Reprint from The Review of DIABETIC STUDIES Vol 10 No 2-3 2013 Special Issue CVD, Lipoproteins, and Diabetes

The Review of DIABETIC STUDIES

REVIEW

Does Combination Therapy with Statins and Fibrates Prevent Cardiovascular Disease in Diabetic Patients with Atherogenic Mixed Dyslipidemia?

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Manuscript submitted March 24, 2013; resubmitted May 20, 2013; accepted May 20, 2013

■ Abstract

Type 2 diabetes mellitus (T2DM) is associated with the development and progression of cardiovascular disease (CVD). Statins have an established efficacy in the management of dyslipidemia primarily by decreasing the levels of low-density lipoprotein cholesterol and thus decreasing CVD risk. They also have a favorable safety profile. Despite the statin-mediated benefit of CVD risk reduction a residual CVD risk remains, especially in T2DM patients with high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) values. Fibrates decrease TG levels, increase HDL-C concentrations, and improve many other atherosclerosis-related variables. Fibrate/statin co-administration improves the overall lipoprotein profile in patients with mixed dyslipidemia and may reduce the residual CVD risk during statin therapy. However, limited data exists regarding the effects of statin/fibrate combination on CVD outcomes in patients with T2DM. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study the statin/fibrate combination did not significantly reduce the rate of CVD events compared with simvastatin/placebo in patients with T2DM. However, it did show a possible benefit in a pre-specified analysis in the subgroup of patients with high TG and low HDL-C levels. Furthermore, in the ACCORD study the simvastatin/fenofibrate combination significantly reduced the rate of progression of retinopathy compared with statin/placebo administration in patients with T2DM. The present review presents the available data regarding the effects of statin/fibrate combination in patients with T2DM and atherogenic mixed dyslipidemia.

Keywords: cardiovascular disease · type 2 diabetes · dyslipidemia · fibrate · HDL cholesterol · statin · triglycerides

1. Introduction

The incidence of type 2 diabetes mellitus (T2DM), which is associated with high morbidity and mortality rates, is increasing dramatically [1]. Presently, over 10% of adults in the USA have T2DM, whereas predictions for the first third of the 21st century show an at least 2 times increase in the prevalence of T2DM in China, Middle East, Sub-Saharan Africa, India, rest of Asia, and Latin America. In economically advanced countries, the increase will be about 50% in 2030 [2].

Patients with carbohydrate metabolism disorders are at increased risk of developing cardiovascular disease (CVD) [3-8]. Current treatment guidelines focus on lowering low-density lipoprotein cholesterol (LDL-C) as the primary strategy for reducing CVD risk [9, 10]. Consequently, statins (i.e. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) constitute the cornerstone of dyslipidemia treatment [11]. However, patients (with or without T2DM) treated with hypolipidemic drugs usually have persistent lipid abnormalities [12-15]. It has also been shown that in large trials at least one in seven treated patients experienced CVD events over five years [16, 17]. These observations indicate that patients with T2DM have a residual CVD risk, which is now considered a target of hypolipidemic therapy.

Therefore, combination drug treatment in T2DM patients is a useful approach [18, 19].

The residual CVD risk is usually attributed to the presence of mixed dyslipidemia with elevated triglyceride (TG) concentration and low levels of high-density lipoprotein cholesterol (HDL-C) [20-23]. It should also be mentioned that HDL has discrete subfractions, and its protein and lipid components can be modified by oxidative processes in T2DM, leading to impaired anti-atherogenic properties [24-28]. These particles with lower antioxidant and anti-inflammatory activity are considered "dysfunctional" [24, 29, 30].

Additional factors that contribute to the increased CVD risk in patients with mixed dyslipidemia and T2DM are, among other atherosclerosis-related variables, the preponderance of the atherogenic small dense LDL particles, the increased concentration of apolipoprotein (apo) C-III and C-II, and the increased levels of inflammation-related markers such as high-sensitivity C-reactive protein (hsCRP) and lipoprotein-associated phospholipase A_2 ($LpPLA_2$) [31-46]. Another consideration is that many patients have a secondary cause of hypertriglyceridemia and/or low HDL-C levels such as excessive alcohol intake, fatty diet, hypothyroidism, nephrotic syndrome, and chronic renal failure, or they receive drugs that alter lipid variables such as thiazide diuretics, beta-blockers, high-dose corticosteroids, isotretinoin, tamoxifen, high-dose estrogens, antipsychotics, anti-tumor necrosis factor agents, and antiretroviral drugs [47-70]. Various lifestyle, dietary, and pharmaceutical interventions have been proposed for the improvement of these atherosclerosis-related variables and consequently the reduction of residual CVD risk [71-100].

Fibrates constitute a class of drugs that seem promising for the reduction of residual CVD risk as they specifically decrease TG levels and elevate HDL-C concentrations [101]. The combination of statins and fibrates is an attractive option for the comprehensive management of high CVD risk patients with T2DM as it affects different aspects of lipoprotein metabolism. The effects of statin and fibrate co-administration in T2DM patients will be discussed in the following sections.

Abbreviations:

ACCORD - Action to Control Cardiovascular Risk in Diabetes
Apo - apolipoprotein
ASPEN - Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus
b.i.d - twice daily
CHD - coronary heart disease
CI - confidence interval
CVD - cardiovascular disease
DAIS - Diabetes Atherosclerosis Intervention Study
DIACOR - Diabetes and Combined Lipid Therapy Regimen study
GFR - glomerular filtration rate
FIELD - Fenofibrate Intervention and Event Lowering in Diabetes study
HbA1c - glycosolated hemoglobin
HDL-C - high-density lipoprotein cholesterol
HMG-CoA - 3-hydroxy-3-methylglutaryl coenzyme A
HOMA - homeostasis model assessment
HPS - Heart Protection Study
hsCRP - high-sensitivity C-reactive protein
IAUC - incremental area under the curve
LDL-C - low-density lipoprotein cholesterol
Lp(a) - lipoprotein (a)
$LpPLA_2$ - lipoprotein-associated phospholipase A_2
NCEP ATP III - National Cholesterol Education Program Adult Treatment Panel
NS - not significant
OR - odds ratio
PCSK9 - proprotein convertase subtilisin kexin/type 9
PPAR - peroxisome proliferator activated receptor
PROVE-IT - Pravastatin or Atorvastatin Evaluation and Infection Therapy study
SENDCAP - Saint Mary's Ealing Northwick Park Diabetes Cardiovascular Disease Prevention
T2DM - type 2 diabetes mellitus
TG - triglyceride
t.i.d. - three times daily
TNF-α - tumor necrosis factor alpha
TNT - Treating to New Targets
VA-HIT - Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial
VLDL - very low-density lipoprotein

2. Methods

A PubMed/Scopus search was performed up to March 2013 using combinations of "diabetes" with the following keywords: cardiovascular risk, cholesterol, triglycerides, HDL-C, statin, simvastatin, atorvastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, fibrate, fenofibrate, fenofibric acid, bezafibrate, gemfibrozil, lipid-lowering medications, and adverse effects. Randomized controlled trials, original papers, review articles, and case reports were included in the present review. References of these articles were scrutinized for relevant articles.

