EXPERT REVIEWS

Combinations of ezetimibe with nonstatin drug regimens affecting lipid metabolism

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In this article we discuss the available data on the effects of combined therapy of ezetimibe with agents affecting lipid metabolism other than statins. We consider studies evaluating the effects of combined therapy of ezetimibe with bile acid sequestrants, fenofibrate, niacin, n-3 fatty acids, plant sterols, orlistat, metformin, acarbose and glitazones. Combination of ezetimibe with bile acid sequestrants (especially colesevelam) was shown to have additional effects on lipid parameters in patients with hyperlipidemia. Combination of ezetimibe with fenofibrate may be a good approach to improve the overall lipid profile of patients with mixed hyperlipidemia. The addition of ezetimibe to niacin-based therapy can be useful for high-risk patients with dyslipidemia who are not achieving their assigned treatment goals. For patients who cannot tolerate statins there are useful combinations of ezetimibe with other drugs affecting lipid metabolism. These combinations improve many metabolic parameters, but more trials should be carried out to reach more robust conclusions about their effects on cardiovascular disease prevention.

KEYWORDS: cholestyramine • colesevelam • colestipol • ezetimibe • fenofibrate • n-3 fatty acids • nicotinic acid • orlistat • pioglitazone • plant stanols • plant sterols • rosiglitazone

Ezetimibe belongs to a class of hypolipidemic agents, the cholesterol absorption inhibitors, which inhibit cholesterol absorption from the intestinal lumen into enterocytes [1]. The molecular target of ezetimibe is the sterol transporter Niemann-Pick C1-like 1 protein (NPC1L1) [2,3]. Ezetimibe is formulated as a 10 mg tablet administered once daily [4].

Ezetimibe lowers LDL-cholesterol (LDL-C) by blocking the intestinal absorption of dietary and biliary cholesterol without affecting triglyceride (TG) or fat-soluble vitamins uptake [5]. A number of ezetimibe-induced pleiotropic effects have been reported [6]. Statins represent the cornerstone of lipid-lowering therapy in dyslipidemic individuals with high cardiovascular disease (CVD) risk [7]. However, a large number of patients are intolerant to statin administration [8] or are unable to reach their assigned LDL-C target despite optimal statin treatment. These patients could be assisted with a combination of ezetimibe with other drugs affecting lipid metabolism. In this article, we discuss the effects of the combined treatment of ezetimibe with lipid-lowering drugs apart from statins (**TABLE 1**).

Methods

We searched PubMed up to December 2010 using combinations of the following keywords: ezetimibe, fenofibrate, fenofibric acid, bile acid sequestrants, colestyramine, cholestyramine, colestipol, colesevelam, nicotinic acid, niacin, n-3 fatty acids, omega-3 fatty acids, thiazolidinediones, glitazones, pioglitazone, plant sterols, plant stanols, phytosterols, orlistat, sibutramine, acarbose, safety. Randomized controlled trials, original papers, review articles and case reports are discussed in this article. References of these articles were scrutinized for other relevant articles.

Ezetimibe plus bile acid sequestrants

The available bile acid sequestrants (BAS) include colestyramine (cholestyramine), colestipol and colesevelam hydrochloride (HCl) [1]. BAS bind to bile acids (BAs) in the intestinal lumen, resulting in bile acid pool depletion and upregulation of hepatic cholesterol 7-α-hydroxylase (CYP7A1). The result is an increase in the conversion of cholesterol to BA, a subsequent decrease in the hepatic cholesterol pool and, finally, increase of the hepatic LDL receptors, which leads to increased LDL clearance [9–11].

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Table 1. Effects of the combined treatment of ezetimibe with lipid-lowering drugs apart from statins†.

Study (year)	Study population	Dose of coadministered drug(s)	Ezetimibe dose (mg/day)	Duration	LDL-C (%)	TC (%)	TG (%)	HDL-C (%)	Other parameters	Ref.
Ezetimibe plus resins										
Rivers *et al.* (2007)	16 statin-intolerant patients with T2DM or the MetS	Colesevelam HCl 3.75 g/day	10	3 months	-42.2‡	-27.5‡			Non-HDL-C: -37.1‡, 50% of patients achieved the LDL-C target ≤100 mg/dl	[15]
Knopp *et al.* (2006)	20 hypercholesterolemic patients	Colesevelam HCl 3.75 g/day	10	12 weeks	-30	-15	+36	+5	ApoB: -22	[16]
Bays *et al.* (2006)	86 patients with primary hypercholesterolemia	Colesevelam HCl 3.75 g/day	10	6 weeks	-32.3§§	-20.3§§			Non-HDL-C: -26.7§§; ApoB: -22.7§§; ApoAI: +6.7§§	[12]
Zema *et al.* (2005)	Eight patients with type IIA hypercholesterolemia and four patients with type IIB mixed hyperlipidemia	Colesevelam HCl 3.75 g/day	10	6 weeks	-37.5‡,§§	-22.5‡,§§	+19.3	-1.7	Non-HDL-C: -28.8‡; LDL-C/HDL-C ratio: -37‡; non-HDL-C/HDL-C ratio: -28.6	[13]
Xydakis *et al.* (2004)	33 hypercholesterolemic subjects	Colesevelam HCl 3.085 g/day	10	107 ± 57 days	-19¶	-18¶	-14¶	-4§		[14]
Ezetimibe plus fenofibrate										
Kumar *et al.* (2009)	43 patients with documented hypercholesterolemia	Fenofibrate 160 mg/day	10	6 weeks	-34.6¶	-25.1¶	-25.4¶	+10§	TC/HDL-C ratio: -29¶; ApoAI: +4.5‡; ApoB: -31.8¶	[29]
Ansquer *et al.* (2009)	60 patients with type IIb dyslipidemia and the MetS	Fenofibrate 145 mg/day	10	12 weeks	-36.2‡,§§	-27.9‡,§§	-38.3‡	+11.5‡	Non-HDL-C: -36.2‡,§§; ApoB: -33.3‡,§§; TC HDL-C ratio: -34.2‡,§§; ApoB/ApoAI ratio: -37.5‡,§§; hsCRP: -25.9‡	[30]
Farnier *et al.* (2005)	625 patients with mixed hyperlipidemia	Fenofibrate 160 mg/day	10	12 weeks	-20.4‡‡,§§	-22.4§,§§	-44††,§§	+19‡‡	Non-HDL-C: -30.4††,§§; ApoB: -26.1††,§§; ApoAI: +9.6††,§§; hsCRP: -27.3††,§§; fibrinogen: -11.5††,§§	[26]

