Evaluating the safety of Liptruzet (ezetimibe and atorvastatin): what are the potential benefits beyond low-density lipoprotein cholesterol-lowering effect?

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Evaluating the safety of Liptruzet (ezetimibe and atorvastatin): what are the potential benefits beyond low-density lipoprotein cholesterol-lowering effect?

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Introduction: The combination of ezetimibe and atorvastatin (Liptruzet – referred to in this article as eze/ator), has recently been approved by the FDA for reducing low-density lipoprotein cholesterol (LDL-c) in patients with primary or mixed hyperlipidemia as in case of homozygous familial hypercholesterolemia. It helps block intestinal absorption of cholesterol and it inhibits the production of cholesterol in the liver.

Areas covered: The safety and effectiveness of the eze/ator combination as treatment of hyperlipidemia. Medline was searched for atorvastatin and/or ezetimibe.

Expert opinion: The combination of (eze/ator) is proven to be effective in lowering LDL-c. It is not only a safe and effective treatment of hyperlipidemia, but it also reduces inflammatory markers and atherosclerosis. It is not yet clear, however, whether the combination therapy can decrease the risk of diabetes associated with statin administration. Insulin sensitivity is improved by the single administration of ezetimibe, a finding that is documented by several clinical and animal studies. More specifically, ezetimibe has been shown to decrease insulin resistance associated with nonalcoholic fatty liver disease (NAFLD). The effects of combination therapy that have to be explored in future research and clinical trials include whether this combination can be used in the treatment of NAFLD, cholesterol gallstones and portal hypertension.

Keywords: atorvastatin, coronary heart disease, ezetimibe, fatty liver, hyperlipidemia, insulin resistance, Liptruzet

1. Introduction

There is general agreement in the literature about the importance of lowering cholesterol and low-density lipoprotein cholesterol (LDL-c) levels and treatment of low high-density lipoprotein cholesterol (HDL-c) and elevated triglycerides for patients at moderately high risk of coronary heart disease (CHD). Combination therapy is often required to achieve multiple lipid treatment goals and to achieve at least 50% reduction in LDL-c [1]. Liptruzet™, referred to in this article as (eze/ator), which is a fixed-dose combination (FDC) of atorvastatin (Lipitor, Pfizer) and ezetimibe (Zetia, Merck/Schering) (eze/ator), has been recently approved by the FDA for reducing LDL-c in patients with primary or mixed hyperlipidemia as an adjunct to dietary changes. It is also used in decreasing cholesterol in patients
with homozygous familial hypercholesterolemia (HoFH) [1]. This review addresses the effectiveness and safety of ezetimibe and atorvastatin combination therapy.

2. Mechanism of action, including key pharmacokinetics/pharmacodynamics data

Liptruzet (eze/ator) is a FDC of ezetimibe and atorvastatin (eze/ator). It helps block intestinal absorption of cholesterol and it inhibits the production of cholesterol in the liver [2]. It is found in the form of tablets in different dose ranges (10/10, 10/20, 10/40 and 10/80 mg of ezetimibe/atorvastatin).

Atorvastatin is one of the popular statins prescribed to prevent adverse cardiovascular events and to lower blood total cholesterol (TC) and LDL-c (Box 1). It is rapidly absorbed, reaching peak plasma concentration within 2 – 3 h, and has a relatively long half-life of 20 h. Atorvastatin is metabolized by CYP3A4 and CYP3A5 to \( \sigma \)-hydroxy atorvastatin and \( \rho \)-hydroxy atorvastatin. The long half-life may explain in part why the lipid-lowering effect of atorvastatin is not influenced by the time of the day the drug is administered. Atorvastatin acts in the liver by inhibiting the rate-limiting enzyme for cholesterol synthesis; 3-hydroxy-3-methylglutaryl-coenzyme A reductase and this ultimately leads to a decrease in LDL-c and to very LDL-c [3]. Despite the fact that statins are associated with decrease in LDL-c, they can activate the transcription factor steroid response element-binding protein 2 and this leads to expression of not only hepatic endosomal and lysosomal degradation of LDLR receptors (LDLRs) but also the expression of other genes involved in cholesterol metabolism, including proprotein convertase subtilisin/kexin type 9 (PCSK9). The increase in PCSK9 is associated with increase in the degradation of LDLR protein.

