

Combination of a Sterol Absorption Inhibitor and Cardiovascular Agents for the Treatment of Dyslipidemia

Christina Chrysohoou* and Steven Singh

1st Cardiology Clinic, University of Athens, Greece, Cardiology Clinic, Veterans Affairs Medical Center, Washington, DC, USA

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Abstract: Although statins are effective in reducing cardiovascular risk, combination therapy may be required to meet recommended target LDL-C levels. However, the utility of current combination therapies with niacin or bile acid sequestrants is limited by side effects and compliance. Ezetimibe, as a selective cholesterol absorption inhibitor, represent a new class of pharmaceutical agents. The combination of ezetimibe with statins has shown a 16-21% increase in the percentage of patients achieving their ATP III LDL-C goal. Randomized, double-blind studies have shown that coadministration of ezetimibe with simvastatin is well tolerated, causing dose-dependent reduction in LDL-C and total cholesterol levels, with no apparent effect on high-density lipoprotein cholesterol or triglycerides. Even in diabetes mellitus type 2 patients; the addition of ezetimibe 10 mg to simvastatin 20 mg is more efficacious than doubling the dose of simvastatin in lowering lipid parameters. Similarly the coadministration of ezetimibe and rosuvastatin, has shown a mean incremental reduction in LDL-C of -16%, compared with rosuvastatin alone, while there was no apparent effect on HDL-C or triglycerides. Ezetimibe and fenofibrate co-administration has shown also improvement in the lipid/lipoprotein profile. The combination therapy with ezetimibe and statin or fibrate may be an effective therapeutic option for patients with dyslipidemia.

Keywords: Sterol absorption inhibitor, hyperlipidemia combination therapy, ezetimibe.

INTRODUCTION

Hypercholesterolemia is an important risk factor for coronary artery disease, which remains a leading cause of mortality and morbidity in industrialized countries [1]. Drug therapy with cholesterol-lowering medications, particularly 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors has shown effectiveness in reducing cholesterol levels after inadequate dietary modification [2-4]. However, not all patients respond to statin treatment; and combination therapy with two or more hypolipidemic drugs may be required to meet target LDL-C levels, according to the recommendations of the European Second Joint Task Force and the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) [5, 6]. Thus treatment options with different mechanisms of actions and improved safety profiles are needed to be used alone or with co-administration to existing therapies in the treatment of patients with hypercholesterolemia [7, 8].

Ezetimibe, 1-(4-fluorophenyl)-3-[[3-(4-fluorophenyl)-3-(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone], is a selective cholesterol absorption inhibitor that effectively blocks intestinal absorption of dietary and biliary cholesterol.

Ezetimibe acts at the brush border of the small intestine and inhibits the uptake of dietary and biliary cholesterol into the enterocytes, without appearing to affect the absorption of triglycerides or fat-soluble vitamins [9, 10].

Sudhop *et al.*, performed one of the first clinical trials to investigate the influence of ezetimibe on cholesterol absorption in patients with mild to moderate hypercholesterolemia. This study showed that ezetimibe inhibited cholesterol absorption by 54% relative to placebo. This inhibition was associated with a compensatory increase in cholesterol syntheses, so on balance, there was a 22.3% reduction in plasma LDL cholesterol concentrations, consistent with LDL -C reductions observed in previous studies [11, 12].

In addition to effects on plasma cholesterol concentrations, ezetimibe has shown a marked reduction in circulating levels of noncholesterol plant sterols, such as campesterol and sitosterol [11]. Furthermore, the observed increase in hepatic cholesterol synthesis, indicated by the ratio lathosterol to cholesterol in plasma [13, 14], might explain the favorable effects of coadministering ezetimibe and statins.

COADMINISTRATION OF EZETIMIBE WITH HMG-CO A REDUCTASE INHIBITORS

Despite the diversity of available cholesterol-lowering therapies, a significant proportion of the hypercholesterolemic population is not achieving the recommended target cholesterol levels [15-17]. Thus, there is a continued search for effective, better-tolerated drugs or combinations of drugs for the treatment of patients with hypercholesterolemia. Preclinical studies have shown that the coadministration of ezetimibe with statins in hypercholesterolemic dogs reduce synergically plasma cholesterol levels without evidence of liver or skeletal muscle toxicity [18, 19].

