscle and liver toxicity as well as renal complications.[133,152,160] In comparison to gemfibrozil, fenofibrate is less associated with rhabdomyolysis when used in combination with statins.[138] Additionally, the combination therapy has the tendency to increase creatinine concentrations, however, this adverse effect is reversible with the discontinuation of the medication.[51,138,139]

Likewise, when renal impairment is present, lower doses of fenofibrate is recommended.[51,138,139] Additionally, simvastatin/

Table 1 Effects of simvastatin/fenofibrate combination therapy on lipid and lipoproteins

Study	Type of study	Study population	Mean age (y)	DM (%)	M/F (%)	Follow-up	Treatment	Lipid parameter	% change from basal	
									Statin alone	Statin/fibrate
Vega G et al[152]	Randomized, double-blinded, placebo, monotherapy and co-administration of study drugs	20 patients with mixed dyslipidemia	53.0±9.2	20/80	none	9 months	Simvastatin 10 mg alone versus simvastatin 10 mg/day plus fenofibrate 200 mg/day	T-Chol	−27.0	−27.0
								TG	−23.0	−52.6
								Non-HDL-C	−30.0	−36.4
								LDL-C	−28.0	−24.5
								Apo B	−21.6	−31.5
								LDL Apo B	−23.0	−25.0
								HDL-C	+06.0	+23.0
								Apo C II	−28.8	−37.9
								Apo C III	−18.4	−26.7
Grundy et al[154]	Randomized, double-blinded, active-controlled	618 patients with combined hyperlipidemia	52.7±8.6	49/51	16.5	18 weeks	Simvastatin 20 mg and fenofibrate 160 mg or simvastatin 20 mg versus placebo or fenofibrate	TG	−20.1	−43.0
								T-Chol	−20.3	−26.3
								VLDL-TG	−20.6	−53.5
								Non-HDL-C	−26.1	−35.3
								LDL-C	−26.8	−31.2
								HDL-C	+09.7	+18.6
								Apo B	−22.8	−32.6
								Apo A I	+04.8	+08.8
Muhlestein et al[143]	Randomized, double-blinded, Placebo-controlled	300 type 2 DM with mixed dyslipidemia and with and without CVD	60.6	45/55	100	12 weeks	Simvastatin 20 mg plus fenofibrate placebo or fenofibrate 160 mg plus simvastatin placebo or simvastatin 20 mg plus fenofibrate 160 mg	TG	−24.8	−49.4
								T-Chol	−26.1	−27.1
								LDL-C	−34.1	−29.1
								Non-HDL-C	−32.5	−34.3
								HDL-C	+07.4	+13.0
Bays et al[156]	Double-blinded, randomized controlled trial	2,201 patients with mixed dyslipidemia	54.8±10.57	51/49	43	52 weeks	Fenofibric acid 135 mg or low, moderate, high statin doses alone or in combination with fenofibric acid	T-Chol	−0.70	−04.7
								TG	−30.5	−04.2
								Non-HDL-C	−04.6	−09.7
								Apo B	−07.0	−09.4
								LDL-C	−03.2	−07.9
								HDL-C	+13.1	+04.8
Mohiuddin et al[158]	Double-blinded, randomized, active-controlled prospective study	650 men and women with mixed dyslipidemia and multiple CVD risk factors	54.5±10.32	51	22.9	22 weeks	Fenofibric acid 135 mg or simvastatin 20–40–80 mg or fenofibric acid 135 mg + simvastatin 20–40 mg	T-Chol	−19.8–30.0	−23.9–27.1
								TG	−14.2–22.4	−37.4–42.7
								VLDL-C	−19.2–35.7	−19.2–35.7
								Non-HDL-C	−24.4–35.9	−24.4–35.9
								Apo B	−22.9–33.6	−32.7–31.2
								LDL-C	−22.4–31.7	−24.0–25.3
								HDL-C	+07.2–08.5	+17.8–18.9
May et al[155]	Randomized, double-blinded, placebo controlled	300 DM patients without CVD and mixed dyslipidemia	61.6±11.5	45/55	100	12 weeks	The patients were randomized to simvastatin 20 mg, fenofibrate 160 mg or simvastatin 20 mg + fenofibrate 160 mg	LDL pattern B	−27.7	−33.9
								Buoyant LDL	−11.6	−11.6
								HDL 2	+0.3	−0.4
								HDL 3	+01.0	+02.3
								Dense VLDL	−06.3	−10.0