3. Effects of statins in patients with T2DM

Statins are the cornerstone of lipid lowering therapy, with many large-scale, randomized, pla-

cebo-controlled trials demonstrating powerful efficacy in preventing CVD outcomes [16, 102-113]. Their effect on CVD risk reduction is primarily attributable to their hypolipidemic properties but statins additionally exert pleiotropic effects [114-118].

The Heart Protection Study (HPS) included 5,963 adults (age 40-80 years) with T2DM and 14,573 with occlusive arterial disease (without T2DM), who were randomized to receive simvastatin 40 mg/day or placebo [119]. Pre-specified analyses included the rate of first major coronary events (non-fatal myocardial infarction or coronary heart disease (CHD) death) and of first major vascular events (major CHD event, stroke or revascularization). Simvastatin treatment resulted in an average reduction of LDL-C by 39 mg/dl (1.0 mmol/l) compared with placebo during the 5-year treatment period. Significant reductions (approximately 25%) in the rate of major CHD events, strokes and revascularizations were observed in all patients. In patients with T2DM a significant reduction of 22% (95% confidence interval (CI) 13-30, $p < 0.0001$) in major vascular events was observed. Additionally, a significant reduction of 33% (95% CI 17-46, $p = 0.0003$) was observed among the 2,912 T2DM participants without occlusive arterial disease. Notably, the reduction of major vascular events was also seen (-27%, 95% CI 13-40, $p = 0.0007$) in the 2,426 patients with T2DM and pre-treatment LDL-C levels <116 mg/dl (3.0 mmol/l) [119].

In the Collaborative Atorvastatin Diabetes Study (CARDS) 2,838 patients (age 40-75 years) with T2DM without high levels of LDL-C (<160 mg/dl (<4.14 mmol/l)) were randomized for a median of 3.9 years to atorvastatin 10 mg/day (n = 1,428) or placebo (n = 1,410) [120]. A significant reduction of 37% (95% CI 17-52, $p = 0.001$) in major CVD events was observed. When different types of events were analyzed separately, a significant reduction in the rate of acute CHD events (hazard ratio 0.64, 95% CI 0.45-0.91, $p < 0.05$), coronary revascularizations (hazard ratio 0.69, 95% CI 0.41-1.16, p = NS), and stroke (hazard ratio 0.52, 95% CI 0.31-0.89, $p < 0.05$) was shown. Notably, atorvastatin treatment resulted in a trend of significant reduction in death rates (-27%, $p = 0.059$) [120].

However, another study with atorvastatin in T2DM patients did not result in significant reductions of CVD events. The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) assessed the 4-year administration of atorvastatin 10 mg/day versus placebo on CVD prevention in 2,410 subjects with T2DM and LDL-C levels below contemporary guideline targets (i.e. LDL-C ≤ 140 mg/dl (3.6 mmol/l) in subjects with documented myocardial infarction or an interventional procedure >3 months before screening, or LDL-C ≤ 160 mg/dl (4.1 mmol/l) if not) [121]. The administration of atorvastatin led to a greater reduction of LDL-C (-29% versus placebo, $p < 0.0001$), total cholesterol and TG concentration, as well as a greater increase in HDL-C, compared with the placebo group (all $p < 0.01$). However, the composite primary end point rates were 13.7% and 15.0% for atorvastatin and placebo, respectively (hazard ratio 0.90, 95% CI 0.73-1.12, $p = 0.34$). Furthermore, no significant difference was found in the subset of 1,905 subjects without prior myocardial infarction or interventional procedure (10.4% with atorvastatin and 10.8% with placebo, hazard ratio 0.97, 95% CI 0.74-1.28, p = NS), or in the 505 subjects with prior myocardial infarction or interventional procedure (26.2% with atorvastatin and 30.8% with placebo; hazard ratio 0.82, 95% CI: 0.59-1.15, p = NS). The authors of the study commented that these results could be attributed to the types of subjects recruited, the nature of the primary endpoint, and the requirement for protocol changes because of newer treatment guidelines [121].

A prospective meta-analysis that included 18,686 patients (1,466 with type 1 and 17,220 with type 2 diabetes) from 14 randomized trials concluded that statin therapy should be considered for all individuals with T2DM who are at sufficiently high risk of vascular events[17]. Indeed, statin treatment safely reduced the 5-year incidence of major CHD events, coronary revascularization and stroke [17].

A meta-analysis of randomized controlled trials evaluated the effects of hypolipidemic therapy among patients with T2DM and non-diabetic subjects [122]. The data suggested that lipid-lowering drug treatment was similarly effective in patients with T2DM and in non-diabetic individuals. The risk reduction of major CHD events in primary prevention was 21% (95% CI 11-30, $p < 0.0001$) in patients with T2DM and 23% (95% CI 12-33, $p = 0.0003$) in non-diabetic patients, whereas in secondary prevention it was 21% (95% CI 10-31, $p = 0.0005$) and 23% (96% CI 19-26, $p < = 0.0001$), respectively. Furthermore, after adjustment for baseline characteristics, patients with T2DM experienced a greater benefit from lipid-lowering therapy compared with non-diabetic subjects in both primary and secondary prevention [122].

Generally, statins are safe drugs [123-127]. Of note, statin therapy has been associated with alterations of glucose homeostasis and insulin resistance [128]. A meta-analysis that included 13 statin trials with 91,140 participants showed that statin therapy is associated with an increased risk of 9% for incident T2DM [129]. However, this risk is substantially low compared with the reduction of CHD events observed with statin treatment.

4. Effects of fibrates in patients with T2DM

Fibrates belong to a class of drugs that activate peroxisome proliferator activated receptor α (PPAR-α) [101, 130]. Bezafibrate, gemfibrozil, and the newer agents, fenofibrate and fenofibric acid, are members of this family. This class of drugs is able to decrease the concentration of plasma TG by 30-50%, to increase levels of HDL-C by 2-20%, and to exert a number of pleiotropic effects [92, 101, 130-135]. As a result, these drugs may have a role in individuals at high risk of CVD events and combined dyslipidemia [136, 137]. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial (VA-HIT), gemfibrozil significantly reduced the risk of major CVD events (CHD, death, stroke, or myocardial infarction) by 32% (p = 0.004) in T2DM patients with established CHD and low levels of HDL-C [138]. In the Saint Mary's Ealing Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) study, bezafibrate significantly reduced the combined incidence of ischemic change on the resting electrocardiography and of documented myocardial infarction in 164 patients with T2DM without previous CHD (p = 0.01) [139].

