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Review

Pleiotropic effects of ezetimibe: Do they really exist?

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ABSTRACT

Ezetimibe represents a new lipid lowering agent which inhibits cholesterol absorption. It effectively reduces low-density lipoprotein cholesterol when administered either alone or in combination with statins. However, its effect on cardiovascular mortality remains under question since it failed to demonstrate any significant changes in the primary endpoints of the recently published ENHANCE and SEAS studies. A possible explanation for this unsuccessful outcome is that ezetimibe lacks pleiotropic effects. This article aims to review the potential pleiotropic effects of the drug mainly on inflammation markers, lipoprotein subfractions and endothelial function.

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1. Introduction

Atherosclerosis is the root cause of cardiovascular disease, which is the biggest killer of the 21st century (Heron, 2007). Increased concentrations of low-density lipoprotein cholesterol (LDL-C) have been shown to play a key role in the pathogenesis of atherosclerosis and have been strongly associated with a greater prevalence of cardiovascular disease (Gordon et al., 1981). Furthermore, the reduction of LDL-C by dietary and/or pharmaceutical means leads to an important reduction in the incidence of cardiovascular events (LaRosa et al., 2005). However, atherosclerosis is a complex process and it cannot be attributed to only one factor. In particular, a number of theories–including the role of dyslipidemia, hypercoagulability, oxidative stress, and endothelial dysfunction, as well as inflammation and infection by certain pathogens–have been propounded from time to time to explain this complex phenomenon (Mallika et al., 2007). Statins is the mainstay

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of lipid-lowering therapy in the recent decades. Some benefit from the use of these drugs has been shown to be accomplished through effects beyond LDL-C reduction (Athyros et al., 2009). These effects represent the beneficial drug involvement in different pathogenetic paths of the complicating process of atherosclerosis.

Ezetimibe is the first of a new class of hypolipidemic agents known as the cholesterol absorption inhibitors. After ingestion ezetimibe is rapidly absorbed and metabolized by the small intestine and the liver to its glucuronide. Both molecules (ezetimibe and its glucuronide) undergo continuous enterohepatic recycling with a half life of approximately 24 h (Kosoglou et al., 2005). Ezetimibe and its metabolite act at the brush border of the small intestine where it selectively inhibits cholesterol absorption from the intestinal lumen into the enterocytes (Toth and Davidson, 2005). This action is managed by the selective blockage of the sterol transporter Niemann–Pick C1-like 1 (NPC1L1) protein. Physiologically, this transporter mediates the intestinal uptake of cholesterol and plant sterols, but, when inhibited by ezetimibe, cholesterol fails to be absorbed by the enterocytes (Altmann et al., 2004; Garcia-Calvo et al., 2005). Consequently, less cholesterol is delivered to the liver. The hepatocytes upregulate the LDL receptor, which in turn leads to increased cholesterol clearance from the circulation (Lammert and Wang, 2005). The NPC1L1 protein contains about 1300 residues with 13 predicted transmembrane domains (Davies et al., 2000). NPC1L1 has been reported to localize on the plasma membrane (Altmann et al., 2004]) or in intracellular compartments ([Sane et al., 2006]). More recently, Yu et al. found that NPC1L1 is transported from the endocytic recycling compartment to the plasma membrane after cholesterol depletion and that only when localized there can it promote cholesterol uptake (Yu et al, 2006). Recently published studies indicate that NPC1L1 recycles between endocytic recycling compartment and plasma membrane in a cholesterol-dependent manner: depletion of cholesterol causes the transport of NPC1L1 from endocytic recycling compartment to plasma membrane, whereas replenishment of cholesterol results in the transportation of NPC1L1 from plasma membrane to endocytic recycling compartment. Meanwhile, cholesterol is internalized together with NPC1L1. The endocytosis of NPC1L1 is dependent on microfilaments and the clathrin/AP2 complex. Blocking NPC1L1 endocytosis decreases cholesterol uptake, indicating that NPC1L1 mediates cholesterol uptake through vesicular endocytosis. Ezetimibe blocks the internalization of NPC1L1, thereby inhibiting cholesterol uptake (Ge et al 2008).The present review considers the lipid-lowering effects and focuses on the potential pleiotropic effects of ezetimibe.