Study	Trial design	Patients	Age			Treatment	Duration	Parameter	Change	Change
Derosa et al[157]	Randomized, double-blinded trial	241 DM patients with combined dyslipidemia without serious CVD	51.6±10.3	50.6	100	The patients received fenofibrate 145 mg or simvastatin 40 mg or fenofibrate 145 mg + simvastatin 40 mg	12 months	IDL	−12.2	−08.8
								Lp(a)	+0.6	−0.5
								T Chol	−20.5	−29.3
								TG	−11.8	−38.8
								LDL-C	−22.8	−40.4
								HDL-C	−16.5	+34.1
								Apo B	+10.8	−28.7
								Apo A I	+05.9	+09.4
								Lp(a)	+10.0	+16.0
Jones et al[159]	Double-blinded, 12 week trial	586 patients with mixed dyslipidemia and type 2 DM	58.6±10.0	53/46	21.7	Fenofibric acid 135 mg alone or low dose of statin or fenofibric acid in combination with low or moderate doses of statins (rosuvastatin 10–20–40 mg, simvastatin 20–40–80 mg, or atorvastatin 20–40–80 mg)	12 weeks	T Chol	−29.4	−33.6
								TG	−24.2	−43.4
								LDL-C	−41.5	−32.6
								HDL-C	+08.7	+16.3
								Apo B	−32.7	−36.2
								Apo A I	+03.0	+10.3

Abbreviations: Apo A I, apolipoprotein A I; Apo C II, apolipoprotein C II; Apo B, apolipoprotein B; Apo C, apolipoprotein C; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; HDL 2, high-density lipoprotein 2; HDL 3, high-density lipoprotein 3; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; M/F, male/female; Non-HDL-C, total cholesterol – HDL-C; T-Chol, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol; VLDL-TG, very low-density lipoprotein triglycerides.

fenofibrate combination therapy should be avoided in patients receiving macrolides, antifungals, cyclosporine, and protease inhibitors, as these agents are cytocromes 3A4 inhibitors and can affect statin metabolism.[138,139]

Discussion

Dyslipidemia characterized by elevated triglycerides, low HDL-C and moderate elevations of LDL-C, is common throughout diverse populations and is often associated with obesity, MetS, and type 2 diabetes.[45–47] The characteristic lipid abnormality present in these patients largely contributes to the increased rate of cardiovascular complications. As indicated above, the association of triglycerides and ASCVD is complex. Conflicting results regarding fasting triglyceride concentrations and ASCVD exists, as this relationship is not sustained after adjusting for other lipid variables. However, it has been recognized that postprandial lipemia (which is associated with the presence of triglyceride rich remnant particles, small LDL-C, and a decrease in HDL-C) correlates with cIMT and predicts the risk of cardiovascular disease more accurately than fasting triglyceride concentrations. The mechanisms that link triglycerides with ASCVD are related to the accumulation of triglyceride rich lipoproteins including chylomicron and VLDL remnants, modifications in HDL composition,[96,97] and to other non-lipidic alterations which lead to endothelial dysfunction and pro-thrombotic effects.[16,93–95] Postprandial lipemia has been observed in various clinical situations. Some examples include individuals with MetS, diabetes mellitus, with increased visceral adipose tissue, postmenopausal states, and patients with coronary artery disease.[87–90]

