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Vascular and metabolic effects of treatment of combined hyperlipidemia:

Focus on statins and fibrates

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Abstract

Combined hyperlipidemia results from overproduction of hepatically synthesized apolipoprotein B in very low-density lipoproteins in association with reduced lipoprotein lipase activity. Thus, this condition is typically characterized by concurrent elevations in total cholesterol and triglycerides with decreased high-density lipoprotein cholesterol. High levels of apolipoprotein B-containing lipoproteins, most prominently carried by low-density lipoprotein (LDL) particles, are an important risk factor for coronary heart disease. Statin therapy is highly effective at lowering LDL cholesterol. Despite the benefits of statin treatment for lowering total and LDL cholesterol, many statin-treated patients still have initial or recurrent coronary heart disease events. In this regard, combined therapy with statins and fibrates is more effective in controlling atherogenic dyslipidemia in patients with combined hyperlipidemia than either drug alone. Furthermore, statins and fibrates activate PPAR α in a synergistic manner providing a molecular rationale for combination treatment in coronary heart disease. Endothelial dysfunction associated with cardiovascular diseases may contribute to insulin resistance so that there may also be additional beneficial metabolic effects of combined statin/fibrates therapy. However, there has been little published evidence that combined therapy is synergistic or even better than monotherapy alone in clinical studies. Therefore, there is a great need to study the effects of combination therapy in patients. When statins are combined with gemfibrozil therapy, this is more likely to be accompanied by myopathy. However, this limitation is not observed when fenofibrate, bezafibrate, or ciprofibrate are used in combination therapy.

Keywords

Statins; Fibrates; Endothelial function; Insulin resistance; Combined hyperlipidemia; Safety

1. Introduction

Combined hyperlipidemia is typically characterized by elevations in total cholesterol and triglycerides with decreased high-density lipoprotein (HDL) cholesterol. This common

disorder results from overproduction of hepatically synthesized apolipoprotein B in very low-density lipoproteins. High levels of apolipoprotein B-containing lipoproteins, most prominently carried by low-density lipoprotein (LDL) particles, are an important risk factor for coronary heart disease (CHD). Statin therapy is highly effective at lowering total and LDL cholesterol. Nevertheless, many statin-treated patients still have initial or recurrent CHD events even with reduction in their LDL cholesterol levels. Indeed, in intervention studies with statins, subgroup analysis of patients with varying baseline lipid levels shows that interactions between relative risk reduction and baseline triglycerides and HDL cholesterol levels are not significant when analyzed as continuous variables (by contrast with LDL cholesterol levels) [1-3].

Many studies show positive associations between serum triglycerides and CHD risk [4,5]. Importantly, low HDL cholesterol levels predict risk for CHD independent of other prognostic factors [6,7]. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) Study shows that compared with placebo, gemfibrozil therapy increases mean HDL cholesterol level by 6% and reduces the mean triglyceride level by 31% and the mean total cholesterol level by 4% in patients with CHD whose primary lipid abnormality is low HDL cholesterol level. LDL cholesterol levels do not differ significantly between the groups. Gemfibrozil therapy reduces relative risk of nonfatal myocardial infarction or death from coronary causes by 22% and the combined outcome of death from CHD, nonfatal myocardial infarction, and stroke by 24% [8].

Several studies report that combined therapy with statins and fibrates is more effective in controlling atherogenic dyslipidemia in patients with combined hyperlipidemia than either drug alone [9-12]. Unfortunately, the combination of statins and the most extensively studied fibrate, gemfibrozil, is more likely to be accompanied by severe myopathy [13,14]. This may be because gemfibrozil significantly affects the pharmacokinetic of statins resulting in increased plasma levels of statins [7,15,16]. Interestingly, other recent studies demonstrate that this limitation is not observed with statin and other fibrates in combination therapy [10,11, 14,17-19].

CHD is frequently associated with insulin resistance and disorders of metabolic homeostasis including obesity and combined hyperlipidemia. Endothelial dysfunction associated with cardiovascular diseases may contribute to insulin resistance [20,21]. Endothelial dysfunction associated with metabolic syndrome and other insulin resistant states is characterized by impaired nitric oxide (NO) release from endothelium with decreased blood flow to insulin target tissues [22]. Insulin signaling pathways regulating glucose transport in skeletal muscle also regulate production of NO in endothelium. Pro-inflammatory signaling stimulated by glucotoxicity and lipotoxicity in dysmetabolic states contributes to shared mechanisms of insulin resistance and endothelial dysfunction. The molecular and cellular mechanisms that mediate insulin resistance and endothelial dysfunction are multiple and reflect complex interactions between inflammatory and metabolic pathways [21,23]. Interestingly, insulin-stimulated increases in blood flow account for up to 40% of the increase in insulin-stimulated glucose disposal in skeletal muscle [22]. The central role of NO in regulating the metabolic actions of insulin is evident by the presence of insulin resistance and hypertension in eNOS knockout mice [24,25]. Thus, improvement in endothelial function is predicted to improve insulin sensitivity and this may be one mechanism by which statins and fibrates decrease the incidence of CHD.