Fenofibrate, is now the most commonly prescribed fibrate worldwide and is indicated for the treatment of combined dyslipidemia, remnant hyperlipidemia and hypertriglyceridemia [140]. Fenofibrate leads to a reduction of TG concentration by 30-50% and an increase of HDL-C by 2-20% [101, 130, 131, 141-143]. Furthermore, fenofibrate, similar to gemfibrozil, exerts a variable effect on LDL-C concentration that is a small decrease in patients with hypercholesterolemia or a slight increase in individuals with mixed dyslipidemia [130, 144-147]. It should be mentioned that the Friedewald equation becomes progressively unreliable when TG concentration exceeds 400 mg/dl (4.5 mmol/l). Hence, at higher TG levels, the Friedewald formula should not be used and other methods of LDL-C determination should be employed [148, 149]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, the largest study that examined the benefits of fenofibrate in 9,795 patients with T2DM, provided mixed results. Fenofibrate (200 mg/day for 5 years) did not significantly reduce the risk of the primary trial outcome of major CHD events (-11%, p = NS), but it reduced the risk of total CVD events (-11%, p = 0.035) compared with placebo, mainly by the prevention of non-fatal myocardial infarctions (-24%, p = 0.01) and coronary revascularizations (-21%, p = 0.003) [142]. It should be mentioned that in the FIELD study significantly more patients in the placebo group (17%) compared with the fenofibrate group (8%, p < 0.0001) also received other lipid treatments, predominantly statins. As a result, the possible beneficial CVD effects of fenofibrate may have been weakened from the statin treatment in the placebo group [142]. Moreover, in the Diabetes Atherosclerosis Intervention Study (DAIS), a double-blind placebo-controlled trial that evaluated the angiographic progression of CHD in patients with T2DM (n = 418), fenofibrate treatment was associated with decreased angiographic progression of CHD [150].

Fenofibrate is a pro-drug, which is converted in the liver to the active drug and then released into the plasma to activate PPAR-α in tissues [151, 152]. The newer fibrate formulation, fenofibric acid is not a pro-drug and does not undergo first-pass hepatic metabolism [153].

5. Effects of statin and fibrate combination on metabolic parameters in patients with mixed dyslipidemia and/or T2DM

In several clinical studies (**Tables 1** and **2**) the combination of statin/fibrate therapy resulted in pronounced decreases in LDL-C, TG and non-HDL-C, as well as increases in HDL-C, compared with either monotherapy [101, 154-156]. For example, a pooled subgroup analysis of three randomized, controlled, double-blind, 12-week trials that included 586 patients with mixed dyslipidemia and T2DM showed that the fenofibric acid/statin combination treatment was associated with a significantly greater improvement of lipid profile compared with either monotherapy [157]. Indeed, it was shown that the combination of fenofibric acid with low- or moderate-dose statin, led to a 5-fold higher percentage of patients achieving the combined optimal levels of LDL-C, non-HDL-C, apoB, TG and HDL-C [157].

Table 1. Selected studies of the combined treatment of statins with fenofibrate in T2DM patients

Study	Study population	Statin dose	Fibrate dose	Duration	LDL-C[a]	TC[a]	TG[a]	HDL-C[a]	Other parameters[a]
Athyros et al. [169]	120 patients with mixed dyslipidemia and T2DM	Atorvastatin 20 mg	Fenofibrate 200 mg	24 weeks	-46%[b,d,e]	-37%[b,d,e]	-50%[b,d,e]	+22%[b,d,e]	ApoA-I: +12%[b,d,e], ApoB-100: -41%[b,d,e], Lp(a): +1%, Fibrinogen: -19%[b,e]
Costet et al. [170]	26 patients with T2DM and atherogenic dyslipidemia	Atorvastatin 10 mg	Fenofibrate 160 mg	6 weeks monotherapy and 6 weeks combined treatment	-17% versus pooled monotherapy[c]	-11% versus pooled monotherapy[c]	-12% versus pooled monotherapy	0% versus pooled monotherapy	After 6 weeks PCSK9: -9% versus monotherapy[b]
Durrington et al. [173]	216 patients with mixed dyslipidemia and T2DM	Rosuvastatin 5 mg	Fenofibrate 67 mg q.d./b.i.d./t.i.d.	24 weeks	-34.1%[b]	-31%[b]	-40.9%[b]	+10.8%[b]	ApoA-I: +4.7%[b], ApoB: -35%[b], VLDL-C: -46.8%[b], LDL-C/HDL-C ratio: -38.8%[b,e], TC/HDL-C ratio: -36.2%[b], Non-HDL-C/HDL-C ratio: -43.5%[b], ApoB/ApoA-I ratio: -37.2%[b]
		Rosuvastatin 10 mg	Fenofibrate 67 mg q.d./b.i.d./t.i.d.	24 weeks	-42.2%[b]	-36.3%[b]	-47.1%[b, e]	+11.7%[b]	ApoA-I: +5.4%[b], ApoB: -40.2%[b], VLDL-C: -44.2%[b], LDL-C/HDL-C ratio: -46.8%[b], TC/HDL-C ratio: -41.9%[b], Non-HDL-C/HDL-C ratio: -50.4%[b], ApoB/ApoA-I ratio: -42.7%[b]
ACCORD Lipid study [154]	5,518 patients with T2DM	Simvastatin 40 mg	Fenofibrate 200 mg on top of simvastatin	Mean follow-up 4.7 years	-18.9% vs. placebo	-13.5% vs. placebo[e]	-22.2% vs. placebo[e]	+8.4% vs. placebo[e]	For the effects on cardiovascular disease events see text
Muhlestein et al. [163]	300 patients with mixed dyslipidemia and T2DM	Simvastatin 20 mg	Fenofibrate 160 mg	12 weeks	-29.1%[b,d]	-27.1%[b,d]	-49.4%[b,e]	+13%[b]	Non-HDL-C: -34.3%[b,d], $LpPLA_2$: -36.2%[b], hsCRP: -15.9%[b]
May et al. [164]	300 patients with mixed dyslipidemia and T2DM	Simvastatin 20 mg	Fenofibrate 160 mg	12 weeks	-	-	-	-	LDL pattern B: -33.9%[b], LDL pattern B%: -11.1%[e], HDL3: +2.3%[b], dense VLDL: -10%[b,d,e], IDL: -8.8%[b,d]
Krysiak et al. [161]	190 patients with mixed dyslipidemia and T2DM	Simvastatin 40 mg	Fenofibrate 200 mg	90 days	-42%[b,c,d]	-36%[b,c,d]	-48%[b,c,e]	+36%[b,c,e]	ApoB: -35.8%[b,c], ApoA-I: +46%[b,c,e], hsCRP: -69%[b,c,d,e], HbA1c: -25%[b, c,e]
Reyes-Soffer [198]	139 patients with T2DM	Simvastatin 40 mg	Fenofibrate 200 mg	10 hours after an oral fat load	-	-	-	-	Postprandial TG IAUC above fasting -26% and postprandial apoB48 IAUC -34% compared with statin[e].
Farnier et al. [179]	291 patients with mixed dyslipidemia and T2DM not at lipid goal with simvastatin 20 mg monotherapy	Simvastatin 40 mg	Fenofibrate 160 mg	24 weeks	-5.3%[b]	-8.7%[b,e]	-28.6%[b,e]	+6.3%[b,e]	Non-HDL-C: -12.9%[b,e], ApoB: -8.9%[b], ApoA-I: +3.6%[b], ApoB/ApoA-I ratio: -10.2%[b], Fibrinogen: -11.5%[b,e], hsCRP: -0.16%