<table>
<thead>
<tr>
<th>Box 1. Drug summary.</th>
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<tbody>
<tr>
<td><strong>Drug name (generic)</strong></td>
</tr>
<tr>
<td><strong>Phase (for indication under discussion)</strong></td>
</tr>
<tr>
<td><strong>Indication (specific to discussion)</strong></td>
</tr>
<tr>
<td><strong>Pharmacology description/mechanism of action</strong></td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
</tr>
<tr>
<td><strong>Chemical structure</strong></td>
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</tbody>
</table>
and hence high cholesterol level. This may limit the therapeutic benefit of statins. Therefore, administration of statin and PCSK9 inhibitors may have an additive or even synergistic effect on LDL-c levels [4,5]. Interestingly, Niemann-Pick C1-like 1 (NPC1L1) inhibitor ezetimibe can increase circulating PCSK9 protein levels [6]. Administration of ezetimibe and PCSK9 inhibitors showed greater reduction in LDL-c in mice. It is plausible to suggest that PCSK9 inhibitor may have an additive effect with atorvastatin and ezetimibe in lowering LDL-c and further research is needed in this area.

Ezetimibe is a selective cholesterol absorption inhibitor that acts at the brush border of the small intestine to inhibit intestinal absorption of dietary and biliary cholesterol across the intestinal wall and decreases the delivery of intestinal cholesterol to the liver. It can be used as monotherapy or in combination with statins to treat hyperlipidemia [7]. Research showed that ezetimibe reduces intestinal absorption of cholesterol by inhibiting the action of NPC1L1. NPC1L1 is the main transporter of intestinal cholesterol and is highly expressed in jejunum and plays a role in lipid metabolism and further research is needed to confirm its role in regulation of insulin sensitivity.

Ezetimibe can reduce LDL-c, TC and apolipoprotein B (apoB) when the drug is combined with dietary measures in the treatment of primary hypercholesterolemia. Ezetimibe is combined with statins for the treatment of HoFH [8]. It has no effect on the activity of the major drug metabolizing enzymes (CYP450). Oral administration, is rapidly absorbed, with the time to maximum concentration (t max) being ~ 1 h (Box 1). When absorbed, ezetimibe undergoes extensive Phase II metabolism in the intestine and liver to form an active glucuronide metabolite. Both ezetimibe and ezetimibe-glucuronide are highly bound (> 90%) to plasma proteins and have relatively long terminal half-lives of 13 ~ 22 h. Ezetimibe and its glucuronide are eliminated primarily in feces, with only ~11% recovered in urine as glucuronide [9]. Statins are contraindicated in pregnancy because of the risk of severe malformations. Ezetimibe per se is contraindicated in pregnancy. Therefore, ezetimibe is contraindicated in pregnant women and also when it is used as an adjunctive therapy with statins. Ezetimibe has no significant CYP effect and does not alter biliary micelle formation and therefore does not interfere with absorption of lipid-soluble nutrients [9]. Therefore, the combination therapy of ezetimibe and atorvastatin appears to be safe and effective in deceeding LDL-c with fewer side effects in comparison with atorvastatin maximum dose of 80 mg.

3. Efficacy of ezetimibe and atorvastatin combination versus titration of atorvastatin

3.1 In hyperlipidemia
Importantly, the combination of atorvastatin 10 mg plus ezetimibe provided more effective treatment than an increased titration of atorvastatin (20/40/80) mg when trying to meet the lipid targets of high-risk individuals for cardiovascular disease (CVD) set by most European and Canadian guidelines. For instance, Constance et al. in their 12-week randomized trial [10] showed that atorvastatin plus ezetimibe (ezel/ator) was found to be more effective in lowering LDL-c than doubling the dose of atorvastatin alone [11-13]. It was found that the combination of 10 mg ezetimibe +10 mg atorvastatin was more effective than increasing atorvastatin to 20 mg or switching to 2.5 mg rosuvastatin in patients with hypercholesterolemia whose LDL-c levels had not reached the recommended target value with 10 mg atorvastatin monotherapy for 4 weeks [14].

Despite the fact that published results of clinical trials that monitor the efficacy of ezetimibe and atorvastatin used together show a variety of possible dose combinations (i.e., 10/10, 10/20, 10/40 and 10/80 mg of ezetimibe/atorvastatin), the use of 10/40 mg is preferred. Fortunately, literature-based meta-data analysis predicted that the observed difference in peak plasma concentration (Cmax) between an ezetimibe + atorvastatin FDC and coadministration of these agents translates directly into a non-clinically significant change of < 1.2% absolute difference in the percentage lowering of LDL-c [15]. These results were supported by Leiter et al. who showed that adding ezetimibe to atorvastatin 40 mg was significantly more effective than uptitrationing the dose of atorvastatin to 80 mg in adult patients at high risk of CHD [12].