Excess body fat is frequently associated with dyslipidemia, metabolic syndrome, and atherosclerotic vascular diseases. Adiponectin is one of a number of proteins secreted by adipose cells that may couple regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance [26]. Decreased plasma adiponectin levels are observed in patients with type 2 diabetes and coronary artery disease [27,28]. Thus, decreased

levels of adiponectin may play a key role in the development of insulin resistance. It is controversial whether statin therapy can improve or worsen insulin resistance in humans [29-31]. By contrast, fibrates improve insulin sensitivity in animal models through activation of peroxisome proliferator-activated receptor (PPAR) α [32,33]. Moreover, a recent clinical study reports that fenofibrate improves insulin sensitivity in patients with metabolic syndrome [34,35]. Therefore, effects of statins, fibrates, or combination therapy to raise adiponectin levels may be an important benefit resulting from the treatment of combined hyperlipidemia.

Laboratory studies also demonstrate synergistic effects of statins combined with fibrates. Statins inhibit the Rho-signaling pathway and activate PPAR α [36] and acute anti-inflammatory properties of statins involve PPAR α via inhibition of the protein kinase C signaling pathway [37]. Indeed, fibrate and statins synergistically increase the transcriptional activities of PPAR α /retinoid X receptor (RXR) α and decrease the transactivation of nuclear transcription factor NF- κ B [38]. Therefore, evidence that statins combined with fibrates activate PPAR α in a synergistic manner provides a molecular rationale for combination treatment with statins and fibrates in CHD.

Because the mechanisms underlying the biological actions of statin and fibrate therapies are distinct, combined therapy with statins and fibrates therapies may be more effective in controlling atherogenic dyslipidemia and improving insulin sensitivity in patients with combined hyperlipidemia than either drug alone. Furthermore, there is evidence that statins combined with fibrates activate PPAR α in a synergistic manner providing a better effect. In this review, we will discuss the safety and vascular and metabolic effects of statins combined with fibrates in patients with combined hyperlipidemia.

2. Vascular effects of combined therapy

2.1. Effects on lipoproteins and lipoprotein particles

Several studies report that combined therapy with statins and fibrates is more effective in controlling atherogenic dyslipidemia in patients with combined hyperlipidemia than either drug alone (Table 1) [9-12]. In one study, the effects of combined simvastatin/ciprofibrate on lipoprotein patterns were compared with each drug alone in patients with combined hyperlipidemia [9]. After a 4-week placebo period, patients were randomly assigned to receive simvastatin (20 mg daily, $n=20$), ciprofibrate (100 mg daily, $n=20$), or combined therapy ($n=20$) for 12 weeks. Combination therapy or ciprofibrate alone significantly reduces plasma triglycerides. Combination therapy or simvastatin alone significantly reduces LDL cholesterol when compared with ciprofibrate therapy alone. Ciprofibrate or combination therapy increases LDL particle size, whereas simvastatin alone has no significant effect on this parameter. The cholesterol content of LDL particles is reduced in dense LDL particles (LDL3-5) and increased in light (LDL1-2) subfractions with ciprofibrate or combination therapy, whereas simvastatin reduces the cholesterol content of all LDL subfractions except LDL2. Ciprofibrate or combination therapy also reduces the triglycerides content of all LDL subfractions. More importantly, there are interactions between HDL and LDL particles that are clinically relevant among patients with low HDL cholesterol disorders [7]. In the VA-HIT study, changes in conventional lipid risk factors with gemfibrozil treatment only partially explain the reductions in CHD events. LDL and HDL particle subclass concentrations predict coronary events and are favorably changed by gemfibrozil therapy. Importantly, both low levels of HDL particles and high levels of LDL particles were independent predictors of cardiac events. For total LDL and HDL particles, odds ratios predicting CHD benefit were 1.28 (95% CI, 1.12 to 1.47) and 0.71 (95% CI, 0.61 to 0.81), respectively. These observations provide one rationale for combined statin-fibrate therapy [39]. In another study of 389 patients with familial combined hyperlipidemia randomly assigned to pravastatin plus gemfibrozil, simvastatin plus gemfibrozil or simvastatin plus ciprofibrate, all 3 combination treatments are more effective

in normalizing lipid profiles than monotherapy with any of the drugs [40]. Statin-fibrate combinations used in this study are safe. Recently, in a placebo-controlled trial, we demonstrated that fenofibrate therapy significantly decreases total cholesterol, non-HDL cholesterol, apolipoprotein B, and triglycerides while increasing HDL cholesterol and apolipoprotein A-I in patients with hypertriglyceridemia [34,41]. Patients with low levels of HDL cholesterol during statin treatment have significant improvements in HDL cholesterol, total cholesterol to HDL ratio, and LDL to HDL ratio with fibrate therapy [42].

