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Cholesterol-lowering drugs: Focus on ezetimibe

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ABSTRACT

Ezetimibe is an intestinal cholesterol/sterol inhibitor. It is generally well-tolerated, and except for coadministration with cyclosporin (which increases concentration of both ezetimibe and cyclosporin), has limited drug interactions. Clinical trial data suggests that ezetimibe 10 mg orally once a day reduces low density lipoprotein cholesterol (LDL-C) levels about 15-25% as monotherapy or when added to statins, depending on the patient and individual clinical trial. Ezetimibe also reduces lipoprotein remnants. Due to its additive effects to statins, international lipid guidelines recommend ezetimibe as an option for patients who do not achieve LDL-C treatment goals with statins alone. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial demonstrated that when added to statin therapy, ezetimibe incrementally lowered LDL-C levels and modestly improved cardiovascular outcomes. Ezetimibe is formulated as monotherapy, or as a fixed-dose combination with statins or bempedoic acid. Finally, ezetimibe is the only pharmacotherapy approved for treatment of beta-sitosterolemia, which is a rare autsomal recessive disorder resulting in enhanced intestinal cholesterol absorption, increased circulating sterols, and tendinous and cutaneous xanthomas, arthritis or arthralgia, and premature cardiovascular disease.

Keywords
Atherosclerosis; Cholesterol; Ezetimibe; Intestinal absorption; LDL cholesterol; Statins

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Introduction

Multiple cardiovascular outcomes studies support reducing atherogenic lipoprotein levels [(via the surrogate of reducing low-density lipoprotein cholesterol (LDL-C) levels] for the purpose of reducing atherosclerotic cardiovascular disease (ASCVD) and reducing the risk of ASCVD events. Various organizations and societies have established LDL-C treatment goals (1) or thresholds (2), with more aggressive LDL-C treatment goals recommended for patients at highest ASCVD risk. Only a minority of patients achieve recommended LDL-C levels (1, 3). Based upon proven safety and efficacy in lowering LDL-C levels and reducing ASCVD events, statins are the pharmacotherapy of first choice for most patients, often at high intensity levels or maximally tolerated doses. Patients not able to achieve recommended LDL-C levels may benefit from further LDL-C lowering with non-statin LDL-C lowering therapies often having a mechanism of action complementary to statins.

The levels of circulating LDL-C are determined by genetics, dietary intake, physical activity, concurrent drugs and illnesses, and interrelated processes including hepatic synthesis, gastrointestinal absorption (i.e., from cholesterol consumed in the diet), and biliary metabolism (i.e., hepatic cholesterol used for bile acid synthesis and hepatic cholesterol excreted in the bile). Individuals vary in the balance of hepatic cholesterol synthesis versus gastrointestinal cholesterol absorption. This variance may influence individual responses to a lipid-lowering treatment. Individuals who are hyperabsorbers of intestinal cholesterol may have a suboptimal LDL-C lowering response to statin therapy, with statins known to reduce hepatic cholesterol production through inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, the rate limiting step of cholesterol synthesis. While the data is not always consistent (4, 5), some suggest that higher responders to statins have higher baseline levels of cholesterol synthesis markers (e.g., lathosterol and desmosterol); lower responders have higher markers of cholesterol absorption (e.g., campesterol, sitosterol, stigmasterol, and cholestanol) (6-8). Others suggest that long-term statin use may promote an increase in cholesterol absorption (9). Conversely, inhibition of cholesterol intestinal absorption (i.e., with ezetimibe) may promote increases in cholesterol synthesis (10).