Legend: [a] Values express the increase or reduction versus baseline in the combination treatment, except otherwise mentioned. [b] $p < 0.05$ versus baseline. [c] $p < 0.05$ versus placebo. [d] $p < 0.05$ versus fibrate monotherapy. [e] $p < 0.05$ versus statin monotherapy. *Abbreviations*: T2DM - type 2 diabetes mellitus; LDL-C - low-density lipoprotein cholesterol; TC - total cholesterol; TG - triglycerides; HDL-C - high-density lipoprotein cholesterol; apo - apolipoprotein; Lp(a) - lipoprotein (a); PCSK9 - proprotein convertase subtilisin/kexin type 9; VLDL - very low-density lipoprotein; VLDL-C - VLDL cholesterol; hsCRP - high-sensitivity C-reactive protein; $LpPLA_2$ - lipoprotein-associated phospholipase A_2; IDL - intermediate-density lipoprotein; HbA1c - glycosylated hemoglobin; IAUC - incremental area under the curve; q.d./b.i.d./t.i.d - once/twice/three times daily.

Table 2. Selected studies of the combined treatment of statins with fenofibric acid or bezafibrate in T2DM patients

Author	Study population	Statin dose	Fibrate dose	Duration	LDL-C[a]	TC[a]	TG[a]	HDL-C[a]	Other parameters[a]
Rosenson et al. [176]	456 patients with mixed dyslipidemia and T2DM	Rosuvastatin 5 mg	Fenofibric acid 135 mg	12 weeks	-32.8%[d]	-	-39.9%[e]	+25.5%[e]	Non-HDL-C: -41.1%[d,e], ApoB: -34.9%[d], hsCRP: -26.8%
		Rosuvastatin 10 mg	Fenofibric acid 135 mg	12 weeks	-36.8%[d]	-	-44.8%[e]	+19.6%[e]	Non-HDL-C: -43.6%[d], ApoB: -36.2%, hsCRP: -28.0%
		Rosuvastatin 20 mg	Fenofibric acid 135 mg	12 weeks	-37.0%[d]	-	-42.6%[e]	+16.4%	Non-HDL-C: -44.9%[d], ApoB: -36.2%, hsCRP: -40.7%
Jones et al. [157]	586 patients with mixed dyslipidemia and T2DM	Moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg or atorvastatin 40 mg)	Fenofibric acid 135 mg	12 months	-32.6%[b,c]	-32.6%[b]	-43.4%[b,c]	+16.3%[c]	hsCRP: -39.3%
		Low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg or atorvastatin 20 mg)	Fenofibric acid 135 mg	12 months	-34%[d]	-33.2%[d,e]	-43.9%[d,e]	+16.8%[e]	hsCRP: -25%
Gavish et al.[167]	148 patients with T2DM	Simvastatin 20 mg	Bezafibrate 400 mg	12 months	-28.9%[b,d]	-22.9%[b,d]	-41.8%[b,d,e]	+20%[b,e]	Fibrinogen: -9%[b]
Dullaart et al. [168]	14 patients with T2DM	Simvastatin 40 mg	Bezafibrate 400 mg	8 weeks	-	-26.3%[b,c,d]	-46.6%[b,c,e]	+14.7%[b]	No significant change in paraoxonase 1 activity compared with monotherapy

Legend: [a] Values express the increase or reduction versus baseline in the combination treatment, except otherwise mentioned. [b] $p < 0.05$ versus baseline. [c] $p < 0.05$ versus placebo. [d] $p < 0.05$ versus fibrate monotherapy. [e] $p < 0.05$ versus statin monotherapy. *Abbreviations*: T2DM - type 2 diabetes mellitus; LDL-C - low-density lipoprotein cholesterol; TC - total cholesterol; TG - triglycerides; HDL-C - high-density lipoprotein cholesterol; apo - apolipoprotein; hsCRP - high-sensitivity C-reactive protein.

5.1 Simvastatin plus fibrate combination treatment

A study assessed the efficacy of fenofibrate administered for 12 months in patients with mixed hyperlipidemia (n = 45, age 58.9 ± 11.3 years) [158]. Patients were included if they had plasma TG levels >300 mg/dl and LDL-C >160 mg/dl after at least 6 months on simvastatin treatment and received simvastatin 10 mg/day plus fenofibrate 200 mg/day (n = 5), simvastatin 20 mg/day plus fenofibrate 200 mg/day (n = 26), simvastatin 20 mg/day plus fenofibrate 300 mg/day (n = 11) and simvastatin 30 mg/day plus fenofibrate 200 mg/day (n = 3). The combination treatment resulted in reductions in total cholesterol (-18% with the lower doses ($p < 0.05$) to -39% with the higher doses ($p < 0.05$)), LDL-C (-21% (p = NS) to -39% ($p < 0.05$)), and TG levels (-35% ($p < 0.05$) to -56% ($p < 0.01$)), as well as an increase in HDL-C (+8% ($p < 0.05$) to +30% (p = NS)), respectively [158].

A multicenter, randomized, double-blind, active-controlled, 18-week study (Simvastatin plus Fenofibrate for Combined Hyperlipidaemia (SAFARI)) [159] included 411 patients with combined hyperlipidemia (age 21 - 68 years), of whom 71% had the metabolic syndrome as defined by The National Cholesterol Education Program Adult Treatment Panel III criteria [10]. After 12 weeks a significantly greater improvement in total cholesterol, TG, non-HDL-C, LDL-C, HDL-C, very low-density lipoprotein (VLDL) cholesterol (VLDL-C),

VLDL-TG, apoA-I, and apoB levels was observed with combination therapy compared with simvastatin monotherapy (all $p < 0.01$) [159].

The efficacy of fenofibrate 145 mg, simvastatin 40 mg or their combination was compared in 241 patients with T2DM and combined dyslipidemia [160]. After 12 months of treatment, fenofibrate plus simvastatin had a more favorable effect in decreasing total cholesterol, LDL-C, TG and apoB levels and in increasing HDL-C and apoA-I concentration compared with monotherapy. Moreover, hsCRP was decreased more with combination therapy than with simvastatin monotherapy [160].

In a double-blind study, 196 patients with recently diagnosed and previously untreated T2DM and mixed dyslipidemia received metformin, and were further randomized to simvastatin 40 mg/day, fenofibrate 200 mg/day, their combination, or placebo [161]. After 90 days of treatment, simvastatin monotherapy and the combined therapy group resulted in greater changes in total cholesterol, LDL-C, and apoB levels compared with fenofibrate monotherapy. In addition, combination treatment improved TG, apoA-I, glucose, homeostasis model assessment (HOMA) index, and glycosylated hemoglobin (HbA1c) more than simvastatin monotherapy (all $p < 0.05$). The combination treatment also resulted in a more pronounced effect on plasma hsCRP and lymphocyte release of interleukin-2, interferon-gamma, and tumor necrosis factor alpha (TNF-α) compared with simvastatin or fenofibrate monotherapy [161].