The effectiveness and tolerability of simvastatin plus fenofibrate compared with simvastatin monotherapy were tested for reducing elevated triglycerides levels in combined hyperlipidemia (the SAFARI trial) [12]. From baseline to 12 weeks, combination therapy significantly reduces median triglyceride levels and mean LDL cholesterol levels when compared with simvastatin monotherapy. In addition, combination therapy significantly increases HDL cholesterol levels when compared with simvastatin alone. We investigate the effects of atorvastatin, fenofibrate and combination therapy in patients with combined hyperlipidemia. Fifty-six patients were given atorvastatin 10 mg and placebo, atorvastatin 10 mg and fenofibrate 200 mg, or fenofibrate 200 mg and placebo daily during each 2 month treatment period of a randomized, double-blind, placebo-controlled cross-over trial with two 2 month washout periods. Combined therapy with atorvastatin and fenofibrate significantly improves the lipoprotein profile when compared with atorvastatin or fenofibrate alone in combined hyperlipidemia (Fig. 1) [18].

2.2. Effects on Vascular Function

2.2.1. Effects on Vasomotor Function—In patients with atherosclerosis, cholesterol lowering with statins improves endothelial function as evidenced by limiting acetylcholine-induced vasoconstriction or peripheral NO-mediated vascular relaxation [43]. Statin therapy reduces degradation of NO by oxidized lipoproteins and may contribute to its clinical benefits by ameliorating endothelial dysfunction. With respect to fibrates, several studies have examined vasomotor function, but results are controversial. Improved flow-mediated dilation after oral fat loading has been shown in type 2 diabetes after 12 weeks of ciprofibrate therapy [44]. However, similar benefits are not observed in healthy volunteers after 3 weeks of gemfibrozil [45]. In patients who underwent coronary angioplasty, exercise-induced coronary artery dilation measured by quantitative coronary angiogram increases after bezafibrate therapy when compared with placebo [46]. In patients with hypertriglyceridemia, fenofibrate significantly improves flow-mediated dilation [47]. We also observe that fenofibrate significantly improves percent flow-mediated dilator response to hyperemia in these patients [34,41].

It is not clear why specific fibrates have slightly different effects. Bezafibrate, ciprofibrate, and fenofibrate are related to the parent compound, clofibrate by their chemical structures. Gemfibrozil is a nonhalogenated phenoxy-pentanoic acid and thus is distinct from other halogenated compounds. A range of potencies for various fibrates to activate human PPAR α exist. The activity of fenofibrate in a cell-based transactivation assay for PPAR α is 40% greater than that of either bezafibrate or clofibrate. Both clofibrate and fenofibrate are dual activators of PPAR α and PPAR γ with 10-fold selectivity for PPAR α while bezafibrate activates all three PPAR subtypes at comparable doses [48]. Indeed, several large intervention trials have investigated the potential of fibrates to reduce cardiovascular events. The results have varied widely [49]. Reasons for the differences between the outcomes of these studies are most likely related to lipid characteristics of the study subjects as fibrates seem more substrate dependent than statins [50].

A plausible mechanism underlying the improvement of vasodilation following fibrates therapy is the change in lipoprotein profile. Consistent with this hypothesis, we observe significant correlations between improvement in flow-mediated dilation and changes in total cholesterol,

LDL cholesterol, and non-HDL cholesterol levels. Furthermore, fenofibrate increases expression of endothelial NO synthase (eNOS) in cultured endothelial cells and increases NO bioactivity by ameliorating oxidative stress [51,52]. Interestingly, PPAR α ligands also decrease expression and activity of inducible NOS, providing another mechanism for their anti-inflammatory effects. Suppression of inflammatory signaling pathways by PPAR α activation is an additional mechanism whereby fenofibrate may enhance eNOS activity [53].

There has been little published evidence that combined therapy is synergistic or even better than monotherapy alone. We demonstrate that atorvastatin, fenofibrate, or combined therapy, significantly improves percent flow-mediated dilator response to hyperemia relative to baseline measurements. Of note, combined therapy significantly improves this response more than atorvastatin or fenofibrate alone (Fig. 2). Following combination therapy, improvement in flow-mediated dilation correlates with changes in total cholesterol, triglycerides, and apolipoprotein B levels [18].