2. Effect on atherosclerosis in animal models

In a study by Davis et al apolipoprotein E (apoE) knockout mice were administered various combinations of low and high fat diet with or without ezetimibe. Ezetimibe administration was associated with a reduction of the aortic atherosclerotic lesion surface area from 20.2% to 4.1% in the western diet group and from 24.1% to 7.0% in the low-cholesterol diet group. Additionally, it reduced carotid artery atherosclerotic lesion cross-sectional area by 97% in the western and low-cholesterol groups and by 91% in the cholesterol-free diet group (Davis et al., 2001). In a similar study, the administration of ezetimibe was associated with a significant reduction in the aortic vessel wall thickness, which was measured by means of magnetic resonance imaging (Dietrich et al., 2009). Greenberg et al utilized apoE knockout mice with inherent deficiency in cholesterol absorption and demonstrated that a moderate decrease in cholesterol absorption (41%) was associated with an impressive reduction in atherosclerosis formation (Greenberg et al., 2009). In another study by Kuhlencordt et al apoE knockout mice and apoE/endothelial nitric oxide synthase (eNOS) double knockout mice received high fat diet with or without ezetimibe. The drug potently reduced atherosclerosis of the aorta in both groups. Atheroprotection with ezetimibe proved to be significantly better in the eNOS competent-apoE knockout mice suggesting that the eNOS pathway augmented the anti-atherosclerotic effect of the drug. However, in this study ezetimibe did not affect eNOS production or activity (Kuhlencordt et al., 2009). In a similar study in apoE deficient mice ezetimibe again demonstrated a significant inhibitory effect in the progression of atherosclerotic plaque. In addition, the drug improved the endothelial function (as assessed by the vasodilator response of acetylcholine) and was associated with an increase in the production of eNOS mRNA and a decrease in the production of interleukin-6 mRNA, suggesting that mechanisms beyond lipid reduction have contributed to the atheroprotective effect (Nakagami et al., 2009). In another study by Zheng et al. C57BL/6J mice were fed a high fat/cholesterol diet for 7 months. The mice became obese with marked hepatomegaly, liver steatosis and increased plasma alanine aminotransferase activity. Ezetimibe significantly reduced hepatomegaly by decreasing hepatic triglyceride, cholesteryl-ester and free cholesterol concentrations. In addition, ezetimibe treatment significantly decreased plasma alanine aminotransferase activity (Zheng et al., 2008). In a rabbit model of atherosclerosis, ezetimibe proved to decrease the macrophage/monocyte content of the atherosclerotic plaque through the reduction of the monocyte chemoattractant protein-1 (Gomez-Garre et al., 2009).

3. Lipid-modifying effects of ezetimibe

3.1. Effects on serum lipids

Ezetimibe monotherapy decreases LDL-C serum levels by 7 to 18% (Bays et al., 2001; Kalogirou et al., 2007a; Knopp et al., 2003; Mikhailidis et al., 2005; Wierzbicki et al., 2005). There is substantial individual variability in LDL-C lowering with ezetimibe. For example, in one study LDL-C changes with ezetimibe varied from −45 to +11% and in another from −60 to +13% (Gazi et al., 2007; Kalogirou et al., 2007a). Therefore, there are poor and good responders to ezetimibe. Genetic variations in the Niemann–Pick C1-like 1 protein may contribute to the inter-individual variation in the LDL-C response to ezetimibe (Simon et al., 2005). High density lipoprotein cholesterol (HDL-C) levels are usually increased by 1.3 to 6.2% following ezetimibe administration as monotherapy, although this change does not always reach significance (Dujovne et al., 2002; Wierzbicki et al., 2005). Remarkably, in the recently published study by Taylor et al, in which ezetimibe was compared with niacin, ezetimibe paradoxically reduced HDL-C levels by 2.8 ± 5.7 mg/dL. Triglyceride levels decrease by 1.7 to 9.4% following ezetimibe administration, but this reduction is not always significant (Bays et al., 2001; Dujovne et al., 2002). Interestingly, triglyceride lowering with ezetimibe is greater in subjects with high baseline triglyceride values (Gazi et al., 2007; Nakou et al., 2008).

The results of the studies that evaluated the efficacy of ezetimibe added to different statins show an additional lipid-lowering effect when ezetimibe is added to statins. Thus, LDL-C is reduced by −13.8 to −25.1% and triglyceride levels decrease by −7.5 to −14% (Bays et al., 2004; Davidson et al., 2004; Melani et al., 2003). The lipid-lowering efficacy of ezetimibe co-administered with simvastatin was compared with rosuvastatin monotherapy in a meta-analysis of pooled data from 14 clinical trials (Catapano et al., 2005). According to this meta-analysis the mean percentage reductions in LDL-C, triglycerides and apolipoprotein B were greater for ezetimibe/simvastatin than for the corresponding dose of rosuvastatin, whereas increases in HDL-C levels were comparable between the two treatments (Catapano et al., 2005). Interestingly, the reduction in LDL-C achieved when ezetimibe is added to on-going statin therapy is greater than that observed with ezetimibe monotherapy (Kalogirou et al., 2007a; Kalogirou et al., 2007b; Meyers et al., 2006). This finding may be attributed to the fact that ezetimibe monotherapy results in a

compensatory increase in HMG-CoA reductase activity, while the ezetimibe–statin combination does not change significantly the activity of this enzyme (Gouni-Berthold et al., 2008b). In this context a study showed that ezetimibe monotherapy reduced fractional cholesterol absorption by 54%, whereas cholesterol synthesis was increased by 89% (both $P<0.001$ vs. placebo) (Sudhop et al., 2002). The ratio of lathosterol to cholesterol (a marker of HMG-CoA reductase activity) was increased by 72% ($P<0.001$ vs. placebo). On the contrary, in the presence of a statin this increase in the de novo hepatic synthesis of cholesterol is inhibited, a fact that may explain the greater LDL-C reduction when ezetimibe is co-administered with statins.