In a multicenter, double-blind, placebo-controlled study, a total of 148 men and women with untreated primary hypercholesterolemia and CHD were randomized to receive treatment for 6 weeks with either ezetimibe 10 mg + atorvastatin 10 mg (n = 72) or placebo/atorvastatin 10 mg (ATV; n = 76). Following this 6 weeks, ezel/ator provided a significantly greater decrease in LDL-c in comparison to atorvastatin monotherapy (-50.5 vs -36.5%; p < 0.0001), equating to an additional 14.1% reduction (95% CI: -17.90, -10.19) in LDL-c [16].

There is a potential beneficial effect of low-dose ezel/ator combination treatment on postprandial triglyceride control after comparable LDL-c lowering in patients with combined hyperlipidemia [17]. However, Bays et al. proved that administering ezel/ator 10/20 and 10/40 mg to hypercholesterolemic patients produced equivalent LDL-c-lowering effects [18,19]. In addition, the LDL-c-lowering effect was comparable when atorvastatin 20 mg and atorvastatin/ezetimibe 5 mg were used after a 4-week periods of dietary restriction in 82 hypercholesterolemic patients [19]. Therefore, it is possible to suggest that the addition of ezetimibe to a lower dose of atorvastatin can help doctors achieve the lower LDL-c target in their patients, while avoiding the risks associated with high-dose atorvastatin such as myopathy or diabetes (Table 1).

3.2 In CHD and type 2 diabetes
The combination of ezetimibe and atorvastatin has a synergistic effect and effectively decreases the deposition of lipids in the vascular wall. This observation has been shown at the level of experimental and human studies.
Table 1. The benefit of adding ezetimibe to atorvastatin in order to achieve therapeutic LDL-c target.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration</th>
<th>No. of patients</th>
<th>LDL-c</th>
<th>Non-HDL</th>
<th>ApoB</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe/atorvastatin</td>
<td>6 weeks</td>
<td>1053</td>
<td>85%</td>
<td>86%</td>
<td>78%</td>
<td>[10]</td>
</tr>
<tr>
<td>10/20 mg</td>
<td></td>
<td></td>
<td>achieved</td>
<td>achieved</td>
<td>achieved</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 20 mg</td>
<td>6 weeks</td>
<td>125</td>
<td>72%</td>
<td>78%</td>
<td>69.5%</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe/atorvastatin</td>
<td>12 weeks</td>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/10 mg</td>
<td></td>
<td></td>
<td>21.9%</td>
<td>26%</td>
<td></td>
<td>[14]</td>
</tr>
<tr>
<td>Atorvastatin 20 mg</td>
<td></td>
<td></td>
<td>11%</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe/atorvastatin</td>
<td>12 weeks</td>
<td>125</td>
<td>26%</td>
<td>N/A</td>
<td>N/A</td>
<td>[23]</td>
</tr>
<tr>
<td>10/10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 2.5 mg</td>
<td></td>
<td></td>
<td>8.3%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe/atorvastatin</td>
<td>12 weeks</td>
<td>243</td>
<td>10%</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>10/10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 20 mg</td>
<td>6 weeks</td>
<td></td>
<td>23%</td>
<td>20.1%</td>
<td>13.7%</td>
<td>[44]</td>
</tr>
<tr>
<td>Ezetimibe/atorvastatin</td>
<td>12 weeks</td>
<td>228</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/10 mg</td>
<td></td>
<td></td>
<td>17%</td>
<td>15.5%</td>
<td>10.4%</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 20/40 mg</td>
<td>12 weeks</td>
<td>125</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The titration of the dose of atorvastatin is not associated with significant decrease in LDL-c and other lipid parameters and in some individuals high-dose atorvastatin may increase risk of side effects. Therefore, addition of ezetimibe to atorvastatin may help in achieving LDL-c target without much side effects related to high statin dose.

ApoB: Apolipoprotein B; HDL: High-density lipoprotein; LDL-c: Low-density lipoprotein cholesterol.