2.2.2. Effects on inflammation—The expression of many adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular CAM-1 (ICAM-1), is regulated by NF- κ B. In addition to VCAM-1, ICAM-1, and E-selectin, NF- κ B also stimulates transcription of genes encoding chemoattractant factors including monocyte chemoattractant peptide and macrophage stimulatory factor. Importantly, elevated levels of free fatty acids associated with insulin resistance, obesity, diabetes, and the metabolic syndrome cause endothelial dysfunction by activating innate immune inflammatory pathways upstream of NF- κ B. Activation of NF- κ B also increases synthesis and release of proinflammatory cytokines interleukin-1, interleukin-2, and interleukin-6, which activate inflammatory cells and enhance their attachment to the vessel wall (Fig. 3) [54,55].

Activation of NF- κ B is inhibited by PPAR α agonists by mechanisms that include increased synthesis of I κ B and thus inhibited translocation of the active component of NF- κ B into the nucleus [56]. PPAR α activators reduce cytokine-induced expression of VCAM-1 and ICAM-1 in cultures of human carotid artery endothelial cells [57]. Fenofibrate almost completely abolishes C-reactive protein (CRP)-induced expression of monocyte chemoattractant protein-1 (MCP-1) in human umbilical vein endothelial cells [58]. In clinical studies, 3 month therapy with the PPAR α agonist fenofibrate decreases the circulating levels of VCAM-1 and ICAM-1 in the fasting state of patients with hypertriglyceridemia [47]. Fenofibrate or atorvastatin lowers plasma concentrations of adhesion molecules E-selectin and VCAM-1 in patients with type 2 diabetes mellitus and mixed hyperlipoproteinemia [59]. In 54 patients with type IIb dyslipidemia, fenofibrate, atorvastatin, or simvastatin significantly decreases MCP-1 secretion from monocytes and soluble MCP-1 levels [60]. Thus, hypolipidemic drugs may directly inhibit the activity of monocytes. However, effects of combined therapy with statins and fibrates on adhesion molecules have not been reported.

Effect of statins and fenofibrate on CRP expression has been studied in nonatherosclerotic transgenic mice expressing human CRP [61]. Therapy with statins and fenofibrate decreases interleukin-1 β -induced plasma CRP levels independently of cholesterol lowering. These direct anti-inflammatory effects *in vivo* occur at the transcriptional level and have been confirmed in cultured human liver slices and in human hepatoma cells. A molecular rationale for suppression of interleukin-1-induced CRP transcription is provided by showing that statins and fenofibrate up-regulate I κ B protein expression. This results in reduced nuclear translocation of p50-NF- κ B and thereby decreases amounts of nuclear p50-NF- κ B and CCAAT/enhancer binding protein beta (C/EBP β) complexes, which help determine CRP transcription rate. These results provide conclusive evidence for a direct suppressive effect of statins and fenofibrate on CRP expression independent of cholesterol lowering and atherogenesis.

Statins lower CRP in hyperlipidemic coronary patients [62,63]. Fenofibrate therapy significantly lowers CRP in combined hyperlipidemia [64]. We also observe that fenofibrate therapy significantly lowers high sensitivity CRP (hsCRP) levels in patients with hypertriglyceridemia [34]. With regard to combined therapy with statins and fibrates, we report that atorvastatin/fenofibrate combination therapy significantly lowers plasma hsCRP levels relative to baseline measurements in combined hyperlipidemia. However, the magnitude of reduction with combination therapy is similar to monotherapy with either agent [18]. Another recent study confirms our initial observations. Simvastatin, fenofibrate, and combination therapy for 12 weeks each significantly lowers hsCRP in patients with type 2 diabetes and mixed dyslipidemia. However, combination therapy is no more effective than either form of monotherapy [65].

Simvastatin causes significant reductions in levels of tumor necrosis factor (TNF)- α in hypercholesterolemic patients when compared with diet alone [66]. Pretreatment of rat cardiac myocytes with fenofibrate inhibits lipopolysaccharide-induced TNF- α mRNA and protein expression in a dose-dependent manner [67]. Fenofibrate significantly lowers plasma levels of TNF- α in patients with hypertriglyceridemia [41]. In human aortic smooth muscle cells, PPAR α activators inhibit expression of interleukin-6. In patients with mild hyperlipidemia, fenofibrate therapy decreases circulating levels of interleukin-6 [68]. Elevated levels of TNF- α and interleukin-6 are associated with increased risk of future myocardial infarction in otherwise healthy women and men. Atorvastatin therapy results in significant reductions of interleukin-6 and interleukin-1 in hypercholesterolemic patients when compared with diet alone [69]. Fenofibrate therapy significantly reduces interleukin-1 β mRNA expression and release by cultured monocytes from patients with type IIb dyslipidemia [70].