3.2. Effects on lipoprotein subfractions

The risk for the development of cardiovascular disease is increased in the presence of excessive amounts of small, dense LDL particles, because these particles have been shown to be more atherogenic than the large, buoyant ones (Lamarche et al., 1997; Stampfer et al., 1996). In a recent study by Ose et al. which included 1397 dyslipidemic patients the effect of ezetimibe alone and in addition to simvastatin on LDL subclasses was determined by means of segmented gradient gel electrophoresis and ultracentrifugation. Ezetimibe, both as monotherapy and in combination with simvastatin, reduced the cholesterol content of all LDL subclasses, thus failing to shift the distribution of LDL particles toward a larger, more buoyant LDL subclass pattern (Ose et al., 2007). Similar were the results of another study in patients with mixed hyperlipedemia, where ezetimibe reduced almost uniformly both the most buoyant and the most dense LDL subfractions, resulting in a limited, non significant reduction in the proportion of the small, dense LDL particles (Farnier et al., 2005). In a study from our group ezetimibe was administered in 50 patients with primary dyslipidemia and resulted in a decrease in the concentrations of all LDL subfractions (Kalogirou et al., 2007a). However, this decrease was more pronounced in the concentrations of small, dense LDL subfractions and, therefore, a trend towards more buoyant LDL particles was observed, especially in patients with triglyceride levels greater than 150 mg/dL (1.7 mmol/L). The same phenomenon was observed in another study by our group in which ezetimibe was administered in overweight and obese patients with dyslipidemia (Nakou et al., 2008). In contrast, the addition of ezetimibe in patients receiving atorvastatin decreased LDL-C values exclusively by reducing the concentrations of large, buoyant LDL subfractions (Kalogirou et al., 2007b). Another study evaluated the effect of ezetimibe on LDL subfraction distribution in 20 severely hypercholesterolemic patients treated with statins and regular LDL apheresis. Ezetimibe significantly decreased the cholesterol content of all LDL subfractions, but with less effect on the cholesterol content of small, dense LDL particles (Geiss et al., 2006). In another study in patients with metabolic syndrome ($n=69$) the effect of the combination of fluvastatin plus fenofibrate were compared with the combination of simvastatin plus ezetimibe. The investigators divided the study population into two groups: those with high levels of small, dense LDL and those without. In patients with high levels of small, dense LDL the combination of simvastatin with ezetimibe was more potent in reducing LDL-C. However the combination of fenofibrate plus fluvastatin was more effective in reducing triglyceride levels and increasing LDL particle size, whereas the combination of simvastatin plus ezetimibe reduced LDL particle size even more (Winkler et al., 2009) (Table 1).

It should be noted that the effects of ezetimibe on LDL size and subfraction distribution come from studies where different methodologies where used. As it has been shown in a previous study (Ensign et al., 2006), there is a substantial heterogeneity of results among different methodologies and complete agreement occurred in less than 10% of the samples studied. Overall, it seems that ezetimibe monotherapy may exert a slight beneficial effect on LDL size, especially in the presence of elevated triglycerides. This impact is diminished in the presence of statin pre-treatment.

3.3. Effects on apolipoprotein concentrations

Total apolipoprotein B value represents the total number of potentially atherogenic lipoproteins. Ezetimibe as monotherapy can reduce apolipoprotein B levels by approximately 10 to 15% (Dujovne et al., 2002; Kalogirou et al., 2007a). Apolipoprotein AI levels, which represent the main apolipoprotein of the HDL particles, increase by 2.5 to 6.5% with ezetimibe (Gazi et al., 2007).

4. Effect of ezetimibe on lipoprotein oxidation

Oxidation of lipoproteins is a fundamental process in the pathogenesis of atherosclerosis because it contributes to foam cell generation, endothelial dysfunction, and inflammatory processes (Rizzo et al., 2009). Studies have shown that oxidised cholesterol in the diet increases the development of atherosclerosis (Staprans et al., 2006). A recent study showed that ezetimibe can reduce the serum levels of oxysterols by 50%, when administered after a meal containing oxidised cholesterol (Staprans et al., 2006). In another study, ezetimibe 10 mg prolonged the lag time of LDL-C oxidation both when it was used as monotherapy (from 144 ± 18 min to 195 ± 16 min, $P<0.001$) and on top of simvastatin (from 55.9 ± 16.5 to 82.7 ± 11.6, $P<0.0001$) (Hussein et al., 2008). Furthermore, it has been shown that macrophages express Niemann–Pick C1-like 1 protein and that ezetimibe can reduce the uptake of oxidised LDL-C by human monocyte-derived macrophages by approximately 50% (Seedorf et al., 2004).

5. Effect on inflammatory markers

It is recognized that atherosclerosis is largely an inflammatory process (Lamon and Hajjar, 2008). High sensitivity C-reactive protein (hsCRP) is an inflammatory marker. It has been observed that the elevated levels of hsCRP are indicative of increased risk for cardiovascular disease (Ridker et al., 2002). There exists substantial evidence that monotherapy with ezetimibe does not significantly reduce serum hsCRP levels (Gazi and Mikhailidis, 2006). However, the combination with a statin provides a further decrease in hsCRP levels compared with statin monotherapy (Ballantyne et al., 2005; Bays et al., 2004; Sager et al., 2005). The effects of ezetimibe, alone or in combination with statins, on hsCRP were recently examined in 2 pooled analyses of randomized, placebo-controlled trials: six 12-week trials as monotherapy ($n=1372$) and seven 6- to 8-week trials as add-on to baseline statin therapy ($n=3899$) (Pearson et al., 2009). It was confirmed that the reduction in hsCRP serum levels by monotherapy with ezetimibe was numerically greater than with placebo but lacked statistical significance (treatment difference 6%, $P=0.09$). Added to statin therapy, ezetimibe was associated with a significant additional reduction in hsCRP (treatment difference 10%, $P<0.001$) (Pearson et al., 2009). On the other hand, in patients with rheumatoid arthritis ezetimibe monotherapy reduced CRP levels similarly to simvastatin (ezetimibe -5.35 ± 9.25 mg/L; simvastatin -5.05 ± 6.30 mg/L; both $P<0.001$) (Maki-Petaja et al., 2007). Interestingly, the addition of ezetimibe to fenofibrate ($n=576$) is not associated with an additional decrease in hsCRP values (McKenney et al., 2006).