†Values express the percentage increase or reduction versus baseline in the combination treatment, except otherwise mentioned.
‡$p < 0.05$ versus baseline.
§$p < 0.01$ versus baseline.
¶$p < 0.001$ versus baseline.
#$p < 0.05$ versus placebo.
††$p < 0.01$ versus placebo.
‡‡$p < 0.001$ versus placebo.
§§$p < 0.05$ versus monotherapy.
##$p < 0.05$ versus ezetimibe/atorvastatin.
Apo: Apolipoprotein; HCl: Hydrochloride; HDL-C: HDL-cholesterol; HOMA: Homeostasis model assessment; hsCRP: High-sensitivity C-reactive protein; LDL-C: LDL-cholesterol; Lp: lipoprotein; Lp(a): Lipoprotein(a); Lp-PLA_2: Lipoprotein-associated phospholipase A_2; MetS: Metabolic syndrome; PON1: Paraoxonase; sdLDL: Small dense LDL; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG: Triglycerides; UA: Uric acid; WC: Waist circumference.

Table 1. Effects of the combined treatment of ezetimibe with lipid-lowering drugs apart from statins†.

Study (year)	Study population	Dose of coadministered drug(s)	Ezetimibe dose (mg/day)	Duration	LDL-C (%)	TC (%)	TG (%)	HDL-C (%)	Other parameters	Ref.
Ezetimibe plus fenofibrate (cont.)										
McKenney *et al.* (2006)	576 patients with mixed hyperlipidemia	Fenofibrate 160 mg/day	10	48 weeks	-22§§	-23.2§§	-46§§	+20.9§§	Non-HDL-C: -31.6§§; ApoB: -25.2§§; ApoAI: +10.1; hsCRP: -25.3	[27]
Kosoglou *et al.* (2004)	32 subjects with primary hypercholesterolemia	Fenofibrate 200 mg/day	10	14 days	-36.3#,§§	-27.8#,§§	-32.4#,§§	-2#	ApoC-III: -27.4#; ApoAI: -1.4; LpA-I: -23; LpA-I/A-II: +12.8; LDL-I: -28; LDL-II: -8; LDL-III: -37#,§§	[35]
Ezetimibe/simvastatin plus fenofibrate										
Farnier *et al.* (2007)	611 patients with mixed hyperlipidemia	Fenofibrate 160 mg/day	Ezetimibe 10 + simvastatin 20	12 weeks	-45.8††,§§	-38.7††,§§	-50††,§§	+18.7††	Non-HDL-C: -50.5††,§§; ApoB: -44.7††,§§; hsCRP: -38.3††,§§; fibrinogen: -13.2#	[39]
Gil-Extremera *et al.* (2007)	380 mixed hyperlipidemic patients with MetS	Fenofibrate 160 mg/day	Ezetimibe 10 + simvastatin 20	12 weeks	-45.9††	-38.9††	-50††	+17.6††	Non-HDL-C: -50.1††; ApoB: -44.7††; CRP: -36.9††	[40]
	227 mixed hyperlipidemic patients without MetS	Fenofibrate 160 mg/day	Ezetimibe 10 + simvastatin 20	12 weeks	-43.9††	-36.5††	-48.4††	+20.7††	Non-HDL-C: -51.4††; ApoB: -44††; CRP: -40††	
Ezetimibe/atorvastatin plus fenofibric acid										
Jones *et al.* (2010)	543 patients with mixed dyslipidemia	Fenofibric acid 135 mg/day	Ezetimibe 10 + atorvastatin 40 mg/day	12 weeks	>-50		-57.3##	+13##	Non-HDL-C: -55.6##; ApoB: -49.1##	[43]

†Values express the percentage increase or reduction versus baseline in the combination treatment, except otherwise mentioned.
‡$p < 0.05$ versus baseline.
§$p < 0.01$ versus baseline.
¶$p < 0.001$ versus baseline.
#$p < 0.05$ versus placebo.
††$p < 0.01$ versus placebo.
‡‡$p < 0.001$ versus placebo.
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Apo: Apolipoprotein; HCl: Hydrochloride; HDL-C: HDL-cholesterol; HOMA: Homeostasis model assessment; hsCRP: High-sensitivity C-reactive protein; LDL-C: LDL-cholesterol; Lp: lipoprotein; Lp(a): Lipoprotein(a); Lp-PLA_2: Lipoprotein-associated phospholipase A_2; MetS: Metabolic syndrome; PON1: Paraoxonase; sdLDL: Small dense LDL; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG: Triglycerides; UA: Uric acid; WC: Waist circumference.