The proinflammatory mediator CD40 ligand (CD40L) is expressed on CD4+ T cells and activated platelets. CD40L plays an important role in a cascade of inflammatory and proatherothrombotic functions [71]. Early statin therapy after acute coronary syndromes counters the risk associated with elevated sCD40L [72]. In cultured human umbilical vein endothelial cells, fenofibrate significantly diminishes expression of CD40, CD40L and gelatinase activities induced by CRP [73]. Fenofibrate therapy reduces soluble CD40L levels in patients with hyperlipidemia [64,74]. The effects of combined therapy with statins and fibrates on TNF- α , interleukin, or CD40L have not been evaluated yet.

2.2.3. Effects on hemostasis—Fluvastatin reduces tissue factor expression and macrophage accumulation in rabbit carotid intimal lesions independently of cholesterol lowering [75]. In a clinical study, simvastatin 20 mg daily during 14 weeks in hypercholesterolemic patients with coronary artery disease significantly lowers plasma levels of tissue factor and plasminogen activator inhibitor type 1 (PAI-1). However, no significant correlations between lipoprotein levels and levels of plaque stability or thrombogenicity markers are determined [76]. PPAR α also inhibits expression of tissue factor in human monocytes and macrophages [77]. However, no effects of fenofibrate on tissue factor activity are observed in patients. Furthermore, no correlations between the degree of changes in lipoproteins or CRP levels and the degree of changes in tissue factor activity on fenofibrate were detectable [41].

Several lipid-lowering agents potentiate fibrinolysis independent of alterations in plasma lipoproteins. Simvastatin reduces levels of PAI-1 antigen released from smooth muscle cells and endothelial cells [78]. The effects of statins on fibrinolysis in humans are controversial [79,80]. We demonstrate that simvastatin therapy significantly reduces PAI-1 in hypercholesterolemic patients with coronary artery disease [76]. However, simvastatin does not significantly change PAI-1 antigen levels from pretreatment in hypercholesterolemic postmenopausal women [81]. By contrast, gemfibrozil, bezafibrate, and fenofibrate reduce

PAI-1 and fibrinogen levels in hypercholesterolemic subjects [82,83]. These actions of fibrates on fibrinogen and PAI-1 antigen levels may decrease thrombogenesis. We observe that fenofibrate significantly reduces fibrinogen and PAI-1 antigen levels [34,41]. In the same study, fenofibrate decreases fibrinogen levels in patients with type IIa and type IIb hyperlipidemia, but pravastatin and atorvastatin do not [84]. Thus, beneficial effects of lipid-lowering drugs cannot be explained solely by their lipid-lowering effects. In our study, fenofibrate alone or combined therapy with atorvastatin significantly lowers plasma fibrinogen levels relative to baseline measurements. Of note, combined therapy reduces this more than atorvastatin alone [18].

2.2.4. Effects on plaque stability—Biologically active lipids in the atheroma not only create mechanical instability but also promote oxidative stress and inflammatory responses such as enhanced monocyte migration. Therefore, lipid-lowering agents that influence the matrix degradation cascade in macrophage-rich areas of the atheroma promote mechanical stability within the plaque. Lowering blood LDL cholesterol levels facilitates plaque stability through a reduction in plaque size as well as by altering the physiochemical properties of lipid cores [54]. However, reduction in plaque size as a result of lipid lowering requires an extended period of time with minimal changes when assessed by angiography. Thus, clinical benefits from lipid lowering are more likely due to decreases in macrophage accumulation in atherosclerotic lesions and inhibition of matrix metalloproteinase (MMP)-9 production by activated macrophages.

Intimal smooth muscle cells in subjects with lower cholesterol display reduced expression of MMP-9 when compared with subjects with higher cholesterol levels [85]. In animal studies, lipid-lowering therapies diminish accumulation of macrophages as well as macrophage expression of MMP-9 [86]. These effects are reversed by co-administration of mevalonate, thus providing further insights into direct antiatherosclerotic actions of statins [87]. PPAR activators also inhibit expression of MMP-9 [88]. This may help prevent rupture of atherosclerotic plaques and subsequent thrombosis. Overexpression of endothelial NO synthase in cultured cells significantly decreases MMP-2 and MMP-9 activities and simultaneously increases tissue inhibitor of matrix metalloproteinase (TIMP)-2 levels in conditioned medium [89]. TNF- α , a proinflammatory cytokine, stimulates synthesis and secretion of MMP-9 [90]. Despite these *in vitro* studies, we observe that fenofibrate therapy in humans does not significantly change serological markers of plaque stability; however, we did observe a weak correlation between the degree of changes in TNF- α and the degree of change in MMP-9 activity with fenofibrate therapy [41]. However, there has been no data published regarding effects of combination therapy on plaque stability.