Lipoprotein-associated phospholipase A2 [Lp-PLA2, also known as platelet-activating factor-acetylhydrolase (PAF-AH)] is mainly associated with apolipoprotein B containing lipoproteins (primarily LDL), whereas a small proportion of circulating enzyme activity is associated with HDL (Tselepis and Chapman, 2002). A positive association between total plasma Lp-PLA2 mass or activity and the risk for atherosclerotic events has been observed (Ballantyne et al., 2004; Oei et al., 2005). In contrast, the HDL-associated enzyme may

Table 1
Effect of ezetimibe on LDL subfractions.

Reference	Patient population	Drugs used	Method	Results
Ose et al., 2007	1397 patients with primary hypercholesterolemia	Ezetimibe monotherapy ($n=139$) and ezetimibe plus various doses of simvastatin ($n=549$)	Ultracentrifugation and gradient gel electrophoresis	Reduction in cholesterol of all LDL subclasses, no change in sdLDL in all groups
Kalogirou et al., 2007a,b	100 patients with primary dyslipidemia	Ezetimibe 10 mg ($n=50$), ezetimibe on top of atorvastatin 20 mg ($n=50$)	Lipoprint (gel electrophoresis)	Reduction of sdLDL especially in patients with triglycerides>150 mg/dL with ezetimibe monotherapy. No change in sdLDL in the combination group
Nakou et al., 2008	86 overweight and obese patients with hypercholesterolaemia	Ezetimibe monotherapy orlistat monotherapy, ezetimibe plus orlistat	Lipoprint (gel electrophoresis)	Significant reduction of sdLDL with ezetimibe(−48%, $P<0.01$), orlistat and their combination
Winkler et al., 2009	56 patients with metabolic syndrome	Fluvastatin 80 mg plus fenofibrate 200 mg vs ezetimibe 10 mg plus simvastatin 20 mg	Ultracentrifugation	Only the combination of fluvastatin plus fenofibrate increased LDL particle size
Farnier et al., 2005	625 patients with mixed hyperlipaedemia	Fenofibrate monotherapy, ezetimibe monotherapy, ezetimibe plus fenofibrate	Ultracentrifugation and gradient gel electrophoresis	Improvement in lipoprotein pattern with fenofibrate alone or with ezetimibe, but not with ezetimibe monotherapy
Geiss et al., 2006	20 severly hypercholesterolaemic patients	Ezetimibe on top of LDL apheresis and statins	Ultracentrifugation	No change in sdLDL concentrations

sdLDL: small dense LDL.

exhibit anti-atherogenic properties (Tselepis and Chapman, 2002). Ezetimibe monotherapy decreased total Lp-PLA2 plasma activity and mass (Kalogirou et al., 2007a; Saougos et al., 2007). However, this drug simultaneously decreased HDL-associated Lp-PLA2 activity (Kalogirou et al., 2007a; Saougos et al., 2007). This may be related to the fall in HDL-C concentration observed in this study. It should be emphasized that Lp-PLA2 activity improved significantly more with the combination of ezetimibe and orlistat compared with either monotherapy (Nakou et al., 2008).

6. Effect on endothelial function

Abnormal endothelial function represents an early feature of atherosclerosis (Kinlay and Ganz, 1997; Luscher and Barton, 1997) and it has been associated with plaque progression and the development of atherosclerotic complications (Kinlay and Ganz, 1997). It has been suggested that the normal, healthy monolayer of endothelial cells may act as a mechanical and biological barrier between the risk factors and their catastrophic impact on vasculature (Bonetti et al., 2003). Statins have been shown to improve endothelial function (Egashira et al., 1994; Treasure et al., 1995), even before any evident decrease in LDL-C levels can be detected (Laufs et al., 2001). Several studies have been recently contacted to examine the possible beneficial effect of ezetimibe on endothelial function (Table 2).