3.2.1 Experimental animal studies

In an interesting study, using hypercholesterolemic zebra fish, Yang *et al.* presented an orchestrated application of Raman spectral measurements and confocal fluorescence imaging to interrogate the pharmacological response of atherosclerotic lesions *in situ* and *in vivo*. They investigated two commonly prescribed antihyperlipidemic drugs ezetimibe and atorvastatin. They found that the treatment of ezetimibe or atorvastatin alone effectively decreased the deposition of lipids in the vascular wall, whereas a combined dose showed a synergistic effect [20]. Interestingly, in a study done in rats fed on an atherogenic diet, the efficacy of a high dose of atorvastatin was found to be comparable to that of combination of low-dose atorvastatin with ezetimibe in improving all lipid profile parameters. Bearing in mind that a high dose of atorvastatin is associated with adverse side effects, this combination can be a good alternative with lesser side effects [21]. However, in another study, the combination of ezetimibe diminished the beneficial effects of atorvastatin on oxidative stress in rats fed a high-cholesterol diet [22].

3.2.2 Clinical human studies

Combination therapy is often required to achieve multiple lipid treatment goals and has been studied thoroughly in patients with increased risk of CHD. In a randomized controlled trial conducted by Matsue *et al.* on 243 patients with coronary artery disease and LDL-c ≥ 70 mg/dl, after initial treatment with atorvastatin (10 mg), patients were prospectively randomized to the ezetimibe addition (10 mg) group (A10E10; n = 117) or to the double atorvastatin dose (to 20 mg; A20; n = 133) group for 12 weeks. The mean percentage changes in LDL-c for the groups were -25.8 and -9.1%, respectively (p < 0.001) [23].

The combination of atorvastatin with ezetimibe has an increased effect on carotid atherosclerosis in elderly patients with hypercholesterolemia. Luo *et al.* [24] in their 12-month trial observed that the levels of carotid intima-media thickness (CIMT), serum LDL-c and high-sensitivity C-reactive protein (hsCRP) were markedly decreased (p < 0.05) after treatment in the control group (atorvastatin alone) and combined group (atorvastatin with ezetimibe), whereas the reduction in the levels of CIMT, serum LDL-c and hsCRP was more significant in the combined group (p < 0.01). Furthermore, the combination of atorvastatin with ezetimibe further reduces circulating endothelial progenitor cells and LDL-c in high cardiovascular risk subjects with elevated CRP as evaluated by Lins *et al.* [25].

Compared with doubling atorvastatin to 80 mg, the addition of ezetimibe to atorvastatin 40 mg resulted in greater reductions in LDL-C, triglycerides, apoB, non-HDL-c, TC and lipid ratios in patients with type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) [13]. Furthermore, Stein *et al.* concluded that the addition of ezetimibe to the starting dose of 10 mg/day of atorvastatin followed by response-based atorvastatin dose titration to a maximum of 40 mg/day provides a more effective means of reducing LDL-c levels in patients at high risk of CHD than the continued doubling of atorvastatin to doses as high as 80 mg/day alone [26]. Moreover, CHD/CHD risk-equivalent patients in a large US managed-care database, who added ezetimibe onto simvastatin, atorvastatin or rosuvastatin, had greater LDL-c reductions and goal attainment than those who only uptitrated these statin therapies [27]. In Japanese patients...
with T2DM or impaired glucose tolerance and coronary artery disease, adding ezetimibe (10 mg/day) to atorvastatin (10 mg/day) significantly improved the lipid profile as compared to atorvastatin monotherapy at 20 mg/day [28].

Coadministration of ezetimibe and atorvastatin decreases secretory phospholipase A2, which is an enzyme that plays an important role in the pathogenesis of atherosclerosis and of adverse cardiovascular events [29].

Combination treatment with atorvastatin and ezetimibe had relatively better lipid-lowering efficacy than atorvastatin monotherapy. Padhy et al. conducted a double-blind study in 30 patients (mean age 54.3 ± 1.6 years) at risk of coronary artery disease [30]. They aimed to assess the effect of the FDC of ezetimibe 10 mg plus atorvastatin 10 mg on lipid profile, oxidized LDL (ox-LDL), hsCRP and soluble intercellular cell adhesion molecule (sICAM) in dyslipemic patients. They found that combination treatment significantly reduced TC, achieved the National Cholesterol Education Program target for LDL-c and led to significant reductions in very LDL-c, triglyceride, ox-LDL and sICAM. However, no significant change was seen in HDL-c or hsCRP levels between the two groups.