3. Metabolic effects of combined therapy

The adipocyte is an active endocrine secretory cell releasing free fatty acids and producing cytokines including TNF- α , interleukins, PAI-1, leptin, and adiponectin. Adiponectin is the most abundant adipocytokine secreted by adipose cells that may couple regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance [26]. Adiponectin stimulates production of NO [91], reduces expression of adhesion molecules in endothelial cells, and decreases cytokine production from macrophages by inhibiting NF- κ B signaling through cAMP-dependent pathways [92,93]. Hypoadiponectinemia correlates significantly and independently with coronary artery disease and the metabolic syndrome [94,95]. Plasma adiponectin levels are an inverse predictor of cardiovascular outcome in patients with end-stage renal disease [96]. In a prospective cohort study, plasma adiponectin concentrations are inversely associated with risk of myocardial infarction [97]. Thus, therapeutic approaches that increase plasma adiponectin levels or adiponectin tissue sensitivity

may improve insulin sensitivity and be beneficial for preventing or treating the metabolic syndrome, diabetes mellitus, and atherosclerosis.

The effects of statins on insulin sensitivity are controversial. In some studies, simvastatin and atorvastatin improve insulin sensitivity in diabetic patients [29]. However, others report that simvastatin either had no effect or worsened insulin sensitivity in diabetic patients [30,31]. Recent large-scale clinical studies demonstrate that high-dose statins may increase, rather than decrease, the onset of new diabetes [3,98]. Atorvastatin 80 mg is associated with an increased risk of developing a $HbA_{1c} > 6$ both in non-diabetics (adjusted HR 1.78) and in diabetics (adjusted HR 2.36). However, we observe that simvastatin 20 mg or atorvastatin 10 mg does not change plasma levels of adiponectin or insulin sensitivity [18,99]. A 12-week treatment with pravastatin 40 mg daily does not change plasma levels of adiponectin or insulin sensitivity in healthy volunteers [100].

PPAR α ligands improve insulin sensitivity and reduce adiposity in rodent models [32]. In experiment studies, AdipoR1 and AdipoR2, receptors for adiponectin, are induced by activation of either PPAR α or PPAR γ [33,101]. The expression of adiponectin mRNA in visceral fat deposits is elevated by fenofibrate treatments when compared to untreated OLETF rats, whereas, TNF- α mRNA is down-regulated by fenofibrate. These results suggest that fenofibrate may be beneficial in the treatment of type 2 diabetes by regulating adiponectin and TNF- α [102]. Indeed, in OLETF rats, fenofibrate therapy for 7 weeks reduces total body fat, fasting plasma insulin, and insulin resistance [103]. Bezafibrate significantly reduces serum triglyceride and free fatty acid levels and improves insulin resistance, but has no influences on abdominal adipose depots in OLETF rats [104]. Fenofibrate improves insulin sensitivity in patients with metabolic syndrome [34,35]. Plasma levels of adiponectin are inversely correlated with body mass index and baseline adiponectin levels are strongly correlated with baseline HDL cholesterol and triglyceride levels [99]. We observe that fenofibrate therapy significantly increases plasma adiponectin levels and insulin sensitivity in primary hypertriglyceridemic patients [34]. Multivariate regression analysis demonstrates that only changes in adiponectin levels persist as an independent predictor of changes in flow-mediated dilation.

With regard to the effects of combined therapy with statins and fibrates on insulin sensitivity, there have been little data. We demonstrated that fenofibrate alone and combined therapy with statins increase plasma adiponectin levels relative to baseline measurements and these effects are significantly greater than those observed with atorvastatin alone (Fig. 4) [18].

4. Drug toxicity and interactions of combined therapy

Combination therapy increases the risk of muscle damage, with an incidence of 0.12%. Risk factors that predispose patients to myopathy caused by combination statin-fibrate therapy include increased age, female gender, renal or liver disease, diabetes, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, and heavy exercise. Although such a combination does increase the risk of myopathy, with an incidence of approximately 0.12%, this small risk of myopathy rarely outweighs the established morbidity and mortality benefits of achieving lipid goals [13]. Combination therapy with statins and gemfibrozil is more likely to be accompanied by severe myopathy [13,14]. This may be due to the fact that gemfibrozil has significant pharmacokinetic interactions with statins that lead to increased plasma levels of statins [15,16]. One example might be through inhibiting glucuronidation of statins resulting in myositis. In dog and human liver micro-somes, gemfibrozil exerts a minimal inhibitory effect on CYP3A-mediated simvastatin hydroxy acid oxidation, but inhibits statins glucuronidation and significantly reduces (2- to 3-fold) the plasma clearance of statins and the biliary excretion of statins glucuronide [16,105,106].