Settergren et al conducted a study in patients with dysglycemia and coronary artery disease. Thirty-nine patients were randomly assigned to receive simvastatin 80 mg or ezetimibe 10 mg/simvastatin 10 mg. Flow-mediated dilation was measured before and after 6 weeks of treatment. The increase in flow-mediated dilation was comparable in both groups (flow-mediated dilation increased from 4.3% at baseline to 5.5% at follow-up in the entire group), as was the case for the changes in LDL-C and hsCRP levels (Settergren et al., 2008). In a sub study of this trial the function of skin microvasculature was assessed in the same two groups of patients. Laser Doppler fluxmetry was performed at rest, after arterial occlusion, and following heating of the forearm and foot. Skin microvascular function was improved in both treatment groups without any significant difference between them (Settergren et al., 2009). In a similar study, Araujo et al compared flow-mediated dilation in hypercholesterolemic patients assigned in two groups: a group treated with simvastatin 80 mg and another group treated with simvastatin 10 mg and ezetimibe 10 mg. Flow-mediated dilation was improved in both treatment groups without significant difference (Araújo et al., 2009). In another recent study fasting and post-fat load flow-mediated dilation was measured in 19 male patients with metabolic syndrome who were randomly assigned in two groups: simvastatin 80 mg and ezetimibe 10 mg/simvastatin 10 mg. Fasting endothelial function was comparable after both treatments, whereas post-fat load measures of flow-mediated dilation were significantly better with the combination therapy ($7.7\pm1.6\%$ vs. $4.3\pm0.6\%$) (Olijhoek et al., 2008). Westerweel et al used endothelial progenitor cells to assess the endothelial function in obese patients with metabolic syndrome receiving low-dose statin with ezetimibe combination or high-dose statin monotherapy. Endothelial progenitor cell levels were comparably increased in both groups (Westerweel et al., 2008). In another report, 20 patients with rheumatoid arthritis received simvastatin 20 mg or ezetimibe 10 mg. Both treatments improved similarly the endothelial function and aortic stiffness (Maki-Petaja et al., 2007). However this study was contacted in a specific patient group and therefore its results may not be applicable to the general population. Another study in male patients with metabolic syndrome assessed the effect of the combination of ezetimibe with atorvastatin 10 mg/d versus atorvastatin 40 mg/d on forearm blood flow. The LDL-C concentration was lower after combination therapy, but this difference was not significant. Forearm blood flow was significantly better with the ezetimibe/atorvastatin combination (Bulut et al., 2005).

Contrary to the above mentioned results, which suggest that ezetimibe exerts a beneficial effect on endothelium, there are a few reports which demonstrate a failure of the drug to improve endothelial function when compared to statins. In a recent study by Ostad et al, 58 patients with coronary artery disease were randomly assigned to receive high dose of atorvastatin (80 mg) or combination treatment with ezetimibe and low-dose of atorvastatin (10 mg). LDL-C levels were significantly reduced with no difference between the two groups, but flow-mediated dilation was significantly improved only in the high dose atorvastatin group. The authors attributed the improvement in the endothelial function in the LDL-C independent effects of high dose of atorvastatin (Ostad et al., 2009). In another recently published study, which included 22 patients with heart failure, rosuvastatin 10 mg was compared with ezetimibe 20 mg in terms of branchial flow-mediated dilation improvement. Although similar LDL-C reduction was achieved in the two treatment groups, endothelial function improved only in the patients who received rosuvastatin (Gounari et al., 2009). However, in this particular study ezetimibe was used in a rather unusual dose and was compared to the most efficient statin which can produce up to 40% decrease in LDL-C levels (McKenney, 2005). In another report by Landmesser et al 20 patients with congestive heart failure were randomly assigned to receive ezetimibe 10 mg or simvastatin 10 mg. At the end of the study the LDL-C levels were comparable in both groups. Flow-dependent

Table 2
Effects of ezetimibe on endothelial function.

Reference	Study population	Drugs used	Outcome	Result
(Settergren et al., 2008	39 patients with dysglycaemia and CAD	Simvastatin 80 mg vs ezetimibe 10 mg and simvastatin 10 mg	FMD and FBF	FMD increased with both interventions (1.5% in the combination group vs 0.9% in the simvastatin 80 group, $P=0.39$)
Olijhoek et al., 2008	19 male obese patients with metabolic syndrome	Simvastatin 80 mg vs ezetimibe 10 mg and simvastatin 10 mg	Fasting and post-fat load FMD	Post-fat load FMD improved only with the combination therapy
Araújo et al., 2009	23 hypercholesterolemic patients	Simvastatin 80 mg vs simvastatin 10 mg and ezetimibe 10 mg	FMD	Significant improvement in both treatment groups
Westerweel et al., 2008	Obese patients with metabolic syndrome	Simvastatin 80 mg vs ezetimibe 10 mg and simvastatin 10 mg	EPC levels	Comparable increase in both groups
Maki-Petaja et al., 2007	20 patients with rheumatoid arthritis	Simvastatin 20 mg vs ezetimibe 10 mg	FMD and Aortic stiffness	FMD ($1.37\pm1.17\%$ and $2.51\pm2.13\%$; $P=0.001$) improved with both interventions
Bulut et al., 2005	14 male patients with metabolic syndrome	Ezetimibe with atorvastatin 10 mg vs atorvastatin 40 mg	FBF response to ACH and SNP	FBF improved only with the combination treatment ($P<0.05$)
Settergren et al., 2009	36 patients with dysglycaemia and CAD	Simvastatin 80 mg vs ezetimibe 10 mg and simvastatin 10 mg	Skin microvascular function assessed by laser Doppler fluxmetry	Skin microvascular function improved by both treatment groups
Ostad et al., 2009	58 patients CAD	Atorvastatin 80 mg vs atorvastatin 10 mg plus Ezetimibe 10 mg	FMD NMD	FMD improved only with Atorvastatin 80 ($2.7\pm3.0\%$ vs $0.6\pm2.9\%$, $P=0.018$)
Gounari et al., 2009	22 patients CHF	Rosuvastin 10 mg vs. ezetimibe 20 mg	FMD	FMD improved only with rosuvastatin
Landmesser et al., 2005	20 patients CHF	Simvastatin 10 mg vs. ezetimibe 10 mg	FMD Active EPC's	Only simvastatin improved FMD ($10.5\pm0.6\%$ vs $5.1\pm0.7\%$; $P<0.01$) and increased EPC's
Fichtlscherer et al., 2006	60 patients with CAD	Ezetimibe 10 mg vs ezetimibe 10 mg plus simvastatin 20 mg vs atorvastatin 40 mg	FBF response to ACH or SNP	Only atorvastatin 40 improved FBF
Liu et al., 2009	60 patients with dyslipidemia	Simvastatin 40 mg vs ezetimibe 10 mg plus simvastatin 10 mg	ROCK activity and FMD	Only simvastatin 40 improved ROCK activity and FMD ($P<0.01$)
Efrati et al., 2007	40 patients with hyperlipidemia	Simvastatin 40 mg vs ezetimibe 10 mg vs ezetimibe 10 mg plus simvastatin 40 mg vs simvastatin 80 mg	Arterial stiffness expressed as Augmentation index (assessed by pulse wave analysis)	Only simvastatin 40 improved AIx ($30.2\pm8.3\%$ before, $21.6\pm6.5\%$ after treatment, $P<0.001$)