Another randomized clinical study examined the effectiveness of fenofibrate plus simvastatin combination given for 6 months on an alternate-day regimen (simvastatin 10 mg every other day and fenofibrate 250 mg on the days that simvastatin was not taken) in patients (n = 69, age 56 ± 7 years) with mixed hyperlipidemia [162]. Patients in the alternate-day regimen and in the every-day combination treatment experienced similar decreases in total cholesterol (-31% versus -31%), TG (-55% versus -54%), LDL-C (-34% versus -36%), and apoB (-20% versus -18%) plasma levels, as well as similar increases in HDL-C and apoA-I levels (p = NS for all comparisons). Of note, at the end of the follow-up period total cholesterol, TG, HDL-C and LDL-C levels were within normal limits in almost all patients in both groups [162].

The DIACOR study (Diabetes and Combined Lipid Therapy Regimen) examined the effects on inflammatory biomarkers of simvastatin 20 mg, fenofibrate 160 mg and their combination in 300 patients with mixed dyslipidemia and T2DM [163]. After 12 weeks of treatment, significant median changes were observed in hsCRP levels and $LpPLA_2$ activity compared with baseline levels (-14.6%, $p = 0.004$ and -16.8%, $p < 0.0001$, respectively), but these changes did not differ significantly with monotherapy. When only patients with high baseline levels of hsCRP (>2.0 mg/l) were examined, a greater reduction was shown in all treatment groups compared with baseline levels (fenofibrate: -18.9%, $p = 0.002$, simvastatin: -24.8%, $p < 0.0001$, combination: -27.3%, $p = 0.002$). Likewise, further reductions were observed in patients with increased baseline $LpPLA_2$ levels (fenofibrate: -41.3%, simvastatin: -47.5%, combination: -46.8%, $p < 0.0001$ for all versus baseline) [163]. In addition, the combination of fenofibrate with simvastatin significantly improved the lipid profile when compared with fenofibrate monotherapy and led to greater reductions in TG levels when compared with simvastatin alone [163].

In an extension of the DIACOR study, lipoprotein subparticle profiles were evaluated [164]. After 12 weeks, the combination therapy and fenofibrate monotherapy led to significant reductions in the LDL pattern B (-11.1% and -13.7%, respectively, $p < 0.0001$ for both) and to significant increases in the percentage of buoyant LDL-C constituting total LDL-C [164]. Thus, fenofibrate and combination therapy favored the shift from LDL pattern B to the more buoyant, less atherogenic LDL. When the same parameters were examined in patients with TG levels >170 mg/dl at baseline, it was observed that they tended to have greater reductions in LDL pattern B than those with TG levels <170 mg/dl [164]

A multicenter, double-blind, placebo-controlled trial included patients (n = 611, age 18-79 years) with mixed hyperlipidemia (including patients with T2DM with LDL-C of 100 to 180 mg/dl) who were randomized for 12 weeks in a 3:3:3:1 ratio to ezetimibe/simvastatin 10/20 mg plus fenofibrate 160 mg, ezetimibe/simvastatin 10/20 mg, fenofibrate 160 mg or placebo [165]. The triple combination significantly decreased TG, non-HDL-C and apoB levels (-50.0%, -50.5%, and -44.7%, respectively) compared with all other treatments. The triple combination significantly reduced LDL-C levels (-45.8%) compared with the other treatments except the ezetimibe/simvastatin administration (-47.1%), whereas it significantly increased HDL-C (+18.7%) concentration compared with the other treatments except the fenofibrate administration (+18.2%) [165].

A study randomized 621 patients with mixed dyslipidemia to fenofibric acid, simvastatin or their combination [166]. The combination of feno-

fibric acid 135 mg/day with simvastatin 40 mg/day resulted in a greater increase in HDL-C (+18.9% versus +8.5%, $p < 0.001$) and a greater decrease in TG levels (-42.7% versus -22.4%, $p < 0.001$) compared with simvastatin 40 mg/day, as well as a greater reduction in LDL-C levels compared with fenofibric acid monotherapy (-25.3% versus -4.0%, $p < 0.001$). The combination of fenofibric acid with simvastatin 20 mg/day produced similar results. Furthermore, the combination of fenofibric acid with simvastatin 40 mg/day produced a greater reduction in VLDL-C ($p = 0.005$) and similar reductions in non-HDL-C, apoB, total cholesterol, and hsCRP compared with simvastatin 40 mg/day [166].

The combination of simvastatin with bezafibrate was assessed in one study, in which 48 patients receiving bezafibrate slow release (400 mg/day) and 100 patients receiving simvastatin 20 mg/day were given for 1 year the combination of both drugs [167]. After 1 year, a significant reduction in the concentration of total cholesterol (-23%), TG (-23%), LDL-C (-29%), and fibrinogen (-10%, all $p < 0.05$) compared with bezafibrate monotherapy and a significant increase in HDL-C levels (+25%, $p < 0.05$) compared with simvastatin monotherapy was observed. Of note, it was shown that during the initial 6 months of monotherapy the CVD event rate was 9.5% but it was reduced to 2% during the combination treatment [167].

A small study in 14 patients with T2DM showed that administration of simvastatin 40 mg/day combined with bezafibrate 400 mg/day over 8 weeks increased HDL-C and apoA-I levels ($p < 0.05$), but did not induce any significant increase in arylesterase ($p = 0.24$) or paraoxonase activity ($p = 0.37$) [168].

5.2 Atorvastatin plus fibrate combination treatment

In a study by Athyros *et al.*, 120 patients with T2DM and mixed hyperlipidemia, who were free of CHD, were randomized to atorvastatin (20 mg/day, $n = 40$), micronized fenofibrate (200 mg/day, $n = 40$), or atorvastatin 20 mg/day plus fenofibrate 200 mg/day ($n = 40$) [169]. The combination treatment led to greater reductions compared with atorvastatin or fenofibrate monotherapy (all $p < 0.05$) in the plasma concentration of LDL-C (-46% versus -40% and -15%, respectively), total cholesterol (-37% versus -31% and -16%, respectively), TGs (-50% versus -30% and -41%, respectively), and apoB (-33.3% versus -24.5% and -18.7%, respectively). The atorvastatin/fenofibrate combination resulted in a significant increase in HDL-C concentration (+22%; $p < 0.0001$ versus baseline; $p < 0.05$ versus atorvastatin), whereas the atorvastatin administration led to minor effects (+9%; $p < 0.0001$ versus baseline) and fenofibrate monotherapy resulted in a non-significant increase (+16%; p = NS). The atorvastatin/fenofibrate combination reduced the 10-year probability of myocardial infarction from 21.6% to 4.2% ($p < 0.005$ versus both monotherapies) [169].