Table 1. Effects of the combined treatment of ezetimibe with lipid-lowering drugs apart from statins†.

Study (year)	Study population	Dose of coadministered drug(s)	Ezetimibe dose (mg/day)	Duration	LDL-C (%)	TC (%)	TG (%)	HDL-C (%)	Other parameters	Ref.
Ezetimibe plus niacin										
Guyton *et al.* (2008)	1220 patients with type IIa/IIb hyperlipidemia	Niacin 2 g/day	Ezetimibe 10 + simvastatin 20	24 weeks	-58.5§§	-37.9§§	-42.5§§	+30.2	Non-HDL-C: -55.6§§; TC/HDL-C ratio: -50.4§§; LDL-C/HDL-C ratio: -66.1§§; non-HDL-C/HDL-C ratio: -63.6§§; ApoB: -48.1§§; ApoAI: +11; ApoB/ApoAI ratio: -52.3§§; hsCRP: -28.4§§	[47]
Fazio *et al.* (2010)	942 patients with type IIa/IIb hyperlipidemia	Niacin 2 g/day	Ezetimibe 10 + simvastatin 20	64 weeks	-54§§	-35.4	-44.5§§	+30.5§§	Non-HDL-C: -52.4§§; TC/HDL-C ratio: -48.4§§; LDL-C/HDL-C ratio: -62.5§§; non-HDL-C/HDL-C ratio: -61.1§§; ApoB: -47.6§§; ApoAI: +7.6§§; ApoB/ApoAI ratio: -50.1§§; hsCRP: -38.8	[48]
Jelesoff *et al.* (2006)	53 patients	Niacin 2 g/day based regimens	10		Additional -25¶	Additional -18¶	Additional -17¶	Additional +2		[46]
Ezetimibe plus orlistat										
Florentin *et al.* (2009)	30 nondiabetic statin-intolerant overweight/obese patients with dyslipidemia	Orlistat 120 mg three times a day	10	3 months	-28.4§		-14.1§		BMI: -8.6§; WC: -5.2§	[73]
Ezetimibe plus orlistat										
Nakou *et al.* (2008)	86 overweight/obese patients with hypercholesterolemia	Orlistat 120 mg three-times daily	10	6 months	-32§,§§	-26§,§§	-23‡	-6	sdLDL-C: -76§,§§; mean LDL diameter: +1.4§,§§; total Lp-PLA$_2$ activity: -25§,§§; bodyweight: -10§,§§; BMI: -10§,§§; WC: -6§,§§; ApoB: -20§,§§; ApoAI: -6; ApoB/ApoAI ratio: -11‡; HOMA index: -35§,§§; UA: -7§,§§	[62]

†Values express the percentage increase or reduction versus baseline in the combination treatment, except otherwise mentioned.
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§$p < 0.01$ versus baseline.
¶$p < 0.001$ versus baseline.
#$p < 0.05$ versus placebo.
††$p < 0.01$ versus placebo.
‡‡$p < 0.001$ versus placebo.
§§$p < 0.05$ versus monotherapy.
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Apo: Apolipoprotein; HCl: Hydrochloride; HDL-C: HDL-cholesterol; HOMA: Homeostasis model assessment; hsCRP: High-sensitivity C-reactive protein; LDL-C: LDL-cholesterol; Lp: lipoprotein; Lp(a): Lipoprotein(a); Lp-PLA$_2$: Lipoprotein-associated phospholipase A$_2$; MetS: Metabolic syndrome; PON1: Paraoxonase; sdLDL: Small dense LDL; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG: Triglycerides; UA: Uric acid; WC: Waist circumference.

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Study (year)	Study population	Dose of coadministered drug(s)	Ezetimibe dose (mg/day)	Duration	LDL-C (%)	TC (%)	TG (%)	HDL-C (%)	Other parameters	Ref.
Ezetimibe plus orlistat (cont.)										
Nakou *et al.* (2008) extended study	86 overweight/obese patients with hypercholesterolemia	Orlistat 120 mg three-times daily	10	6 months	-32§,§§	-26§,§§	-23‡	-6	HDL-2: +4; HDL-3: -9§; HDL-Lp-PLA_2 activity: -7; HDL-Lp-PLA_2 activity/LDL-C ratio: +31§,§§; PON1: -12; PON1/LDL-C ratio: +21§	[67]
Nakou *et al.* (2010) extended study	86 overweight/obese patients with hypercholesterolemia	Orlistat 120 mg three-times daily	10	6 months	-32§,§§	-26§,§§	-23‡	-6	ApoC-II: -12.5§; ApoC-III: -13§	[72]
Ezetimibe plus plant sterols										
Jakulj *et al.* (2005)	40 patients with mild hypercholesterolemia	25 g/day spread containing 2.0 g of plant sterols	10	4 weeks	-25.2‡	-17.5‡	-11.7	-1		[52]

†Values express the percentage increase or reduction versus baseline in the combination treatment, except otherwise mentioned.
‡ $p < 0.05$ versus baseline.
§ $p < 0.01$ versus baseline.
¶ $p < 0.001$ versus baseline.
# $p < 0.05$ versus placebo.
†† $p < 0.01$ versus placebo.
‡‡ $p < 0.001$ versus placebo.
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Apo: Apolipoprotein; HCl: Hydrochloride; HDL-C: HDL-cholesterol; HOMA: Homeostasis model assessment; hsCRP: High-sensitivity C-reactive protein; LDL-C: LDL-cholesterol; Lp: lipoprotein; Lp(a): Lipoprotein(a); Lp-PLA_2: Lipoprotein-associated phospholipase A_2; MetS: Metabolic syndrome; PON1: Paraoxonase; sdLDL: Small dense LDL; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol; TG: Triglycerides; UA: Uric acid; WC: Waist circumference.