Interestingly, ox-LDL, which is a better predictor of adverse cardiovascular events than standard lipid parameters, was also significantly decreased when ezetimibe and atorvastatin were combined together [31]. Furthermore, several studies showed an association between ox-LDL and cardiovascular events. For instance, the Multi-Ethnic Study of Atherosclerosis showed that ox-LDL is associated with subclinical CVD by its relationship with many cardiovascular risk factors [32]. In patients undergoing coronary angiography, ox-LDL was also shown to be associated with CVD events [33].

Recently, Li et al. demonstrated that it is feasible to initiate combination therapy during acute phase for patients with acute coronary syndrome and T2DM, which can have a more significant effect on LDL-c-lowering and improve the control rate of LDL-c levels safety [34]. Recently, the IMPROVE-IT trial, launched 9 years ago, has finally provided physicians with long-term efficacy and safety evidence for ezetimibe. The large-scale study in acute coronary syndrome patients showed a clear benefit in reducing cardiovascular events when added to simvastatin in this population. The size of the benefit was proportionate to the reduction in LDL-c [35].

Moreover, Laires et al. found that prescribing ezetimibe to high cardiovascular risk patients being treated with atorvastatin instead of switching them to rosuvastatin is projected to be a cost-effective use of resources [36]. It is worth mentioning that cardiovascular benefit of administration of atorvastatin/ezetimibe is mainly attributed to atorvastatin.

### 3.3 Insulin resistance and MetS

It is proven that coadministration of ezetimibe with statins is a useful therapeutic option for treatment of dyslipidemia in different patient populations. In low dose, atorvastatin/ezetimibe 5/5 mg, ezet/ator has effects on LDL-c and homeostasis model assessment-insulin resistance that are similar to the effects of atorvastatin 20 mg and rosuvastatin 10 mg. However, the ezetimibe-statins combination is more effective in reducing apoB:A1 ratio and hemoglobin A1c than statin used alone [2].

Several studies have shown that ezetimibe administration is associated not only with improvement in insulin sensitivity but also with improvement in fatty liver [37]. Nonalcoholic fatty liver disease (NAFLD) is the hepatic component of MetS and is known to be associated with marked insulin resistance. Studies in animals showed that ezetimibe is associated with improvement in insulin sensitivity. For instance, the administration of ezetimibe in mice and rats was shown to be associated with improvement in insulin liver signaling, insulin secretion, protection of B pancreatic cells and glycemic control in animal models of T2DM. Administration of ezetimibe for 3 months in different human studies was also associated with improvement in insulin sensitivity, liver enzymes and improvement in glycemic control in T2DM individuals [38,39]. It is not yet clear whether this improvement in insulin sensitivity associated with ezetimibe administration will decrease the risk of diabetes associated with atorvastatin administration.

Interestingly, both statins and ezetimibe administration are associated with significant improvement in NAFLD and cholesterol gallstones. Important reviews on the subject have recently been published by Ahmed et al. [40,41]. Future studies are urgently needed to determine the impact of the FDC of ezetimibe and atorvastatin on insulin sensitivity, NAFLD and cholesterol gallstones.

In their recent study, Ioannou et al. found that mice treated with ezetimibe and atorvastatin showed near complete resolution of cholesterol crystals (0.01% [SD], 0.02% of surface area) and crown-like structures (0 per high-power field), with amelioration of fibrotic nonalcoholic steatohepatitis – another feature of MetS that is also noted [42].

### 3.4 Platelets and proinflammatory cytokines

In a randomized small study, 56 patients with coronary artery disease were assigned randomly to receive either 40 mg/day of atorvastatin or 10 mg/day of ezetimibe plus 10 mg/day of atorvastatin for 4 weeks, in order to study the pleiotropic effects of the two therapies such as platelet inhibition. More substantial reductions in platelet reactivity and proinflammatory chemokines were seen in the higher dose of atorvastatin sample than in the ezetimibe plus low-dose atorvastatin sample. The investigators concluded that in patients with coronary artery disease, it might be important to combine ezetimibe with higher statin dosages to benefit from the latter’s cholesterol-independent pleiotropic effects [43].