CAD: coronary artery disease, FMD: Flow-mediated dilation, NMD: nitroglycerin mediated dilation, CHF: congestive heart failure, EPC: endothelial progenitor cells, FBF; forearm blood flow, ROCK: Rho-associated coiled-coil containing protein kinase.

dilation was markedly improved by simvastatin ($10.5\pm0.6\%$ versus $5.1\pm0.7\%$; $P<0.01$) but not ezetimibe administration ($5.6\pm0.5\%$ versus $5.8\pm0.6\%$; $P=$NS). Additionally, in the same study, the number of functionally active endothelial progenitor cells was increased by simvastatin, whereas ezetimibe had no effect (Landmesser et al., 2005). Another study failed to show any improvement in acetylcholine induced forearm blood flow responses in patients with stable coronary artery disease administered ezetimibe either as monotherapy or on top of simvastatin 20 mg. In contrast, the two other subgroups that received increasing dose of atorvastatin (from 10 mg to 40 mg) or directly atorvastatin 40 mg demonstrated significant increases in forearm blood flow (Fichtlscherer et al., 2006). However, in this study, groups differed significantly in LDL-C levels both before and after treatment, a fact that may have hampered the results of the study. In another study 60 dyslipidemic patients were treated with simvastatin 40 mg, ezetimibe 10 mg/simvastatin 10 mg or placebo. Rho-associated coiled-coil containing protein kinase (ROCK) activity and flow-mediated dilatation was assessed. ROCKs have been found to regulate a wide range of fundamental cell functions such as contraction and motility through their effect on actin organization. Abnormal activation of the RhoA/ROCK pathway has been observed in major cardiovascular disorders such as atherosclerosis, restenosis, hypertension, pulmonary hypertension, and cardiac hypertrophy (Loirand et al., 2006). Only simvastatin was associated with reduction in ROCK activity and improvement of flow-mediated dilatation, despite the fact that LDL-C and hsCRP levels were similar in both groups. Decrease in ROCK activity with simvastatin 40 mg remained significant even after controlling for changes in low-density lipoprotein cholesterol ($P=0.01$) and correlated with the improvement in flow-mediated dilation ($R^2=-0.78$, $P<0.01$), suggesting a possible pleiotropic effect for the high dose of simvastatin, but not for the combination treatment (Liu et al., 2009). Efrati et al examined the arterial stiffness expressed as the Augmentation Index (assessed by pulse wave analysis) in dyslipidemic subjects ($n=40$) who received various combinations of simvastatin and ezetimibe:

- group 1 comprised previously untreated patients, who received simvastatin at doses of 40 mg/day during the study.
- group 2 comprised patients previously treated with simvastatin at 40 mg/day, who received simvastatin at 80 mg/day during the study.
- group 3 consisted of patients previously untreated, who received ezetimibe at doses of 10 mg/day during the study.
- group 4 comprised patients previously treated with simvastatin at 40 mg/day, who received simvastatin at 40 mg/day and ezetimibe at 10 mg/day during the study.

The authors found that ezetimibe either as monotherapy or on top of simvastatin did not produce favourable changes in arterial stiffness, in contrast to the first group of patients who developed significant improvement (Efrati et al., 2007). However, in this study, the LDL-C levels differed significantly among the four groups, whereas in groups 2 and 4 patients were already on a statin therapy.