The combined administration of BAS with ezetimibe, drugs that act at the level of the gastrointestinal system, is interesting.

Ezetimibe plus colesevelam

In a multicenter, randomized, double-blind, placebo-controlled study, 86 patients with primary hypercholesterolemia received colesevelam HCl 3.8 g/day plus ezetimibe 10 mg/day or colesevelam HCl placebo plus ezetimibe 10 mg/day for 6 weeks [12]. The primary efficacy end point was the mean percent change in LDL-C during randomized treatment. After 6 weeks of treatment, ezetimibe plus colesevelam HCl reduced LDL-C by 32.3% compared with a 21.4% reduction with ezetimibe monotherapy ($p < 0.0001$). In addition, ezetimibe plus colesevelam HCl significantly reduced total cholesterol (TC) by 20.3%, non-HDL-C by 26.7%, apolipoprotein (Apo)B by 22.7% and increased ApoAI by 6.7% when compared with ezetimibe monotherapy (-14.4, -19.5, -14.8 and 1.3%, respectively; $p < 0.005$ between treatment groups). Neither treatment resulted in significant changes in median TG levels compared with baseline (p = not significant). It should be noted that 25.6% of patients receiving ezetimibe plus colesevelam versus 9.3% of patients receiving only ezetimibe experienced gastrointestinal side effects. However, these side effects typically resolved for most patients with longer term use of colesevelam [12].

In an open-label study, eight patients with primary hypercholesterolemia and four patients with mixed hyperlipidemia after 6 weeks of treatment with colesevelam 3.8 g/day or ezetimibe 10 mg/day were administered combination therapy with both agents for another 6 weeks [13]. Combination therapy further reduced LDL-C and non-HDL-C concentrations by approximately 20 and 16%, respectively ($p < 0.01$ compared with monotherapy). HDL-C and TG levels did not change significantly during the study [13].

The addition of ezetimibe 10 mg/day in 40 patients already on stable treatment with a BAS (33 of them on colesevelam) resulted in significant reductions in TC by 18% ($p < 0.001$), LDL-C by 19% ($p < 0.001$) and TG plasma levels by 14% ($p = 0.03$), whereas HDL-C was nonsignificantly reduced by 4% [14]. No patient discontinued treatment during follow-up and the combined treatments were well tolerated [14].

In conclusion, colesevelam/ezetimibe combination therapy seems to be an efficacious alternative for statin-intolerant patients [15]. However, a study with nonsignificant results should be

mentioned. In total, 20 patients with LDL-C levels ≥130 mg/dl were randomly allocated to receive ezetimibe 10 mg/day with placebo twice daily or ezetimibe 10 mg/day plus 1.875 g colesevelam HCl twice daily [16]. After 12 weeks of treatment, ezetimibe plus colesevelam reduced LDL-C by 30%, TC by 15%, non-HDL-C by 21% and ApoB levels by 22%, whereas TG levels were raised by 36%. However, these results were not significantly different compared with ezetimibe monotherapy (-24, -19, -25, -22 and -19%, respectively; all p = nonsignificant between two groups, except for TG levels at 6 weeks; p = 0.009 [16]. The discrepancies observed in the studies examining the ezetimibe–BAS combination could be due to the same site of action (intestine), which could reduce the additive effect of these drugs in some patients. However, it should be noted that the LDL-C reduction in the study with the nonsignificant results was 30% [16], similar to the reduction observed in other studies [12]. Hence, the nonsignificant result may be due to the smaller number of patients (n = 20) compared with the studies that showed significant differences.

Ezetimibe plus colestipol or cholestyramine

There are no studies specifically examining ezetimibe/colestipol or ezetimibe–cholestyramine administration.

Ezetimibe plus fibrate

Fenofibrate belongs to a class of drugs that activate specific transcription factors known as PPARα [17]. These drugs reduce the concentration of plasma TGs by 30–50% and raise the level of HDL-C by 2–20%, with a variable effect on LDL-C concentration [17–24].