*Address correspondence to this author at the Christina Chrysohoou, 46 Paleon Polemiston Str., 16674 Athens, Greece; E-mail: chrysohoou@usa.net

Kosoglou *et al.* [20], conducted two randomized, evaluator-blind, multiple dose, parallel-group studies in otherwise healthy hypercholesterolemic subjects in order to test whether ezetimibe enhances the LDL-C lowering effects of simvastatin in humans. In the first study the subjects were randomized to receive one of the following five treatment: simvastatin 10 mg with placebo, simvastatin 10 mg with ezetimibe 0.25 mg, 1 mg or 10mg, or placebo alone. In the second study the subjects were randomized to receive one of the following three treatments: simvastatin 20 mg with ezetimibe 10 mg, simvastatin 20 mg with placebo, or ezetimibe 10 mg with placebo. All subjects were stabilized as outpatients on an NCEP Step I diet. In both studies, reported side effects were generally mild, nonspecific, and similar among treatment groups. There were no serious adverse effects with any of the treatments. Overall 41% reported treatment-emergent adverse effects, most commonly headache (10%), flatulence (7%), viral infections (6%), loose stools (4%) and diarrhea (4%). Most adverse events were mild to moderate in intensity. Neither subject had increased creatinine phosphate kinase levels or any other laboratory test abnormalities associated with their adverse event during the study period. According to the pharmacokinetics, ezetimibe seemed to have no apparent effect on the pharmacokinetics of simvastatin or -hydroxysimvastatin, as the relative oral bioavailability of simvastatin and -hydroxysimvastatin after the coadministration of ezetimibe with simvastatin compared with simvastatin alone ranged from 96% to 138%. In both studies, all active treatment caused statistically significant decreases in LDL-C vs placebo from baseline to day 14. The coadministration of ezetimibe and simvastatin caused a dose-dependent reduction in LDL-C and total cholesterol, with no apparent effects on high density cholesterol (HDL-C) or triglycerides. Specifically, the coadministration of ezetimibe 10 mg and simvastatin 10 mg or 20 mg caused a statistically greater percentage reduction (mean -17% and -18%, respectively) in LDL-C than simvastatin alone. These reductions are similar to those one might expect from titration three times with a statin. Unlike the preclinical findings, those incremental reductions in mean LDL-C appears to be more additive than synergistic. In another recent work by Kosoglou *et al.* the coadministration of ezetimibe with rosuvastatin was evaluated [21]. In this study all patients after NCEP Step I diet stabilization periods, were randomized to rosuvastatin 10 mg plus ezetimibe 10 mg, rosuvastatin 10 mg plus placebo, ezetimibe 10 mg plus placebo or placebo. In this study the coadministration of ezetimibe and rosuvastatin caused a significantly greater reduction in mean LDL-C (-61.4%) than rosuvastatin alone (-44.9%), with a mean incremental reduction of -16.4%. Again reported side effects were mild, nonspecific and similar among treatment groups; furthermore, there were no significant increases or changes in clinical laboratory tests, and no significant pharmacokinetic drug interaction between ezetimibe and rosuvastatin was observed.

Bennett *et al.* conducted a recent gender subset analysis on pooled data from four studies cited to assess whether ezetimibe coadministered with statins for treating hypercholesterolemia is equally efficacious in women and men [22]. These studies were multicenter, randomized,

double-blind, placebo-controlled, balanced-parallel group trials consisting of three phases with a total of 1861 patients enrolled. Phase I was a 2-12-week screening phase that included washout of previous lipid-modifying drug therapy and the instruction to follow NCEP Step I diet. Phase II was a 4-week pre-randomization phase consisting of a single blind placebo run-in plus diet. Phase III was a 12-week randomization phase during which all qualifying subjects were randomized to placebo, ezetimibe 10 mg, statin monotherapy (lovastatin or pravastatin 10, 20, 40 mg; simvastatin or atorvastatin 10, 20, 40, 80 mg) or 10 mg ezetimibe coadministered with one of the above statins [23-26]. The primary efficacy endpoint was the percentage reduction in LDL-C from baseline to final assessment. Secondary endpoints included the percentage change in other lipid parameters and the proportion of patients attaining their NCEP ATP II LDL-C goal.