In a randomized, open-label, cross-over study in patients with T2DM and atherogenic dyslipidemia, after treatment with either atorvastatin 10 mg or fenofibrate 160 mg for 6 weeks, patients received the combination of them for another 6 weeks. Combination therapy after 6 weeks of treatment led to a further decrease in LDL-C by 17% ($p = 0.05$) but did not show further benefit in total cholesterol, TG, HDL-C and proprotein convertase subtilisin kexin/type 9 (PCSK9) levels [170].

In a study that assessed the combination of fenofibric acid with atorvastatin in patients with mixed hyperlipidemia ($n = 577$), the fenofibric acid/atorvastatin combination led to significantly greater reduction in TG (-42.1% versus -23.2%, $p < 0.001$) and a significantly greater increase in HDL-C levels (+12.6% versus +5.3%, $p = 0.01$) compared with atorvastatin monotherapy, as well as a greater reduction in LDL-C concentration compared with fenofibric acid monotherapy (-35.4% versus -3.4%, $p < 0.001$) [171].

In another 12-week double-blind study, a total of 543 patients with mixed hyperlipidemia received atorvastatin 40 mg/day plus ezetimibe 10 mg/day and were randomized to fenofibric acid 135 mg/day or placebo [172]. The triple combination (fenofibric acid plus atorvastatin and ezetimibe) produced a significantly greater improvement in HDL-C (+13.0% versus +4.2%, $p < 0.001$) and TG levels (-57.3% versus -39.7%, $p < 0.001$), as well as a significantly greater effect on non-HDL-C, apoB, apoA-I, apoC-III, VLDL-C, and hsCRP, than atorvastatin/ezetimibe combination alone [172].

5.3 Rosuvastatin plus fibrate combination treatment

A randomized, parallel-group, multicenter trial, evaluated the effects of rosuvastatin plus fenofibrate in patients with T2DM and combined hyperlipidemia [173]. The study population ($n = 216$) was randomized to placebo/rosuvastatin, placebo/fenofibrate, rosuvastatin 5 mg/fenofibrate and

rosuvastatin 10 mg/fenofibrate. At 24 weeks, combination therapy of rosuvastatin 10 mg with fenofibrate significantly reduced TG levels compared with the placebo/rosuvastatin group (-47.1% versus -30.3%, p = 0.001). Regarding LDL-C concentration, the greater reductions were observed in placebo/rosuvastatin (-46.7%) compared with rosuvastatin 10 mg/fenofibrate (-42.2%, p = NS), placebo/fenofibrate (+0.7%, p < 0.001) and rosuvastatin 5 mg/fenofibrate (-34.1%, p < 0.001) [173].

In a study that randomized 1,377 patients with mixed hyperlipidemia for 12 weeks to either fenofibric acid 135 mg, rosuvastatin 10, 20, or 40 mg, or fenofibric acid plus rosuvastatin 10 or 20 mg, fenofibric acid plus rosuvastatin 20 mg produced greater improvements in TG (-42.9% versus -25.6%, p < 0.001) and HDL-C (+19.0% versus +10.3%, p < 0.001) levels compared with rosuvastatin 20 mg monotherapy [174]. Furthermore, a significantly greater LDL-C reduction (-38.8% versus -6.5%, p < 0.001) compared with fenofibric acid monotherapy was seen. The comparison of fenofibric acid plus rosuvastatin 10 mg with rosuvastatin 10 mg or with fenofibric acid monotherapy produced similar results. Fenofibric acid plus rosuvastatin 10 or 20 mg resulted in significantly greater reduction of hsCRP compared with the corresponding dose of rosuvastatin monotherapy (p <0.05) [174].

In another randomized, double-blind study, the combination of rosuvastatin 5 mg/day with fenofibric acid 135 mg/day for 12 weeks in patients with mixed dyslipidemia (n = 758) produced a significantly greater increase in HDL-C plasma concentration (+23.0% versus +12.4%, p < 0.001) and a significantly greater reduction in TG levels (-40.3% versus -17.5%, p < 0.001) compared with rosuvastatin monotherapy. Also, this combination caused a greater reduction in LDL-C levels (-28.7% versus -4.1%, p < 0.001) compared with fenofibric acid monotherapy [175].

In a post-hoc analysis of the two aforementioned trials [174, 175], 456 patients with T2DM and mixed dyslipidemia were treated with rosuvastatin (5, 10, or 20 mg), fenofibric acid 135 mg, or the combination of them for 12 weeks [176]. The realization of LDL-C <100 mg/dl, HDL-C >40/50 mg/dl in men and women, respectively, TG <150 mg/dl, non-HDL-C <130 mg/dl, and apoB <90 mg/dl and the combined targets of the above parameters were evaluated. Combination therapy with rosuvastatin plus fenofibric acid resulted in a significantly greater proportion of T2DM patients achieving the above individual and combined lipid targets than the corresponding dose rosuvastatin monotherapies [176].

A recent trial randomized patients to receive combination of fenofibric acid 135 mg/day with rosuvastatin 5, 10, or 20 mg/day or to monotherapy with simvastatin 40 mg/day [177]. The combination treatments produced significantly greater improvements in LDL-C, HDL-C, non-HDL-C, apoB, TG, hsCRP, total cholesterol and apoC-III compared with simvastatin 40 mg/day. Of note, optimal levels for LDL-C (<100 mg/dl, p < 0.001), non-HDL-C (<130 mg/dl, p < 0.001), apoB (<90 mg/dl, p ≤ 0.02), and TG (<150 mg/dl, p < 0.001) were achieved in a significantly higher proportion of patients in each fenofibric acid/rosuvastatin group compared with monotherapy with simvastatin 40 mg/day [177].

In a post-hoc analysis of two 12-week controlled studies and a 52-week extension study, patients were treated with fenofibric acid 135 mg, rosuvastatin 5, 10, 20, or 40 mg or rosuvastatin 5, 10, or 20 mg plus fenofibric acid 135 mg in the controlled studies, and with rosuvastatin 20 mg plus fenofibric acid 135 mg in the extension study [178]. When patients who had high hsCRP (≥2 mg/l) levels after 12 weeks of rosuvastatin 10, 20, or 40 mg monotherapy were examined, it was shown that hsCRP was reduced by approximately 36% after switching to rosuvastatin 20 mg plus fenofibric acid 135 mg for up to 52 weeks and approximately 36% of patients shifted from hsCRP levels ≥2 mg/l to a concentration <2 mg/l [178].