Ezetimibe plus fenofibrate

Ezetimibe and fenofibrate coadministration has been shown to improve lipid and lipoprotein profile [25]. For example, fenofibrate plus ezetimibe combination therapy was evaluated in 625 patients with mixed dyslipidemia who were randomly allocated to receive placebo, ezetimibe 10 mg, fenofibrate 160 mg, and fenofibrate 160 mg plus ezetimibe 10 mg for 12 weeks [26]. Plasma concentrations of LDL-C (-20.4%), non-HDL-C (-30.4%) and ApoB (-26.1%) were decreased significantly more with the combination treatment compared with both monotherapies (p < 0.001 for all) (Figure 1). Median TG reduction was greater with combination therapy compared with fenofibrate alone (p = 0.02) [26]. On the other hand, there was no significant difference in the reductions of high-sensitivity C-reactive protein (hsCRP) and fibrinogen levels between the fenofibrate plus ezetimibe and fenofibrate-alone groups [26]. In a 48-week double-blind extension study (n = 576), patients in the fenofibrate/ezetimibe and fenofibrate groups continued on their respective base study treatment, while patients in the ezetimibe and placebo groups were switched to fenofibrate/ezetimibe and fenofibrate, respectively [27]. Fenofibrate/ezetimibe combination therapy produced greater changes in LDL-C (-22.0 vs -8.6%) non-HDL-C (-31.6 vs -19.4%), TG (-46.0 vs -41.8%), HDL-C (20.9 vs 17.8%) and ApoB (-25.2 vs -16.2%) levels compared with fenofibrate alone [27]. It seems that the mode of action of ezetimibe (i.e., inhibition of intestinal cholesterol absorption) is additive to fenofibrate-induced PPARα activation and leads to complementary effects on lipid and lipoprotein metabolism.

In a recent *post hoc* analysis (625 patients with mixed dyslipidemia), the combination of ezetimibe with fenofibrate resulted in generally similar effects on LDL-C, ApoB and non-HDL-C levels in patients with or without the metabolic syndrome (MetS) [28]. By contrast, ezetimibe monotherapy resulted in greater LDL-C and ApoB reduction in the MetS group compared with patients who did not fulfil the criteria for the diagnosis of the MetS group (p < 0.05 for both) [28].

The hypolipidemic effects of ezetimibe/fenofibrate combination have been directly compared with statins. In a randomized, unblinded crossover study, 43 hypercholesterolemic patients received fenofibrate 160 mg/day plus ezetimibe 10 mg/day or atorvastatin 10 mg/day for 6 weeks [29]. LDL-C and TC levels were similarly decreased and HDL-C levels were similarly increased. In fact, the combination therapy showed a trend towards a greater reduction in TG levels.

In another randomized, double-blind study, 60 patients were randomized to fenofibrate 145 mg, ezetimibe 10 mg or both daily for 12 weeks [30]. Combination treatment significantly reduced, compared with either monotherapies (p < 0.001 for all comparisons), the LDL-C, TC, non-HDL-C, ApoB and ApoB/ApoAI ratio. Among patients with low HDL-C at baseline, normalization of HDL-C was observed in significantly more patients receiving fenofibrate/ezetimibe (52.9%) or fenofibrate (58.8%) compared with ezetimibe alone (20.0%) [30].

Among LDL subspecies, small dense LDL (sdLDL) particles are considered the

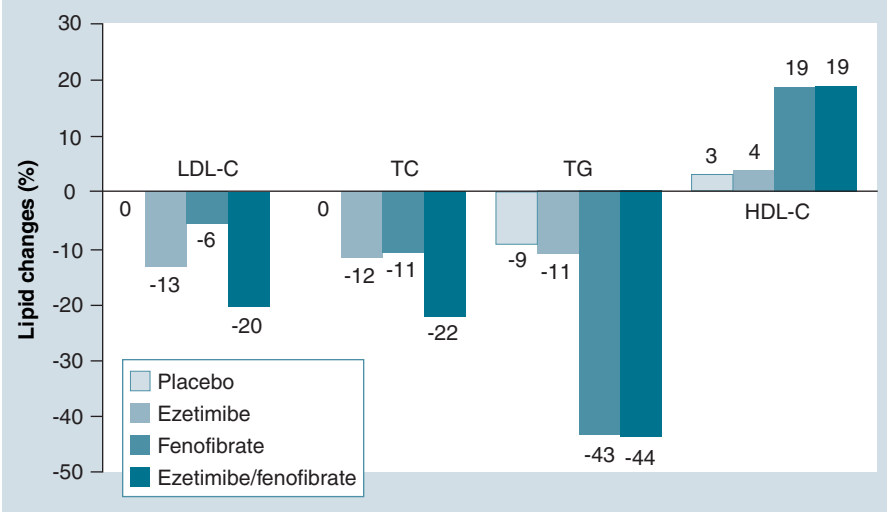

Figure 1. Alterations of lipid profile with ezetimibe/fenofibrate combination in patients with mixed hyperlipidemia.
HDL-C: HDL-cholesterol; LDL-C: LDL-cholesterol; TC: Total cholesterol; TG: Triglycerides.

most atherogenic [31–33]. A study evaluated the effects of ezetimibe/fenofibrate combination on lipoprotein subfractions and LDL particle size distributions [34]. The combination treatment resulted in a preferential decrease in dense LDL subfractions [34]. In another study, fenofibrate/ezetimibe was comparably effective to fenofibrate and more effective than ezetimibe in reducing remnant-like particle cholesterol (-36.2 and -30.7 vs -17.3%, respectively), and in increasing LDL size (2.1 and 1.9 vs 0.7%, respectively) and ApoAII (24.2 and 21.2 vs 2.7%, respectively) [30].

Furthermore, combination therapy has been reported to significantly decrease plasma levels of ApoC-III (-27.4%; $p < 0.05$ compared with placebo) and sdLDL particles (-37%; $p < 0.05$ compared with ezetimibe or fenofibrate monotherapy, or placebo) [35]. Reductions in ApoC-III levels result in increases in the catabolic rate of TG-rich particles [36].