However, the proportion of patients achieving ATP III LDL-C goals was also determined in a post hoc analysis [22]. In a total of 1861 patients, the coadministration of ezetimibe plus statin compared with statin monotherapy demonstrated a greater efficacy in reducing plasma levels of LDL-C in both men and women. The between-group differentials for women and men were -13.8% and -13.5%, respectively. The relative effects on LDL-C of ezetimibe with statins versus statins alone were generally similar across the four statins (atorvastatin, simvastatin, lovastatin, pravastatin) tested. In the ezetimibe plus statin group, 92% of women and 87% of men reached their LDL-C target after treatment, compared with 78% and 69% respectively, in the statin monotherapy group. ATP III goal attainment were achieved in 89% of women and 84% of men in the ezetimibe plus statin group compared with 73% of women and 63% of men in the statin monotherapy group. The between-treatment group differences for women and men achieving their ATP III LDL-C goal were 16% and 21%, respectively. In all studies ezetimibe plus statin was more efficacious than statin monotherapy at lowering blood levels of apo B and triglycerides and raising HDL-C, similarly in both sexes. Furthermore, ezetimibe plus statin was generally well tolerated, with an overall safety profile similar to that of statin monotherapy and similar across different genders [25-27].

Even in patients with refractory familial hyperlipidemia or intolerant to statin therapy, the ezetimibe-statin combination has shown an additional up to 27% reduction in LDL-C levels and an 18% reduction in apolipoprotein B, compared with ezetimibe monotherapy. According the investigators of this study [28], the co administration of ezetimibe and statins shows a highly variable response profile as the percentage of patients achieving the LDL-C target of 3mmol/l rose from 5.5% to 18%. In a recent study by Gaudiani *et al.*, the efficacy and safety of ezetimibe coadministered with simvastatin in type 2 diabetic patients was evaluated [29]. In this high risk group of patients treated with thiazolidinedione, LDL-C was more reduced by adding ezetimibe 10 mg to simvastatin 20 mg (-20.8%) than doubling the dose of simvastatin to 40 mg (-0.3%). Furthermore, ezetimibe plus simvastatin 20 mg produced significant incremental reduction in non-HDL -C, very low density lipoprotein cholesterol and apolipoprotein B relative

to simvastatin 40 mg. Additionally, among those patients who were above the LDL-C goal of 100 mg/dl at randomization, a greater proportion of patients in the ezetimibe plus simvastatin group attained goal by the end of the study compared with the simvastatin 40 mg group (76% versus 39%, respectively). Similar results were also reported in a previous study by Cagne *et al.* [32], where 769 adults with primary hypercholesterolemia receiving statin were randomized to receive concurrent treatment with placebo or ezetimibe 10 mg /day for 8 weeks. Ongoing statin therapy plus ezetimibe led to changes of -25.1% for LDL-C compared with -3.7% for placebo added to statin therapy. Furthermore HDL-C was increased by 2.7% and triglycerides were decreased by 14% on the combination therapy compared with +1% and -2.9%, respectively, on the statin plus placebo therapy.

In another multicenter recent study by Ballantyne *et al.* [33], the efficacy of the combination ezetimibe plus simvastatin versus atorvastatin on LDL-C reduction was evaluated. In this study, 1902 patients with LDL-C above ATP-III goal were randomized to atorvastatin (10, 20, 40 or 80 mg) or to the combination of ezetimibe and simvastatin (10/10, 10/20, 10/40 or 10/80 mg). This study illustrated that the combination of ezetimibe plus simvastatin provided greater LDL-C reductions than atorvastatin (47%-59% versus 36%-53%, respectively), at each milligram-equivalent statin dose comparison. Furthermore, ezetimibe/simvastatin 10/40 and 10/80 mg provided significantly greater high-density lipoprotein cholesterol increases than atorvastatin 40 and 80 mg monotherapy; while no myopathy or liver-related adverse events led to study discontinuation with either drug. In another study of 2020 patients randomized to ezetimibe added to statin therapy the combination therapy reduced the LDL-C levels by an additional 25.8% in the total population compared with an additional 2.7% reduction with placebo plus statin. The treatment difference in this study ranged from -19.9% to -24%, in each NCEP ATP III risk category subgroup. There was also a significant difference between patients treated with ezetimibe with statins reaching their NCEP ATP III target LDL-C level, and those treated with placebo plus statin (71% versus 20.6%, respectively) [34]. Similarly, Brohet *et al.* illustrated that the combination therapy of ezetimibe/simvastatin led to a greater percentage of patients attained the LDL-C goals than statin monotherapy (80.4% vs. 17.4%, respectively) [35]. Furthermore, mean percentage reduction in LDL-C from baseline was significantly larger in the ezetimibe group compared to placebo (27.1% vs. 4.1%, respectively).

The ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial tests the hypothesis whether the combination of ezetimibe and simvastatin can provoke larger beneficial effects on carotid artery intima-media thickness than simvastatin monotherapy [36]. This international 2-year, ongoing, randomized, double-blind, controlled trial which has recruited 725 men and women with heterozygous familial hypercholesterolemia will address the question of whether a regimen that uses drugs with different mechanisms of action will be of further benefit in terms of atherosclerosis reduction compared to statin monotherapy.

Lipka *et al.* [37] in a recent study compared the efficacy and safety of statin monotherapy versus ezetimibe 10mg plus statin in older and younger adults with primary hypercholesterolemia. After washout and placebo run-in period, 1861 men and women ≥ 18 years of age with primary hypercholesterolemia were randomized to either placebo, statin monotherapy (lovastatin or pravastatin 10, 20 or 40 mg, simvastatin or atorvastatin 10, 20, 40 or 80 mg) or ezetimibe plus statin for 12 weeks. In this study, age subset analyses on data pooled across these four trials were carried out to determine whether coadministration of ezetimibe and statin was equally efficacious across age groups: < 65 versus ≥ 65 years, < 75 versus ≥ 75 years. This study illustrated that the beneficial effects of ezetimibe plus statin on LDL-C, triglycerides and HDL-C were overall independent of age groupings. Furthermore the combination therapy was generally well tolerated, with similar incidence of adverse events, serious adverse events and changes in liver function and muscle enzymes in all age groups compared with statin therapy alone.

In a recent meta-analysis of 14 randomized, double-blind clinical trials that compared the efficacy results of ezetimibe 10 mg with simvastatin or the ezetimibe/simvastatin combination product (10/10, 10/20, 10/40, 10/80 mg) with the efficacy results of rosuvastatin 5, 10, 20 and 40 mg in patients with primary hypercholesterolemia or combined hyperlipidemia. Those investigators used pooled data for LDL-C, HDL-C, non HDL-C, triglycerides, total cholesterol, apolipoprotein A-1 and apolipoprotein B for the two therapies at their lowest through the highest doses [38]. Percentage reductions from baseline in LDL-C for the pooled data were 46.2% and 41.8% for ezetimibe/simvastatin 10/10mg and rosuvastatin 5 mg; 50.6% and 47.4% for ezetimibe/simvastatin 10/20 mg and rosuvastatin 10 mg, respectively; 55.9% and 52.1% for ezetimibe/simvastatin 10/40 mg and rosuvastatin 20 mg, respectively; and 59.7% and 58.5% for ezetimibe/simvastatin 10/80 mg and rosuvastatin 40 mg, respectively. Similar results have been reported by Mikhailidis *et al.* in a position statement of a United Kingdom consensus panel, where the percentage reduction of LDL-C from baseline with a statin plus ezetimibe combination therapy was from 34% to 53% [39], while the proportion of patients achieving LDL-C goals according the recent guidelines was substantially increased.

COADMINISTRATION OF EZETIMIBE WITH FIBRATES

Mixed or combined hyperlipidemia is a common metabolic disorder characterized by both elevated LDL cholesterol and triglycerides, a preponderance of small dense LDL particles, and reduced HDL cholesterol [40]. Beyond lowering LDL-C the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommends non-HDL as a secondary treatment target for patients with elevated triglycerides [5]. Although, statins and fibrates have complementary mechanisms and can be coadministered to patients with mixed hyperlipidemia, safety concerns are increased with higher doses or certain combinations of statin and fibrate, especially gemfibrozil [41]. Ezetimibe as a non-inhibitor of cytochrome P450

Table 1. Summary of Various Clinical Trials According to the Lipid Level Reduction Achieved by Combination Therapy with Ezetimibe and Statins/Fibrates