Overall, the impact of ezetimibe in the endothelial function is controversial. Interestingly, it seems that ezetimibe demonstrated a beneficial effect mostly in subjects with metabolic syndrome or dysglycaemia. This population exhibits a high prevalence of insulin resistance, a disorder that is positively associated with endothelial dysfunction (Caballero, 2003; Steinberg et al., 1996). It may be that ezetimibe exerts its beneficial effect on the endothelial function of these patients by improving insulin resistance. Indeed, in a study ($n=100$) with pravastatin vs ezetimibe 10/pravastatin 10 mg on lipid and glucose metabolism showed that insulin resistance decreased

with the combination treatment in contrast to the statin monotherapy (Dagli et al., 2007). In a study with Zucker fatty rats, an experimental model of the metabolic syndrome, ezetimibe demonstrated a significant improvement of insulin resistance and liver steatosis (Deushi et al., 2007). In addition, the same research group provided in vitro evidence that the beneficial effects of ezetimibe on insulin resistance and hepatic steatosis are exerted through the inhibition of the hepatic Niemann–Pick C1-like 1 cholesterol transpoter (Nomura et al., 2009). Also, ezetimibe either alone or in combination with acarbose for 24 weeks reduced lipid deposits in the liver of mice fed high fat diet in comparison with the control group (Nozaki et al., 2009). However, in another study ezetimibe monotherapy failed to improve insulin sensitivity, as assessed by the euglycaemic–hyperinsulinaemic clamp technique, in 6 obese dyslipidemic subjects (Gonzalez-Ortiz et al., 2006). Based on the above mentioned data it is obvious that further investigation is needed with large scale, long-term clinical trials especially in population with confirmed insulin resistance in order to clarify the impact of ezetimibe on the endothelial function and carbohydrate homeostasis.

7. Effect on platelet aggregation

In a study by Hussein et al, 16 statin-naive patients received ezetimibe monotherapy and 22 patients received ezetimibe on top of on-going simvastatin treatment. Ezetimibe 10 mg daily for 3 months decreased maximal platelet aggregation from 83 ± 15% to 60 ± 36% ($P = 0.04$). However, ezetimibe on top of simvastatin 20 mg did not affect platelet aggregation (Hussein et al., 2008). In another study, 32 patients with type 2 diabetes mellitus and coronary artery disease were randomly assigned to receive simvastatin 80 mg or ezetimibe 10 mg/simvastatin 10 mg. LDL-C decreased similarly in both treatment groups. Platelet function was assessed by whole blood flow cytometry and turbidimetric aggregometry with agonist stimulation ex vivo before and after treatment. Both groups demonstrated similar basal and adenosine diphosphate (ADP)- or thrombin-induced platelet P-selectin expression, as well as fibrinogen binding and platelet–leukocyte aggregation. Similarly, neither treatment affected ADP-induced platelet aggregation, suggesting that both regimens failed to demonstrate any pleiotropic effect regarding platelet aggregation (Malmstrom et al., 2009). In another study 56 patients with coronary artery disease were administered atorvastatin 40 mg or ezetimibe 10 mg/atorvastatin 10 mg. Platelet activation markers (P-selectin) after stimulation with adenosine diphosphate were reduced by atorvastatin monotherapy (−5.2 ± 1.6 arbitrary units) but not by ezetimibe–low-dose atorvastatin combination (2.1 ± 1.8 arbitrary units; $P<0.005$) despite a similar reduction of LDL-C, suggesting that the combination therapy lacks any effect concerning platelet aggregation (Piorkowski et al., 2007).

8. Effect on adipokines

In a recent study 72 healthy men were randomized to receive ezetimibe, simvastatin 40 mg/d or their combination for 2 weeks (Gouni-Berthold et al., 2008a). Neither ezetimibe nor simvastatin or their combination had any effect on serum leptin, total and high molecular weight adiponectin and resistin concentrations. Moreover, ezetimibe did not significantly affect visfatin serum levels either as monotherapy or when it was added to a statin (Derdemezis et al., 2008).

9. Other effects of ezetimibe

In a recently published study ezetimibe was administered in 10 patients with type IIb hyperlipidemia and lipid and lipoprotein profiles were examined during fast and after an oral fat loading test. In addition to improving the fasting lipoprotein profile, ezetimibe reduced the postprandial cholesterol and triglyceride content of chylomicrons as assessed by high performance liquid chromatography analysis. The authors concluded that this finding may suggest a postprandial suppression of intestinal chylomicron production, which is of significant benefit in patients with type IIb hyperlidemia (Masuda et al., 2009).

Ezetimibe potently reduces the circulating levels of campesterol and sitosterol (Salen et al., 2004). In a study with 18 hypercholesterolemic patients reduction of sitosterol levels by 41% ($P<0.001$) and campesterol levels by 48% ($P<0.001$) was noted after ezetimibe administration (Salen et al., 2004). This effect could translate in clinical benefit, since excessive sitosterol levels have been associated with a 1.8-fold increase in coronary heart disease risk (Assmann et al., 2006).

In a recent report cholesterol reduction with ezetimibe resulted in a retardation of cancer growth possibly by inhibiting tumor angiogenesis in mice (Solomon et al., 2009).

In a study by Nakamura et al, the efficacy of ezetimibe in reducing circulating levels of asymmetric dimethylarginine was evaluated in patients with chronic kidney disease. Asymmetric dimethylarginine inhibits nitric oxide synthase and aggravates the progression of atherosclerosis (Kielstein et al., 2001), whereas it may play a role in the progression of chronic kidney disease (Fliser et al., 2005). Ezetimibe treatment for six months reduced serum levels of asymmetric dimethylarginine and decreased proteinuria in 10 non-diabetic early stage CKD patients (Nakamura et al., 2009a). In addition, recently published data from the same authors confirm the efficacy of ezetimibe in terms of proteinuria reduction. More specifically, ezetimibe on top of pitavastatin produced significant incremental reduction in proteinuria in comparison with pitavastatin therapy alone (Nakamura et al., 2009b).