Although the coadministration of ezetimibe with fenofibrate increased the bioavailability of ezetimibe [35,37,38], there is no evidence of increased rate of adverse events of this combination compared with monotherapy treatment [26,27,30,34].

Ezetimibe/simvastatin plus fenofibrate

In a randomized, double-blind, placebo-controlled study, 611 patients with mixed hyperlipidemia received ezetimibe/simvastatin 10/20 mg plus fenofibrate 160 mg or ezetimibe/simvastatin 10/20 mg or fenofibrate 160 mg, or placebo [39]. The triple combination resulted in a significantly greater LDL-C reduction compared with fenofibrate or placebo, but not compared with ezetimibe/simvastatin. Furthermore, the triple-combination treatment increased the HDL-C concentration significantly more compared with ezetimibe/simvastatin, but not compared with fenofibrate alone. Triple combination also resulted in a greater reduction in TG, non-HDL-C and ApoB levels compared with the other treatments ($p < 0.01$ for all comparisons) [39]. Ezetimibe/simvastatin plus fenofibrate led to significant reductions in hsCRP and fibrinogen levels [39]. These results were consistent even when mixed hyperlipidemic patients were divided according to the presence or not of the MetS [40].

An extension of this study examined the effects of the triple combination on lipoprotein subfractions and LDL particle size [41]. Ezetimibe/simvastatin plus fenofibrate led to greater reductions in VLDL, IDL and LDL, a greater decrease in more dense LDL subfractions, and a greater increase in the cholesterol mass of HDL compared with ezetimibe/simvastatin.

Ezetimibe/atorvastatin plus fenofibric acid

A newer fibrate formulation, fenofibric acid, which was recently approved by the US FDA, is the choline salt of fenofibrate. Fenofibric acid is not a prodrug and does not undergo first-pass hepatic metabolism [42]. In a recent double-blind study, 543 patients with mixed dyslipidemia were randomized to atorvastatin 40 mg plus ezetimibe 10 mg with or without fenofibric acid 135 mg for 12 weeks [43]. Although both treatment groups lowered LDL-C by more than 50%, fenofibric acid plus atorvastatin/ezetimibe led to greater reductions in TG, non-HDL-C and ApoB levels (-57.3, -55.6 and -49.1%, respectively) than placebo group (-39.7. -51.0 and -44.7%, respectively; $p < 0.001$ between groups) [43]. Fenofibric acid plus atorvastatin/ezetimibe led also to a significantly greater increase in HDL-C levels when compared with placebo group (13.0 vs 4.2%; $p < 0.001$) [43].

Ezetimibe plus niacin

Nicotinic acid (niacin) has beneficial effects on lipid and lipoprotein profile. It is the only drug that particularly reduces lipoprotein-(a) (Lp[a]) plasma levels [44]. Recently, the combination of extended-release niacin with laropiprant (an antiflushing agent) in a fixed-dose tablet has been shown to reduce flushing, that is commonly observed with niacin [45].

The ezetimibe/niacin combination has not been studied in randomized trials. In a retrospective review of medical records, 53 patients received ezetimibe as add-on therapy to stable doses of niacin and other lipid medications [46]. The niacin formulation was extended release in 31 patients (58%), immediate release in 17 (32%) and slow-release in five patients (9%). Most patients (75%) were also taking a statin. The addition of ezetimibe resulted in reductions of TC (-18%; $p < 0.001$), LDL-C (-25%; $p < 0.001$) and TG (-17%; $p < 0.001$) levels. In total, 24 patients (45%; $p < 0.001$ compared with baseline) met Adult Treatment Panel III (ATP III) LDL-C goals with the addition of ezetimibe compared with seven patients at baseline.

Ezetimibe/simvastatin plus niacin

In a randomized, double-blind study the combination of ezetimibe/simvastatin plus niacin was examined. In this study, 1220 patients with type IIa/IIb hyperlipidemia received ezetimibe/simvastatin (10/20 mg) or niacin (up to 2 g), or both, for 24 weeks [47]. The triple-combination therapy resulted in significantly greater reductions in LDL-C, non-HDL-C, TG and ApoB levels compared with monotherapy ($p < 0.001$) and in significantly greater improvements in HDL-C and ApoAI compared with ezetimibe/simvastatin ($p < 0.001$). The triple combination also reduced hsCRP levels to a greater degree than niacin ($p = 0.005$). It should be noted that a greater portion of patients discontinued the study owing to clinical adverse events (primarily flushing) in the niacin (25.0%) and triple-combination (23.3%) groups compared with ezetimibe/simvastatin (9.6%; $p < 0.001$) [47].

After completing the previous 24-week randomized, double-blind base study [47], 942 patients entered in a 64-week double-blind extension study [48]. In the extended study, patients were allocated to receive ezetimibe/simvastatin (10/20 mg) plus niacin (up to 2 g) or ezetimibe/simvastatin (10/20 mg) for 64 weeks, or niacin (up to 2 g) for 24 weeks and then ezetimibe/simvastatin (10/20 mg) plus niacin (2 g) or ezetimibe/simvastatin (10/20 mg) for an additional 40 weeks [48]. Ezetimibe/simvastatin plus niacin resulted in significantly greater improvements in HDL-C, TG, non-HDL-C, LDL-C, ApoB and ApoAI levels compared with ezetimibe/simvastatin ($p < 0.004$). The most common adverse event related to niacin, flushing, led to a greater rate of discontinuations in the triple combination group (10.3%) compared with ezetimibe/simvastatin alone (0.7%; $p < 0.001$). The fasting glucose levels increased during the first 12 weeks (ezetimibe/

simvastatin +3.2 mg/dl, triple combination +7.7 mg/dl) and gradually decreased to pretreatment levels at week 64 in both groups. The occurrence of new-onset diabetes was 3.1% for the ezetimibe/simvastatin and 4.9% for the ezetimibe/simvastatin plus niacin group [48].