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| Catapano A, <i>et al.</i> Curr Med Res Opin 2005 | meta-analysis of 14 clinical trials EZE/SIMV (10/10, 10/20, 10/40, 10/80 vs. ROSU 5, 10, 20, 40 mg) | LDL-C reduction by: 46.2% EZE/SIMV 10/10 41.8% ROSU 5 50.6% EZE/SIMV 10/20 47.4% ROSU 10 55.9% EZE/SIMV 10/40 52.1% ROSU 20 59.7% EZE/SIMV 10/80 58.5% ROSU 40 |
| Mikhailidis D, <i>et al.</i> Curr Med Res Opin 2005 | Statins monotherapy vs. statin plus EZE | LDL-C reduction by 34-53% with combination therapy vs. 17-18% monotherapy |
| Brohat C, <i>et al.</i> Curr Med Res Opin 2005 | In CHD patients EZE or placebo plus SIMVA | 80.4% of patients on combination therapy achieved LDL-C<100 mg/dl vs. 17.4% on statin monotherapy. |
| Cagne C, <i>et al.</i> Am J Cardiol 2002 | Primary Hypercholesterolaemia pts Statin monotherapy vs. statin plus EZE | LDL-C reduction by 25.1% on combination vs. 3.7% on monotherapy HDL-C increased by 2.7% on combination vs. 1% on monotherapy TG increased by -14% vs. -2.9% on monotherapy |
| Kosoglou T, <i>et al.</i> Br J Clin Pharmacol 2002 | SIMVA 10/SIMVA (10) plus EZE (0.25, 1, 10) or placebo SIMVA 20 vs. EZE 10 vs.combination | EZE 10 plus SIMVA 10 or 20 cause -17% and -18% reduction on LDL-C |
| Farnier M, <i>et al.</i> Eur Heart J 2005 | Mixed hyperlipidaemia pts: placebo, EZE 10, FENO 160, FENO 160 plus EZE 10 | LDL-C was increased by 0.2% with placebo, reduced by -13.4% with EZE 10, 5.5% with FENO 160 and 20.4% with EZE 10 plus FENO 160. TG was reduced by 0.4% with placebo, -15.3% with EZE 10, -9.9% with FENO 160 and -27.8% with EZE 10 plus FENO 160. |
| Reyderman L, <i>et al.</i> In J Clin Pharmacol Ther 2004 | 3-way crossover study: EZE 10, GEMFIB 600/12h, GEMFIB 600/12 plus EZE 10 | No significant drug interaction |
| Kosoglou T, <i>et al.</i> Curr Med Res Opin 2004 | ROSU 10 plus EZE 10 ROSU 10 plus placebo EZE 10 plus placebo Placebo | ROSU plus EZE 61.4% reduction in LDL-C |
| Bennett S, <i>et al.</i> J Women's Health | Statin monotherapy (LOVA or PRAVA 10,20,40, SIMVA or ATORVA 10,20,40,80) vs. EZE 10 plus statin | Combination therapy vs. monotherapy: LDL-C was reduced by -47.1% vs. -33.4% in women -44.8% vs. 31.3% in men HDL-C was increased by +7.9% vs.5% in women, and by 8.9% vs. 6.2% in men TG was reduced by -25.8% vs. -16% in women, and -28.6% vs. -21.1% in men. |
| Gardiani L, <i>et al.</i> Diabetes, Obesity and Metabolism 2005 | Type 2-DM patients treated with SIMVA 20 were randomized to SIMVA 40 vs. SIMVA 20 plus EZE 10 | Combination therapy vs. monotherapy reduced LDL-C by -20.8% vs. -0.3% and non-HDL-C by -20% vs. 1.7%. |
| Xydakis AM, <i>et al.</i> Am J Cardiol 2004 | EZE plus bile acid resin | Total Cholesterol was reduced by -18%, TG by -14% and LDL-C by -19%. |

(Table 1) Contd....