### 3.5 Elderly patients

CHD risk increases with age; in spite of this, lipid-lowering therapies are significantly underutilized in elderly patients. Ben-Yehuda et al. evaluated the safety and efficacy of lipid-lowering therapies in patients aged > 65 years with...
atherosclerotic vascular disease (LDL-c ≥ 1.81 mmol/L) or at high risk of CHD (LDL-c ≥ 2.59 mmol/L) treated with atorvastatin 10 mg + ezetimibe 10 mg (ezetimibe/atorvastatin) versus increasing the atorvastatin dose to 40 mg [44]. They found that the fixed dose of ezetimibe and atorvastatin is associated with a decrease in LDL-c and it was well tolerated in this age group, whereas the dose titration of atorvastatin to 40 mg was not well tolerated. Furthermore, adding ezetimibe to atorvastatin 10 mg produced significantly greater favorable changes in most lipids at 6 and 12 weeks and significantly greater attainment of prespecified LDL-c levels than doubling or quadrupling the atorvastatin dose in patients aged ≥ 65 years at high risk of CHD in the ZETELD study [45].

4. Safety evaluation

Ezetimibe plus atorvastatin is well tolerated, with a safety profile similar to atorvastatin alone and to placebo [46]. It offers a highly efficacious new treatment option for patients with hypercholesterolemia. Atorvastatin was found to be one of the only two statins (rosuvastatin is the other) that could reduce LDL-c > 40% at a dose of ≥ 20 mg/day [47]. Teramoto et al. found that there were no adverse reactions when they studied the tolerability of ezetimibe coadministration with atorvastatin in 125 Japanese patients with high LDL-c [14]. In spite of the studies mentioned above, other studies have reported some adverse effects of each of the components of Liptruzet (ezetimibe and atorvastatin).

The Study of Heart and Renal Protection (SHARP) was a randomized, double-blind trial that included 9270 patients with chronic kidney disease (3023 on dialysis and 6247 not) with no known history of myocardial infarction or coronary revascularization. The aim of the study was to assess the effects of lowering LDL-c with simvastatin plus ezetimibe in patients with chronic kidney disease. Patients were randomly treated with simvastatin 20 mg plus ezetimibe 10 mg/day versus matching placebo. The key outcome was first major atherosclerotic event (nonfatal myocardial infarction or coronary death, non-hemorrhagic stroke or any arterial revascularization procedure). Reduction of LDL-c with simvastatin 20 mg plus ezetimibe 10 mg/day safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease [48]. The potential benefits of statins beyond LDL-c can also be seen in individuals with portal hypertension and liver cirrhosis. For instance, simvastatin decreased portal hypertension and improved liver perfusion in patients with cirrhosis and these effects were additive with those of β-adrenergic blockers. The potential mechanism was thought to be due to associated increases in hepatopancreatic output of nitric oxide products and decreases in hepatic resistance in patients with cirrhosis [49,50].

4.1 Atorvastatin potential adverse effects

Rhabdomyolysis, which is a rare but serious side effect that may lead to renal failure and dangerous electrolyte abnormalities in patients with decreased hepatic clearance, has been reported with atorvastatin and other statin use in some cases [51]. Despite the fact that muscle ache and pain are most common side effects reported with statins, the incidence of myopathy, rhabdomyolysis and/or abnormal elevation of creatine kinase (CK) concentrations is still low [52]. Furthermore, when combined with warfarin, atorvastatin can cause acute rhabdomyolysis, so ezetimibe/atorvastatin should not be given with warfarin [53].

A study was done on the safety and tolerability of the use of atorvastatin 40 mg in common daily practice in short-term observation in 3227 patients. Fifty-two patients (1.6% of all study participants) interrupted atorvastatin therapy due to drug-related adverse effects, which comprised mainly of increased liver transaminases (0.4%) and myalgia (0.5%), whereas no cases of rhabdomyolysis were reported [54]. The frequency of statin-associated myopathy, which represents a broad spectrum of disorders from insignificant myalgia to fatal rhabdomyolysis, ranges from 1 – 5% in clinical trials to 15 – 20% in everyday clinical practice [55]. Similar observations were also noted in Thai patients [56].

Atorvastatin is one of the statins that is metabolized through CYP3A4, and enzymatic inhibition of CYP450 was the most common mechanism for hypolipidemic drug interactions mainly associated with the occurrence of rhabdomyolysis [57]. Caution should be taken when prescribing ezetimibe/atorvastatin in patients using other CYP450 inhibitors such as clarithromycin, erythromycin, itraconazole and HIV protease inhibitors [58,59]. Although the risk of rhabdomyolysis among patients receiving ezetimibe/atorvastatin is low, care should be taken in prescribing ezetimibe/atorvastatin for patients with impaired hepatic clearance or high CK [60,61].