In another study, ezetimibe was administered in 56 renal transplant recipients on top of simvastatin. A group receiving statin therapy ($n = 28$) served as the control group. In addition to the improvement of the lipid profile, mean creatinine clearance remained stable in ezetimibe-treated patients but decreased significantly in control group, suggesting that ezetimibe exerts a possible protective renal effect in kidney transplant recipients (Turk et al., 2008).

Premature atherosclerosis of the coronary vasculature occurs in high prevalence in cardiac transplant recipients (Trulock et al., 2007) and appears to be dependent on T lymphocyte activity (Szeto et al., 2002). In a recent study mononuclear cells were isolated from the blood of 30 cardiac transplant recipients and were co-cultured with ezetimibe, atorvastatin or placebo. Flow cytometry was performed to analyse T lymphocyte counts and functional characteristics. Both ezetimibe and atorvastatin demonstrated significant dose-dependent reductions in CD3 + CD4 + T cell counts. This in vitro observation was independent of LDLreduction and may prove of significant clinical benefit in cardiac transplant recipients (Shaw et al., 2009).

10. Clinical efficacy of ezetimibe

Many studies have shown that ezetimibe decreases LDL-C concentration (Bays et al., 2001; Kalogirou et al., 2007a; Knopp et al., 2003; Mikhailidis et al., 2005; Wierzbicki et al., 2005) and thus it would be expected that the drug might also decrease the incidence of cardiovascular disease. Nevertheless, in the recently published Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study the use of ezetimibe in patients with familial hypercholesterolemia as add-on therapy to simvastatin failed to produce significant changes in the carotid intima media thickness, which is a surrogate marker of cardiovascular disease (Kastelein et al., 2008). In response to these findings a recent secondary analysis of the Stop Atherosclerosis in Native Diabetics (SANDS) study demonstrated similar regression of carotid intima media thickness either with (−0.025 [−0.05 to 0.003] mm) or without ezetimibe (−0.012

[−0.03 to 0.008]mm) within the aggressive treatment group (LDL-C≤70 mg/dl, systolic blood pressure≤115 mm Hg) (Fleg et al., 2008). Furthermore, in the recently published Vytorin on Carotid Intima-Media Thickness and Overall Arterial Rigidity (VYCTOR) study the combination of ezetimibe plus simvastatin produced similar reduction in carotid intima media thickness when compared with the higher doses of pravastatin and simvastatin in 90 high-risk Mexican patients (Meaney et al., 2009). To make matters more complicating, a study by Taylor et al, which compared the efficacy of ezetimibe vs niacin on carotid intima media thickness, was recently terminated early on basis of efficacy. More specifically, niacin reduced potently mean carotid intima media thickness, whereas ezetimibe paradoxically increased carotid intima media thickness, despite managing greater reduction in LDL-C levels than niacin (Taylor et al., 2009). On the other hand, in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study ezetimibe 10 mg plus simvastatin 40 mg reduced the need for coronary artery bypass grafting but did not affect significantly the primary outcome which was a composite of cardiovascular events and need for aortic valve replacement (Rossebo et al., 2008).

11. Conclusion

Ezetimibe potently reduces LDL-C levels both as monotherapy and when added to statins. The possible pleiotropic potential of the drug was placed recently under question, since the drug failed to demonstrate any significant changes in the primary endpoints of the ENHANCE and SEAS studies (Table 3). The published data concerning the impact of ezetimibe on beyond LDL-C cardiovascular disease risk factors derive mostly from small scale studies. On the basis of this limited data the pleiotropic effects of ezetimibe remain controversial and it is far from clear whether these effects are related to LDL reduction or can be attributed to lipid-lowering-independent mechanisms. Most importantly, even if these effects really exist their clinical relevance is doubtful. Thus, the true clinical benefit of ezetimibe remains to be seen until studies with hard endpoints are available. The IMPROVE-IT study ($n=18{,}000$) compares the combination of ezetimibe 10 mg/simvastatin 40 mg with simvastatin 40 mg in patients with coronary artery disease. Clinical benefit is defined as a reduction in the risk of occurrence of the composite endpoint of cardiovascular death, major coronary events and stroke. Also, the SHARP study ($n=9000$) compares the combination of ezetimibe 10 mg plus simvastatin 20 mg with placebo in patients with chronic kidney disease. The primary endpoint of this study is the time to first major vascular event (non-fatal myocardial infarction or cardiac death, stroke, revascularization).

Table 3
Main effects of ezetimibe.

Parameter	Drug action	Remarks
LDL-C	Reduction by 7 to 18% when used as monotherapy, 13.8 to 25.1% on top of a statin	Great inter-individual variability
HDL-C	Increase by 1.3 to 6.2%	Not always significant
Triglycerides	Decrease by 1.7–9.4%	Perhaps greater in individuals with higher levels before treatment
hsCRP	Decrease by 10% on top of statin	Not significant reduction when used as monotherapy
Atherosclerosis in animal models	Overall, substantial atheroprotective effect	Possible improvement of liver statosis
Small dense LDL particles	Possible reduction of sdLDL	Especially in individuals with high levels before treatment
Endothelial function	Possible beneficial effect	Especially in individuals with insulin resistance

sdLDL: small dense LDL particles, hsCRP: high sensitivity CRP.

12. Disclosure

The authors have no relevant financial interests to disclose.

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