A recent subgroup analysis of the aforementioned study showed that the triple combination is generally a safe treatment option for patients with Type 2 diabetes mellitus and the MetS, although it requires monitoring of glucose and uric acid levels [49].

A recent study showed that there is a small pharmacokinetic drug interaction between extended-release niacin and ezetimibe/simvastatin, probably with no clinical significance [50]. However, patients receiving this drug combination should be monitored carefully.

Ezetimibe plus plant sterols

Dietary phytosterols and phytostanols reduce LDL-C levels and exert many other effects on atherosclerotic risk factors [51]. In a double-blind, placebo-controlled crossover study, 40 patients with mild hypercholesterolemia were randomized to ezetimibe 10 mg/day combined with control spread 25 g/day; or ezetimibe 10 mg/day combined with spread 25 g/day containing 2 g of plant sterols; or control spread 25 g/day containing 2 g of plant sterols; or placebo treatment consisting of 25 g/day control spread for 4 weeks [52]. Combination treatment of plant sterols and ezetimibe reduced LDL-C by 25.2% ($p < 0.001$) and TC by 17.5% ($p < 0.001$) compared with placebo, but there was no significance compared with ezetimibe monotherapy ($p = 0.13$). This nonsignificant result may be due to the similar mode of action of these drugs – that is, the inhibition of intestinal cholesterol absorption.

High-density lipoprotein cholesterol and TG levels were not altered significantly by any treatment. Similar alterations were observed on concentrations of the cholesterol precursor lathosterol and the cholesterol-absorption markers cholestanol, sitosterol and campesterol, as well as the ratios of the noncholesterol sterols to cholesterol [52].

Ezetimibe & anti-obesity drugs

Ezetimibe plus orlistat

Orlistat is a licenced anti-obesity drug that inhibits intestinal lipases, which are responsible for the breakdown of dietary TGs into fatty acids and monoglycerides [53,54]. This drug has a well-established hypolipidemic activity and decreases LDL-C levels to a greater degree than expected from weight loss alone. Orlistat, alone or combined with hypolipidemic drugs, also has beneficial effects on other metabolic variables [53,55–61].

In a study performed by our group, 86 overweight and obese patients with hypercholesterolemia were randomly assigned to orlistat 120 mg three-times/day, ezetimibe 10 mg/day or both for 6 months [62]. Ezetimibe plus orlistat significantly decreased ($p < 0.05$) LDL-C levels by 32% compared with orlistat (-19%) and ezetimibe monotherapy (-21%). The atherogenic sdLDL-C concentration decreased significantly more with the combination treatment (-76%) compared with orlistat (-45%) and ezetimibe (-48%; $p<0.05$). Furthermore, ezetimibe plus orlistat led to significant reductions in BMI, homeostatic model assessment (HOMA) index, serum uric acid and transaminase activities. Lipoprotein-associated phospholipase A_2 activity ($LpPLA_2$; an enzyme that degrades oxidatively fragmented phospholipids, is mainly associated with ApoB-containing lipoproteins, and may play a role in atherogenesis [63–66]) decreased significantly more with the combination treatment compared with either orlistat or ezetimibe monotherapy [62]. In an extension study, plasma HDL subclasses and HDL-associated enzyme activities were assessed [67]. HDL-C and ApoAI levels did not change significantly in any group. In the combination group, HDL-2 subclass did not significantly change, while the cholesterol concentration of the HDL-3 decreased significantly. Similar results were observed in the ezetimibe group, whereas in the orlistat group, the cholesterol concentration of the HDL-2 subclass increased significantly and the cholesterol of the HDL-3 subclass decreased significantly. A nonsignificant decrease in the HDL–$LpPLA_2$ (the small proportion of the enzyme that is associated with HDL and has atheroprotective role) and paraoxonase-1 (PON1; an esterase present in plasma in association with HDL, which retards LDL oxidation and reduces the proinflammatory properties of oxidized LDL [68–71]) activity was observed in all groups. However, the ratios of both enzyme activities to LDL-C levels (an indirect index of the atheroprotective function of HDL) significantly increased in all groups [67]. Furthermore, the combination group significantly decreased plasma ApoC-II by 12.5 and ApoC-III by 13% ($p < 0.05$ for both). Similar results were observed in the ezetimibe group, while in the orlistat group a significant reduction was observed only in plasma ApoC-III concentrations. In the ezetimibe plus orlistat group, alterations in ApoC-III levels were independently and significantly positively correlated with TG lowering [72]. The additive effects of ezetimibe and orlistat are interesting, since these drugs act in the intestine and inhibit lipid and cholesterol absorption.