5.4 Pravastatin plus fibrate combination treatment

In a multicenter randomized, double-blind, parallel-arm study, a fixed-dose of pravastatin 40 mg/fenofibrate 160 mg or simvastatin 20 mg monotherapy was administered over 12 weeks in 291 patients with T2DM and mixed hyperlipidemia who were receiving simvastatin 20 mg and were not achieving lipid goals [179]. After 12 weeks of treatment, fixed-dose combination led to significantly greater improvements in non-HDL-C (-12.9%), TG (-28.6%), total cholesterol (-8.7%) and HDL-C concentration (+6.3%) compared with simvastatin (-6.8%, +5%, -5.2%, +1.8% respectively, all p < 0.05). In this study, the proportion of patients who achieved the non-HDL-C goal <130 mg/dl at week 12 was significantly greater in the fixed-dose group (42.4%) compared with simvastatin monotherapy (24.1%, p = 0.001). Similarly, the fenofibrate/pravastatin combination led to a significantly greater proportion of patients achieving the

combined end-point of non-HDL-C <130 mg/dl and LDL-C <100 mg/dl compared with simvastatin monotherapy (41% versus 26%, $p < 0.05$) [179].

Another study of the same group compared a triple therapy of pravastatin 40 mg/fenofibrate 160 mg plus ezetimibe 10 mg with dual therapy of simvastatin 20 mg plus ezetimibe 10 mg over 12 weeks in 273 patients with T2DM, mixed hyperlipidemia, and CVD [180]. After the initial 12-week treatment, all patients received the triple therapy for another 12-week period. After 12 weeks, the triple therapy was better in terms of reducing TG levels (-14.6% compared with dual therapy, $p = 0.007$), but dual therapy was better at terms of LDL-C decrease (-5.3% compared with triple therapy, $p = 0.05$). At week 24 the fenofibrate/pravastatin plus ezetimibe triple therapy resulted in significant reductions in the levels of non-HDL-C, TG, LDL-C, and apoB and significant increases in HDL-C and apoA-I levels compared with the baseline (on simvastatin 20) lipid levels [180].

5.5 Fluvastatin plus fibrate combination treatment

A 12-month randomized double-blind trial assessed the combination of fluvastatin 80 mg with fenofibrate 200 mg in 48 patients with combined hyperlipidemia, T2DM and CVD [181]. After 12 months, a greater effect of the combination therapy on the levels of LDL-C, total cholesterol, and HDL-C was observed (-35%, -32%, +34%, respectively) compared with fluvastatin monotherapy (-25%, -17%, +14%, respectively, all $p < 0.05$ between groups) [181].

Another study compared the effect on LDL subfractions of fluvastatin/fenofibrate combination (80/200 mg) or simvastatin 20 mg/ezetimibe combination (20/10 mg) in 56 patients with metabolic syndrome and/or T2DM [182]. The simvastatin/ezetimibe combination produced greater reduction in total cholesterol and LDL-C levels in the whole population compared with fluvastatin/fenofibrate. No effect of therapy on LDL subfraction was shown in patients with no predominance of small dense LDL subfractions, but when patients with increased small dense LDL subfractions were assessed a greater improvement of TG levels and LDL radius of fluvastatin/fenofibrate compared with simvastatin/ezetimibe treatment was observed [182].

5.6 Pitavastatin plus fibrate combination treatment

Pitavastatin has not been studied in combination with fibrates in patients with T2DM.

6. Effects of statin-fibrate combination on microvascular complications in patients with T2DM

The effect of fenofibrate on the incidence of laser treatment for diabetic retinopathy was examined as an endpoint in the main analysis of FIELD [142]. Fenofibrate led to lower numbers of patients receiving laser treatment for retinopathy compared with placebo (178 versus 253, difference between groups 1.6%, $p = 0.0003$). A significant benefit of fenofibrate administration was observed in the rate of first or any laser treatment for maculopathy or for proliferative retinopathy without macular involvement. A FIELD sub-study showed that the progression of diabetic retinopathy was reduced significantly in patients with retinopathy at baseline [183]. A beneficial effect of fenofibrate treatment on non-traumatic amputations was also shown in another FIELD sub-study [184].

The effects of an intensive glycemia and lipid treatment and of a standard therapy on the progression of diabetic retinopathy were assessed in a subgroup of 2,856 participants of the ACCORD trial [185]. After 4 years, the rate of progression of diabetic retinopathy was 6.5% with the simvastatin/fenofibrate intensive dyslipidemia therapy, and 10.2% with simvastatin/placebo (adjusted odds ratio (OR) 0.60, 95% CI 0.42-0.87, $p = 0.006$), whereas it was 7.3% with intensive glycemia treatment and 10.4% with standard therapy (adjusted OR 0.67, 95% CI 0.51-0.87, $p = 0.003$) [185].

Fenofibrate administration is associated with an increase in creatinine serum levels [186, 187]. Possible explanations for this increase include a decrease in creatinine clearance, an impairment of vasodilatory prostaglandin generation or an increase of the metabolic production of creatinine [186-189]. On the other hand, the increase of serum creatinine with fenofibrate is transient and reversible even without treatment discontinuation [190]. Furthermore, evidence exists that fenofibrate exerts a protective action against pathological changes in diabetic nephropathy and hypertensive glomerulosclerosis [190].

In the FIELD study, fenofibrate reduced the rate of progression to albuminuria [142]. In the ACCORD Lipid study, serum creatinine levels

were increased from 0.93 to 1.10 mg/dl in the fenofibrate group, whereas in the placebo group, they were increased from 0.93 to 1.04 mg/dl ($p < 0.05$) [154]. Furthermore, significantly more patients in the fenofibrate group experienced at least one increased creatinine measurement (>1.3 mg/dl in women, >1.5 mg/dl in men), whereas discontinuation because of a decrease in the estimated glomerular filtration rate (GFR) was observed in 2.4% of patients in the fenofibrate group and 1.1% in the placebo group ($p < 0.05$). However, these differences did not result in a significant difference in the incidence of end-stage renal disease and the need for dialysis between treatment groups (75 patients in the fenofibrate group versus 77 in the placebo group). Notably, a lower incidence of microalbuminuria (38.2% versus 41.6%, $p = 0.01$) and macroalbuminuria (10.5% versus 12.3%, $p = 0.04$) was observed in the fenofibrate group compared with the placebo group [154].

7. Effects of statin-fibrate combination therapy on CVD risk in patients with T2DM

There is limited clinical evidence examining the beneficial effects of statin plus fibrate combination on CVD events. In the ACCORD trial [154], patients with T2DM (n = 5,518) who were already treated with open-label simvastatin were randomly allocated to receive fenofibrate or placebo. The primary outcome of the study was the first occurrence of a major CVD event such as nonfatal myocardial infarction, nonfatal stroke, or death from CVD causes. The mean duration of follow-up was 4.7 years for the primary outcome. By the end of the study, the fenofibrate/simvastatin combination resulted in greater improvements of total cholesterol, TG and HDL-C ($p = 0.02$, $p < 0.001$, $p = 0.01$, respectively) when compared with the placebo/simvastatin group. On the other hand, there was no significant difference in the reduction of LDL-C levels between treatment groups ($p = 0.16$). The annual rate of the primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group ($p = 0.32$). In addition, there was no significant difference in the rates of secondary outcomes between groups (primary outcome plus revascularization or hospitalization for congestive heart failure, $p = 0.30$; major CHD event, $p = 0.26$; nonfatal myocardial infarction, $p = 0.039$; any stroke, $p = 0.80$; non-fatal stroke, $p = 0.48$; death from any cause, $p = 0.33$; death from CVD cause, $p = 0.26$; fatal or nonfatal congestive heart failure, $p = 0.1$). As a consequence, the combination of fenofibrate and simvastatin did not significantly reduce the rate of major CVD events compared with simvastatin alone. Similar results were seen comparing patients <65 years of age (n = 3,660) versus those ≥65 years (n = 1,858) [154].