This limitation is not observed with fenofibrate, bezafibrate, or ciprofibrate and no significant side effects have been observed with combination treatment with statins and fibrates [10-12, 14,17-19,40,107,108]. The SAFARI trial reports effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia [12]. From baseline to 12 weeks, no drug-related serious adverse experiences are observed and no patient experiences clinical myopathy or severe abnormalities in liver function with combined therapy. Jones et al. [19] evaluate differences in the rate of myotoxicity between fenofibrate and gemfibrozil in combination with statins. Data from the United States Food and Drug Administration's Adverse Event Reporting System are reviewed to determine how many adverse events are reported from patients treated concomitantly with statins and fibrates. Fenofibrate results in fewer reports of rhabdomyolysis than gemfibrozil when used in combination with any statin medication. Of the total number of reports of rhabdomyolysis for combined fibrate and statin therapies, only 2.3% (14 of 606) are associated with fenofibrate/cerivastatin therapy whereas 88% (533 of 606) are associated with gemfibrozil/cerivastatin therapy. Similarly, the number of reports of rhabdomyolysis per million prescriptions dispensed is ~33 times lower for fenofibrate than for gemfibrozil when used in combination with cerivastatin. We recently report that combination therapy with atorvastatin and fenofibrate significantly improves lipoprotein profiles when compared with atorvastatin or fenofibrate alone in patients with combined hyperlipidemia [18]. Importantly, no patients on combined therapy (atorvastatin+fenofibrate) are withdrawn due to serious adverse events. Elevations in liver and muscle enzymes and gastrointestinal upset are typically transient and resolved spontaneously after finishing the study. Indeed, a recent randomized clinical trial reports combination therapy with statins and fenofibrate is safe in patients with type 2 diabetes over 5 years follow-up [109]. The efficacy and safety of a simvastatin 20 mg-bezafibrate 400 mg combination were investigated in 148 type 2 diabetes patients. Each patient first received the single drug for 6 months and then a combination of the two for 1 year. Only two patients develop myopathy on the combined regimen and one on the single statin regimen [107]. A total of 333 patients were randomly allocated to receive 40 mg fluvastatin alone ($n=80$), 400 mg bezafibrate ($n=86$), 20 mg fluvastatin+400 mg bezafibrate ($n=85$) or 40 mg fluvastatin+400 mg bezafibrate ($n=82$) for 24 weeks. This large study shows 40 mg fluvastatin in combination with 400 mg bezafibrate to be highly effective and superior to either drug given as monotherapy in mixed hyperlipidemia, and to be safe and well tolerated [108]. Simvastatin 20 mg+ciprofibrate 100 mg are given in patients with refractory familial combined hyperlipidemia for a mean period of 29 months. No patient exhibits myopathy or rhabdomyolysis [40].

5. Clinical implications and future prospects

Statins and synthetic PPAR α ligand fibrate therapies that reduce cardiovascular events in randomized clinical trials improve lipoprotein profiles, endothelium-dependent dilation, and reduce vascular inflammation, thrombus formation, and plaque rupture (Fig. 3). Distinct biological actions of statins and fibrates may improve endothelium-dependent vascular function and insulin sensitivity by different mechanisms. Experimental studies demonstrate synergistic effects of statins combined with fibrates [36,37]. Statins and fibrates synergistically increase the transcriptional activities of PPAR α /RXR α and decrease the transactivation of NF- κ B [38]. Therefore, evidences that statins combined with fibrates activate PPAR α in a synergistic manner provide a molecular basis for combination treatment with statins and fibrates in CHD. However, there has been little published evidence that combined therapy is synergistic or even better than monotherapy alone in clinical studies. We demonstrated that combination therapy has beneficial additive effects on endothelial function, inflammatory markers, adiponectin levels, and insulin sensitivity [18]. This may be due to combined effects of respective monotherapies to improve endothelial function, raise adiponectin levels, and increase insulin sensitivity. Importantly, combination therapy with statins and fibrates is very safe. Combining statin therapy with fibrates is not associated with a clinically important

increase in the prevalence of myopathy. However, one should be more cautious when combining statins with gemfibrozil because of the potential for myotoxicity.