In another study, 30 nondiabetic statin-intolerant overweight/obese patients with dyslipidemia were randomized to ezetimibe (10 mg/day) plus orlistat (120 mg three-times/day; $n = 15$) or rimonabant (20 mg/day; $n = 15$) [73]. Rimonabant is an anti-obesity drug that was recently withdrawn due to psychiatric adverse effects. Ezetimibe plus orlistat led to similar reductions in bodyweight, BMI and waist circumference in the ezetimibe plus rimonabant group ($p < 0.01$ vs baseline for both). Ezetimibe plus orlistat had a more potent effect on LDL-C levels (-28.4%) compared with the ezetimibe plus rimonabant group (-15.3%; $p < 0.01$ vs baseline for both). However, there was a slight reduction in HDL-C levels in the ezetimibe plus orlistat group, whereas in the ezetimibe plus rimonabant group HDL-C levels remained unaltered [73].

Ezetimibe plus antidiabetic treatment

Ezetimibe plus metformin

Metformin reduces glycated hemoglobin by 0.5–1.5% and improves lipid profile [74]. In the UK Prospective Diabetes Study (UKPDS) trial, metformin compared with insulin and

sulphonylureas decreased the risk of diabetes-related end points in overweight diabetic patients [75]. There are no studies in humans examining the ezetimibe/metformin combination treatment.

Ezetimibe plus thiazolidinediones

Thiazolidinediones are antidiabetic drugs that activate the PPARγ receptors. These drugs increase insulin sensitivity and improve several CVD-related variables [76]. In a randomized, double-blind, parallel group, multicenter study, Type 2 diabetes mellitus patients on a stable dose of thiazolidinediones for at least 3 months and LDL-C >100 mg/dl prior to study entry, received open-label simvastatin 20 mg/day for 6 weeks and were then randomized to the addition of either blinded ezetimibe 10 mg/day (n = 104) or an additional blinded simvastatin 20 mg/day (total simvastatin: 40 mg/day; n = 110) for 24 weeks [77]. Ezetimibe plus simvastatin 20 mg reduced LDL-C by 20.8%, whereas the additional reduction of LDL-C when doubling the dose of simvastatin to 40 mg was only 0.3% ($p < 0.001$ between groups). Ezetimibe plus simvastatin 20 mg also produced significant reductions in non-HDL-C ($p < 0.001$), VLDL ($p < 0.05$) and ApoB levels ($p < 0.001$), whereas no change was observed in TG and HDL-C levels [77].

Ezetimibe plus acarbose

Acarbose is an α-glucosidase inhibitor that delays the absorption of carbohydrate from the small intestine, resulting in reduction of postprandial hyperglycemia [78]. There are no studies in humans examining the ezetimibe/acarbose combination. In a high-fat diet-induced nonalcoholic fatty liver disease mouse model, a 24-week combination therapy with ezetimibe and acarbose significantly reduced steatosis, inflammation and fibrosis of the liver compared with monotherapy [79]. The combination therapy also significantly increased the expression of microsomal TG transfer protein and PPARα in the liver compared with either monotherapy [79].

Conclusion

This article, based on a PubMed search, focuses on studies that examined combination regimens of ezetimibe with nonstatin hypolipidemic drugs. Combined therapies including ezetimibe may be useful for patients intolerant to statins or unable to reach their assigned LDL-C targets. The combination of ezetimibe with fenofibrate can be useful in patients with mixed hyperlipidemia. Moreover, the combination of ezetimibe with colesevelam appears to be an efficacious and well-tolerated alternative for patients with hypercholesterolemia. The addition of ezetimibe to niacin-based therapy can be useful for high-risk patients with mixed dyslipidemia. The administration of combined ezetimibe and orlistat treatment improves the lipid parameters of overweight/obese patients with the MetS. It should be noted that the effect of ezetimibe with nonstatin regimens has not been extensively studied in large-scale clinical studies.

Expert commentary & five-year view

Cardiovascular disease events are a major cause of death in Western countries. A growing number of patients receive hypolipidemic treatment for primary or secondary CVD prevention. Statin administration is the cornerstone of CVD prevention treatment, with a large number of studies with clinical CVD end points showing their efficacy. However, a number of patients are intolerant to statins or cannot reach their assigned LDL-C targets in the clinical setting. Furthermore, the number of patients intolerant to statins is expected to increase in the next 5 years in parallel with the increase in their use for primary or secondary CVD prevention. The use of nonstatin drug therapies will be required for these patients. Different drug combinations are useful for these patients. Ezetimibe is a hypolipidemic drug that can be combined with other drugs with hypolipidemic activity with limited adverse effects.

There is a growing need for studies examining hypolipidemic drug combinations. Unfortunately, there are no randomized, double-blind studies examining drug combinations including nonstatin hypolipidemic drugs. The absence of randomized studies on the hypolipidemic treatment of patients intolerant to statins means that treatment decisions are often based on small studies or even personal opinions.

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Key issues

- Ezetimibe combinations with lipid-lowering drugs apart from statins may be useful in the clinical setting for patients intolerant to statins or unable to reach their assigned LDL-cholesterol targets.
- Ezetimibe plus fenofibrate combination can be useful in patients with mixed hyperlipidemia.
- Ezetimibe plus colesevelam combination is efficacious for patients with hypercholesterolemia.
- Ezetimibe plus niacin combination can be useful for patients with mixed dyslipidemia.
- Ezetimibe plus orlistat combination improves anthropometric and lipid variables in overweight/obese patients with the metabolic syndrome.
- These drug combinations, although useful in the clinical setting, have not been investigated in large, randomized, double-blind studies with clinical end points.

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