These observations suggest that the addition of fenofibrate to simvastatin did not produce a significant decrease in the rate of CVD events. However, the ACCORD Lipid study had some limitations; the enrollment of patients did not achieve the predetermined power and simvastatin was given in open-label fashion.

It should also be mentioned that in a prespecified analysis in the subgroup of ACCORD patients (regardless of age) with high baseline TG (≥204 mg/dl) and low baseline HDL-C (≤34 mg/d) values, there was a 28% ($p < 0.05$) reduction in the relative risk of CVD events in the fenofibrate plus simvastatin group. It should be mentioned that the effects of the addition of fenofibrate in the subgroup of patients with high TG and low HDL-C values are similar to previous subgroup analyses in other fibrate trials [136, 191-196]. For example, a significant reduction of CVD risk (-27% relative risk reduction, 95% CI 9-42, $p = 0.005$) was seen with fenofibrate in patients with marked dyslipidemia in a sub-analysis of the FIELD trial [197].

A recent study examined the effects of simvastatin plus fenofibrate or placebo in postprandial concentrations of plasma TG, apoB48, and apoC-III, over 10 hours, after an oral fat load in 139 subjects (mean age 61 years) of the ACCORD Lipid trial [198]. The fenofibrate plus simvastatin administration resulted in a significant reduction in TG incremental area under the curve (IAUC) compared with the placebo plus simvastatin group (572 (352-907) versus 770 (429-1,420) mg/dl/h (adjusted $p = 0.008$)), as well as in a significant reduction in plasma apoB48 IAUC (23.2 ± 16.3 versus 35.2 ± 28.6 µg/ml/h (adjusted $p = 0.008$)). However, plasma apoC-III IAUC was not different between fenofibrate and placebo groups, despite the fact that plasma apoC-III concentrations were reduced by 10-20% with fenofibrate compared with placebo during the 10-hour study. Notably, although the fenofibrate-induced reduction of postprandial TG IAUC was constant across the entire range of fasting TG levels, the postprandial apoB48 IAUC was only reduced in subjects with increased fasting TG levels [198]. The fact that the levels of atherogenic apoB48 were reduced only in individuals with increased fasting TG levels may provide an explanation for the results of the overall ACCORD Lipid trial, which suggested a benefit from fenofibrate

plus simvastatin treatment only in individuals with mixed dyslipidemia.

Overall, based on current evidence, it seems that the administration of fibrates in patients with atherogenic dyslipidemia, either as monotherapy or combined with statins, is associated with a reduction of CVD risk. Nonetheless, this effect was not significant in patients without mixed dyslipidemia [199].

8. Safety

The combination of statin with fibrates is generally believed to increase the risk of myopathy and rhabdomyolysis [127, 200-202]. Renal and/or hepatic insufficiency, increased age, and administration of several medications are suggested risk factors for the development of these adverse events [203-205].

A meta-analysis that estimated the safety of statin with fenofibrate combination included 1,628 subjects who participated in a total of 6 studies [206]. The results showed that the rates of serious adverse events (2.0% versus 1.5%, p = 0.71) and adverse events related to study drug (10.9% versus 11.0%, p = 0.95), as well as the rate of discontinuation due to any adverse events (4.5% versus 3.1%, p = 0.20) or any adverse events (42% versus 41%, p = 0.82) were not significantly different between statin and statin/fenofibrate combination. Myopathy or rhabdomyolysis did not appear in any of the 1,628 subjects included in this meta-analysis. However, a significantly greater incidence of alanine aminotransferase and/or aspartate aminotransferase ≥3 times the upper limit of normal was observed in the combination treatment compared with statin monotherapy (3.1% versus 0.2%, p = 0.0009) [206]. It should be mentioned that the fenofibrate or fenofibric acid plus statin combination is safer compared with gemfibrozil plus statin combination [207, 208]. Hence, gemfibrozil should not be combined with a statin; treatment with other fibrates should be carried out.

9. Conclusions

Statin therapy has been shown to be both effective and safe in the treatment of hyperlipidemia. However, in high CVD risk patients such as T2DM patients there is a considerable residual CVD risk despite statin therapy. Indeed, the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines establish goals for both LDL-C and non-HDL-C in high-risk patients [209]. As a result, it is of great importance to identify these patients and take the necessary steps to minimize as much as possible this residual CVD risk. To achieve this, a higher titration of statin dosage could be given in order to achieve the desired goals. Indeed, a high-dose statin therapy has been associated with improved outcomes [210]. However, this increase of statin dosage is not always desirable or even safe. Indeed, statin side effects such as myopathy are dose related [211]. Furthermore, although they are very efficacious in terms of CVD event reduction, higher statin dosages are associated with a greater incidence of T2DM development [212, 213].

Beyond LDL-C levels, HDL-C and TG have an important role in CVD. Indeed, among subjects with LDL-C <70 mg/dl in the Treating to New Targets (TNT) study, those with low HDL-C levels had a greater incidence of CVD events compared with subjects with high HDL-C levels [214]. Similarly, among subjects with LDL-C <70 mg/dl in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study a concentration of TG >150 mg/dl was associated with a 27% higher CVD risk compared with TG levels <150 mg/dl [215]. In addition, the combination of elevated TG and decreased HDL-C levels was associated with increased CVD risk independently of LDL-C levels. Therefore, the combination of a statin with a fibrate may have an important role to play in the minimization of residual CVD risk during statin treatment.

Based on the current evidence, statin/fibrate combination therapy favorably alters the lipid profile of T2DM patients characterized by high TG and low HDL-C profile, which is associated with increased CVD risk. The micro- and macrovascular benefits associated with the statin/fibrate administration makes this combination an attractive treatment choice for the T2DM patient. However, to date, limited data exists on the effect of statin/fibrate combinations on "hard" clinical outcomes in T2DM patients with high TG and low HDL-C values. Based on current evidence, statins continue to be the cornerstone of dyslipidemia management. A fibrate could be added in patients with mixed dyslipidemia that do not reach the desired non-HDL-C or TG and/or HDL-C concentrations. Certainly, larger prospective studies are needed, specifically those designed to assess the effect of statin/fibrate combination on CVD morbidity and mortality of T2DM subjects with mixed dyslipidemia.

Disclosures: There were no declared conflicts of interest. This manuscript has been prepared independently.

Some of the authors have attended conferences sponsored by various pharmaceutical companies.

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