4.2 Ezetimibe potential adverse effects

Ezetimibe is less likely than atorvastatin to cause myopathy or rhabdomyolysis. The incidence of creatine phosphokinase (CK) > 10 times upper limit of normal (ULN) was 0.2% for ezetimibe versus 0.1% for placebo and 0.1% for ezetimibe coadministered with a statin versus 0.4% for statins alone [29,62]. Risk of skeletal muscle toxicity increases with higher doses of statin, advanced age (> 65 years), hypothyroidism, renal impairment and, depending on the statin used, concomitant use of other drugs [63]. Nevertheless, myopathy presented with muscle pain and elevated CK levels have been reported when ezetimibe has been added to high-dose atorvastatin [64].

Although ezetimibe improves hepatic fibrosis, it has also been found to increase hepatic long-chain fatty acids and HbA1c in patients with NAFLD. The incidence of consecutive hepatic enzyme elevations (≥ 3 times the ULN) was 0.6% for patients receiving ezetimibe/atorvastatin. Fortunately, these elevations were generally asymptomatic and were not associated with cholestasis; transaminase levels
returned to baseline values after therapy was interrupted or discontinued [1].

### 4.3 Precautions to ezetimibe and atorvastatin combination

Since atorvastatin and ezetimibe, to a lesser extent, have both been associated with a degree of rhabdomyolysis or myopathy, it is advised that liver enzyme test results should be obtained before starting ezetimibe and atorvastatin therapy and should be repeated as indicated. Moreover, the drug should be used with caution in patients who drink substantial quantities of alcohol or who have a history of liver disease and during pregnancy [65]. Active liver disease and unexplained persistent transaminase elevations are contraindications to the use of ezetimibe and atorvastatin [1].

Several studies have shown the association of the administration of statins with development of diabetes. For instance, in a meta-analysis of randomized clinical trials, it was shown that statin therapy is associated with a slightly increased risk of developing diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events [66]. These observations were also endorsed by another meta-analysis of five statins trials, which showed that intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate-dose statin therapy [67]. Furthermore, statins are shown to be

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**Figure 1. Illustration showing the complex relationship between statin and ezetimibe as potential treatment for NAFLD and cholesterol gallstones.** It is not yet clear whether the Liptruzet will be free from the risk of statin-induced diabetes. Future research is urgently needed to explore these potential benefits of Liptruzet.

NAFLD: Nonalcoholic fatty liver disease.
associated with increased risk of diabetes in the Women’s Health Initiative study [68]. Important reviews on the subject were recently published by Athyros et al. [69, 70]. Therefore, as atorvastatin is part of the Liptruzet combination, it is plausible to suggest that further research is needed to assess the risk of diabetes associated with administration of this medication.

Since statins are contraindicated in pregnancy because of the risk of severe malformations, the FDC of ezetimibe and atorvastatin should not be prescribed to pregnant women. The effect of atorvastatin and ezetimibe combination in pediatric population is a subject of further research.

5. Postmarketing data

The following are rare side effects reported by the manufacturer: thrombocytopenia, headache, peripheral neuropathy, reversible cognitive impairment, pancreatitis, angioedema, bullous rash, anaphylaxis and depression [2].

Other events identified during post-approval use of ezetimibe and/or atorvastatin include hepatitis, cholelithiasis, cholecystitis and elevated creatine phosphokinase [71].

6. Comparison with safety of other drugs

Blagden et al. found no difference in adverse events when they randomized 148 patients with primary hypercholesterolemia and CHD into two groups to receive treatment for 6 weeks with either ezetimibe 10 mg + atorvastatin 10 mg (n = 72) or placebo/atorvastatin 10 mg (n = 76) [16].

Finally, FDA approval of ezetimibe and atorvastatin was based on the above randomized, double-blinded, controlled trials in patients with hyperlipidemia, heterozygous familial hypercholesterolemia, CHD or multiple cardiovascular risk factors and patients with HoFH [18, 25].

It is difficult to directly compare adverse reaction rates observed in the clinical studies of a drug to rates in the clinical studies of another drug because clinical studies are conducted under widely varying conditions; the rates reported in clinical studies may not accurately reflect the actual rates observed in clinical practice.