The viewpoint that combining statin therapy with fibrates affords biological and clinical benefits over monotherapy is strongly supported, despite the absence of any clinical trial data with cardiovascular morbid-mortality endpoints for such combinations. The efficacy of a simvastatin 20 mg-bezafibrate 400 mg combination was investigated in 148 type 2 diabetes patients. Each patient first received the single drug for 6 months and then a combination of the two for 1 year. Cardiovascular event rate is significantly reduced from 9.5% during the first 6 months of the study to less than 2% during the last year of the study (whilst on combination therapy) [107]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study assesses the effect of fenofibrate on cardiovascular disease events in 9795 participants aged 50-75 years, with type 2 diabetes mellitus. Fenofibrate does not significantly reduce the risk of the primary outcome of coronary events. It does reduce total cardiovascular events, mainly due to fewer non-fatal myocardial infarctions and revascularizations [109]. There are several important potential confounding factors that need to be taken into account when interpreting the results of the FIELD study. These include normal to mildly elevated mean basal triglyceride levels in study subjects, a high dropout rate, uneven allocation of patients between placebo (17%) and fenofibrate (8%) treatment, and concurrent treatment with other lipid-lowering agents (predominantly statins) and cardioprotective therapies such as aspirin, beta blockers, and angiotensin converting enzyme inhibitors [50]. Thus, the higher rate of starting statin therapy in patients allocated to placebo may have masked a moderately larger treatment benefit. Because of these substantial limitations, conclusions drawn from the FIELD study regarding combining statin therapy with fibrates need to be interpreted cautiously.

In conclusion, evidence that statins combined with fibrates activate PPAR α in a synergistic manner provides a molecular basis for combination treatment with statins and fibrates in CHD. The beneficial effects of combined therapy on endothelial function, insulin sensitivity, and inflammation are highly relevant to cardiovascular diseases and are likely to simultaneously improve both cardiovascular and metabolic health in patients with combined hyperlipidemia. Thus, statin/fibrates therapy is predicted to reduce cardiovascular events more than monotherapy with either drug alone. However, there has been little evidence that combined therapy is synergistic or even better than monotherapy alone in clinical studies. Therefore, there is a great need to study the effects of combination therapy in patients.

Abbreviations

HDL, high-density lipoprotein
 LDL, low-density lipoprotein
 CHD, coronary heart disease
 PPAR, peroxisome proliferator-activated receptor
 NF- κ B, nuclear transcription factor
 NO, nitric oxide
 eNOS, endothelial NO synthase
 VCAM, vascular cell adhesion molecule
 ICAM, intercellular cell adhesion molecule
 CRP, C-reactive protein
 MCP, monocyte chemoattractant protein
 TNF, tumor necrosis factor
 CD40L, CD40 ligand
 PAI-1, plasminogen activator inhibitor type 1
 MMP, matrix metalloproteinase
 TIMP, tissue inhibitor of matrix metalloproteinase

QUICKI, Quantitative Insulin-Sensitivity Check Index

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Fig. 1. Fenofibrate alone or combined therapy significantly lowered triglycerides and increased HDL cholesterol levels when compared with atorvastatin alone. Used with permission from Koh et al. [18].

Fig. 2. Percent change in flow-mediated dilation from respective pretreatment values after treatment with atorvastatin alone, combined therapy, and fenofibrate alone. Used with permission from Koh et al. [18].

Fig. 3.

In experimental studies with endothelial cells in culture, many stimuli initiate transcription of genes that encode protein mediators of inflammation. Statins and fibrates may modulate this process by inhibiting the activation of nuclear transcription factors. Used with permission from Koh et al. [54,55].

Fig. 4. Percent change in adiponectin levels (left) and in QUICKI (Quantitative Insulin-Sensitivity Check Index, right) from respective pretreatment values after treatment with atorvastatin alone, combined therapy, and fenofibrate alone. Used with permission from Koh et al. [18].

Table 1

Effects of combined therapy on lipoprotein levels in patients

Treatments	Lipoproteins	Statins	Statins+fibrates	Fibrates
Simvastatin/ciprofibrate [9]	TG	↓	↓	↓
	LDL-C		↓	
	LDL particle		↑	↑
Atorvastatin/fenofibrate [18]	TC	↓	↓	
	TG		↓	↓
	LDL-C	↓	↓	
	Apo B	↓	↓	
	HDL-C		↑	↑
	Apo A-I		↑	↑
Statin/fibrate [42]	HDL-C		↑	
	TC/HDL-C		↓	
	LDL-C/HDL-C		↓	
Simvastatin/fenofibrate [12]	TG		↓	
	LDL-C		↓	
	HDL-C		↑	
Pravastatin/gemfibrozil [40]	More effective in normalizing lipid profile than any monotherapy			
Simvastatin/gemfibrozil				
Simvastatin/ciprofibrate				

TC=total cholesterol; TG=triglycerides; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; Apo=apoprotein. Arrows indicate significant increase or decrease of lipoprotein levels following treatment compared with other treatment.