As demonstrated in the large interventional studies that target LDL-C with statins, a decrease in cardiovascular risk has been noted throughout a wide range of patients, including diabetics with borderline LDL-C concentrations.[40–43] In the ACCORD lipid trial, hard cardiovascular end points with the statin/fibrate combination therapy, in the total population study were unfavorable. However, those individuals with fasting and postprandial hypertriglyceridemia seemed to have benefited from the simvastatin/fenofibrate combination therapy.[166] Although not confirmed, differences in the lipid characteristics throughout the participants may explain the negative outcomes. The patients who could benefit the most from this therapeutic strategy (high triglycerides/low HDL, postprandial lipemia, and small dense LDL) were not significantly represented. Of note, in the ACCORD lipid study only 15% of the overall cohort had dyslipidemia.[51] Similarly, in the FIRST study, changes in cIMT-favored subgroups of

Table 2 Effects of simvastatin/fenofibrate combination therapy on cardiovascular end points

Study	Type of study	Study population	Mean age (years)	M/F (%)	DM (%)	Follow-up	Treatment	Outcomes	Cardiovascular end points
ACCORD lipid trial[51]	Randomized double blind	5,518 type 2 DM with multiple CV risk factors or ASCVD	62.3±6.8	69.3/30.7	100	4.7 years	All patients received simvastatin ≤40 mg (open label) and fenofibrate 160 mg or placebo	Nonfatal myocardial infarction, nonfatal stroke or death from ASCVD	• No differences in primary cardiovascular outcomes were observed (10.3% vs 11.3%)† • Patients with high levels of TG and low levels of HDL-C outcome rate: 12.4% vs 17.3% in placebo group††
Karbasi-Afshar et al[163]	Randomized clinical trial	124 patients with dyslipidemia and CVD	54.3±5.6	46.7/53.2	13.2	12 months	Simvastatin 20–60 mg/day and fenofibrate 200 mg/day or simvastatin 20–60 mg/day	Myocardial structure and function in CAD patients with dyslipidemia	Combination therapy • Change in left ventricular ejection fraction* • Increase in left ventricular mass index** • Exercise test time (min) increased*** • Metabolic task index increased*
Davidson et al[164]	Double blinded, placebo controlled study	682 patients with mixed dyslipidemia and history of CAD or risk equivalent	61	68/32	50.0	104 weeks	Atorvastatin 40 mg plus fenofibric acid 135 mg or placebo	Rate of change from baseline through week 104 of the mean posterior-wall cIMT	Combination therapy • No decrease in the progression of cIMT • Changes in the posterior wall cIMT were larger in participants: o ≥60 years of age o History of CAD o Prior statin use o Highest tertile of baseline cIMT o Middle tertile of baseline TG

Notes: †P=0.32; ††P-values not reported; *P=0.01; **P=0.039; ***P=0.001.
Abbreviations: ACCORD, The Action to Control Cardiovascular Risk in Diabetes; DM, diabetes mellitus; CV, cardiovascular; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; CAD, coronary artery disease; cIMT, carotid intima media thickness; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; M/F, male/female; vs, versus.

patients including those with baseline triglycerides in the middle tertile.[164]

In conclusion, statin–fenofibrate therapy should theoretically benefit the subgroup of patients with high triglycerides/low HDL. Although there is not enough evidence to prove this correct. It is reassuring that a new intervention study: Simvastatin and Fenofibrate vs Simvastatin Alone in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome is ongoing.[167] This study hypothesizes that early administration of combined simvastatin/fenofibrate therapy in an extremely high-risk population of patients with type 2 diabetes mellitus and hypertriglyceridemia with acute coronary syndrome will be effective. However, to accurately address the effects on cardiovascular mortality of the combination therapy, a more specific clinical trial is necessary. This can be achieved by recruiting the specific patient population whose benefits were mentioned in previous studies.[16,51,164] Until this investigation is complete, weight loss must be encouraged in dyslipidemic patients and in diabetics strict glycemic control should be mandatory. Thus for now, the use of simvastatin/fenofibrate combination therapy should only be used at physician's discretion.

Acknowledgments

Disclosure

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