7. Conclusion

The combination of ezetimibe and atorvastatin has recently been approved by the FDA for reducing LDL-c in patients with primary or mixed hyperlipidemia as well as in the HoFH. Clinical studies have shown that the combination of ezetimibe and atorvastatin is a safe and effective treatment of hyperlipidemia in individuals with or at high risk of CVD. The cardiovascular benefit of ezetimibe and atorvastatin is not more than that demonstrated for atorvastatin. The effect of ezetimibe and atorvastatin on insulin sensitivity, NAFLD and cholesterol gallstones should be the subject of future research.

8. Expert opinion

Several studies have shown the association of statin administration with development of diabetes. Therefore, as atorvastatin is part of the ezet/ator, it is plausible to suggest that further

Table 2. The effect of ezetimibe/atorvastatin on LDL-c reduction on CVD and the effects of the combination therapy beyond LDL-c reduction.

<table>
<thead>
<tr>
<th>Cardiovascular and LDL-c effect of eze/ator</th>
<th>Effect beyond LDL-c of eze/ator</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ezetimibe and atorvastatin combination leads to significant decrease in LDL-c</td>
<td>Improve insulin resistance</td>
<td>[23]</td>
</tr>
<tr>
<td>Marked Decrease in levels of carotid intima-media thickness, serum LDL-c and hsCRP (p &lt; 0.05) after treatment</td>
<td>Potential treatment of NAFLD</td>
<td>[25]</td>
</tr>
<tr>
<td>Significant reductions in very LDL-C, triglyceride, ox-LDL and sICAM. However, no significant change was seen in HDL-c or hsCRP levels between the two groups</td>
<td>Decrease in platelet reactivity and proinflammatory chemokines</td>
<td>[30, 43]</td>
</tr>
<tr>
<td>IMPROVE-IT trial showed a clear benefit in reducing cardiovascular events when added to simvastatin. The size of the benefit was proportionate to the reduction in LDL-c</td>
<td>Safe to use in elderly patients</td>
<td>[35, 44, 45]</td>
</tr>
<tr>
<td>The SHARP study showed ezetimibe and simvastatin administration is associated with decrease in CVD events in patients with advanced CKD</td>
<td>Potential benefit in decreasing portal hypertension due to liver cirrhosis (statin effect only)</td>
<td>[48-50]</td>
</tr>
</tbody>
</table>

The table clearly demonstrates that eze/ator is associated with decrease in CVD and also decrease in CVD among patients with advanced CKDs. The numerous effects of eze/ator beyond LDL-c are listed in the table.

ApoB: Apolipoprotein B; CKD: Chronic kidney disease; CVD: Cardiovascular disease; HDL-c: High-density lipoprotein cholesterol; hsCRP: High-sensitivity C-reactive protein; LDL-c: Low-density lipoprotein cholesterol; NAFLD: Nonalcoholic fatty liver disease; ox-LDL: Oxidized low-density lipoprotein; sICAM: Soluble intercellular cell adhesion molecule.
research is needed to assess the risk of diabetes associated with administration of this medication. This is crucial as several studies have shown that ezetimibe administration is associated with improvement not only in insulin sensitivity but also with improvement in NAFLD, which is the hepatic component of the MetS and is known to be associated with marked insulin resistance. It is not yet clear whether this improvement in insulin sensitivity associated with ezetimibe administration will decrease the risk of diabetes associated with atorvastatin administration.

Interestingly both statins and ezetimibe administration are associated with significant improvement in NAFLD and cholesterol gallstones (Figure 1). Future studies are urgently needed to determine the impact of eze/ator on insulin sensitivity, NAFLD and cholesterol gallstones. The potential benefits of statins beyond LDL-c can also be seen in individuals with portal hypertension due to liver cirrhosis. Interestingly, administration of statins was associated with decreases in portal hypertension. The SHARP study showed that the decrease in LDL-c with combination of ezetimibe and simvastatin decreased the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease. The combination of ezetimibe/atorvastatin is a safe and effective treatment of hyperlipidemia in individuals with or at high risk of CVD. Several potential benefits of the ezetimibe/atorvastatin (treatment of insulin resistance, cholesterol gallstones, NAFLD and portal hypertension) may be explored if future researches in these exciting areas are to be conducted (Table 2).

**Declaration of interest**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents, received or pending, or royalties.

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Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.

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   **Summary of effect of statins.**


   **Excellent study.**


   **This study is of considerable importance.**


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**This study added more evidence.**
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