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| VYVA Study Ballantyne CM, <i>et al.</i> Am Heart J 2005 | Pts with LDL-C above ATPIII goal ATORVA (10,20,40,80) or EZE/SIMVA (10/10, 10/20, 10/40, 10/80) | Combination therapy was more effective at each dose comparison |
| EASE trial Pearson TA, <i>et al.</i> Mayo Clin Proc 2005 | EZE or placebo plus statin | Combination treatment reduced LDL-C from -19.9 to - 24% |

EZE=ezetimibe, SIMVA= simvastatin, ATORVA=atorvastatin, LOVA=lovastatin, PRAVA=pravastatin, FENO=fenofibrate, GEMFIB=Femfibrozil, ROSU=rosuvastatin, TG=triglycerides, LDL-C=low-density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol. Numbers after medication names refer to mg.

isoenzymes, may provide a concomitant treatment with fibrates with lower incidence of potential drug interactions. In this field, Farnier *et al.*, in a multicenter, randomized, double-blind, placebo-controlled, parallel arm trial examined the efficacy and safety of coadministered ezetimibe with fenofibrate in patients with mixed hyperlipidemia [42]. In this study the coadministration therapy reduced LDL-C by 20.4%, non-HDL-C by 30.4%, triglycerides by 44% and increased HDL-C by 19%, statistically significant compared with fenofibrate plus placebo treatment. Furthermore, a greater proportion of patients on fenofibrate plus ezetimibe and fenofibrate alone treatments shifted from a more atherogenic LDL size pattern to a larger, more buoyant and less atherogenic LDL size pattern at study endpoint than those on placebo or ezetimibe alone. Furthermore, in these patients with mixed hyperlipidemia, the coadministration of fenofibrate plus ezetimibe did not seem to influence the rate of adverse events beyond that noted with fenofibrate alone. The proportion of patients with consecutive elevations in liver function tests or serum creatinine was similar between fenofibrate plus ezetimibe versus fenofibrate groups, but greater than the proportion noted with ezetimibe treatment.

In a small pilot study by Kosoglou *et al.* [43], fenofibrate significantly increased steady state exposure of total ezetimibe by 50%, which was not considered clinically relevant; while ezetimibe did not significantly affect fenofibrate pharmacokinetics.

Similarly Reyderman *et al.* [44] evaluated any potential pharmacokinetic interaction between ezetimibe and gemfibrozil, in a randomized, open-label, 3-way crossover, multiple-dose study in 12 healthy male volunteers, who received orally for 7 days ezetimibe 10 mg once daily, gemfibrozil 600 mg every 12 hours, and ezetimibe 10 mg once daily plus gemfibrozil 600 mg every 12 hours. This study showed that ezetimibe did not alter the bioavailability of gemfibrozil; while, conversely, gemfibrozil significantly increased the plasma concentrations of ezetimibe and total ezetimibe, however this increase was not considered to be clinically relevant and ezetimibe and gemfibrozil administered alone or concomitantly for 7 days was well tolerated.

The potential additive effects of combining the cholesterol absorption inhibitor ezetimibe with a bile acid resin was evaluated in a prospective study by Xydakis *et al.* in a group of 40 patients in whom ezetimibe 10 mg/ day was added to a stable regimen that included bile acid resin [45].

In a average follow-up of 107+/- 57 days, ezetimibe coadministration significantly reduced total cholesterol by 18%, triglycerides by 14%, and LDL-C by 19%, without any significant change on HDL-C.

CURRENT AND FUTURE DEVELOPMENTS

The fact that lowering serum cholesterol reduces coronary risk has led treatment guidelines to set progressively lower targets for LDL-C. Nevertheless, a great percentage of patients treated with statins is unable to achieve these LDL-C goals; while the combination therapy may increase the risk of serious adverse effects and affect patients' compliance. Ezetimibe, a selective cholesterol transport inhibitor, reduces the intestinal uptake of cholesterol without affecting absorption of triglycerides and fat soluble vitamins. In clinical studies the combination therapy of ezetimibe with statins led to percentage reductions of LDL-C from baseline from 34% to 59.7%. Additionally, the combination therapy with fenofibrate has shown a reduction to the levels of triglycerides up to 44%, from baseline. Furthermore, all clinical studies up to now, have shown that the combination therapy of statin plus ezetimibe was well-tolerated with low levels of serious adverse effects.

In summary co-administered of ezetimibe (at doses up to 10 mg) with simvastatin (10 or 20mg) to healthy subjects with hypercholesterolaemia can be well tolerated, reducing significantly serum LDL-C levels. What remains to be confirmed from randomized clinical trials is whether this coadministration has an additive effect on the reduction of circulating inflammatory markers, like hs-CRP, more than statin monotherapy, and if this additive reduction has a remarkable effect on the prevalence of future cardiovascular events.

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