A key protein involved in cholesterol absorption in the intestine is Niemann-Pick C1-Like 1 (NPC1L1) protein that promotes cholesterol transport through the enterocyte brush border membrane, acting opposite to ABCG5/G8, which mediates efflux of sterols (**Figure 1**). In humans, NPC1L1 is expressed in the liver and on the apical surface of absorptive enterocytes (11), with the highest expression in

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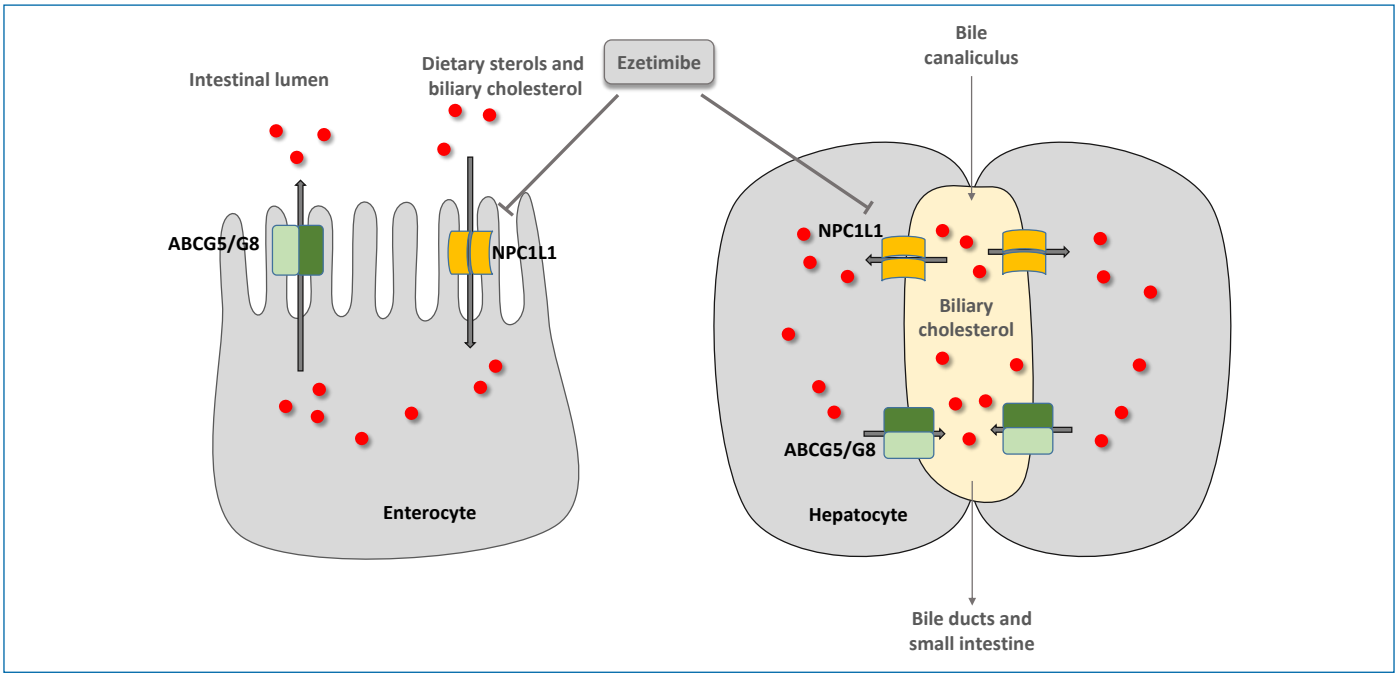

Figure 1 | NPC1L1 localization and function. NPC1L1 is localized on the brush border of the enterocytes, where it mediates the uptake of dietary and biliary cholesterol. Internalized cholesterol can be re-secreted into the lumen via the ABCG5/G8 system. NPC1L1 is expressed also at hepatocanalicular membrane, where it facilitates the transfer of secreted biliary cholesterol back into hepatocytes. ABCG5/G8) also localizes at apical membrane of hepatocytes.
NPC1L1, Niemann-Pick C1-Like 1; ABCG5/G8, ATP-binding cassette transporters G5/G8.

the proximal jejunum, which is the major site of intestinal cholesterol absorption. Mice deficient in NPC1L1 have markedly reduced intestinal sterol absorption. In humans, mutations that inactivate NPC1L1 are associated with a 0.31 mmol/L (12 mg/dL) reduction in LDL-C, and 53% reduction in the risk of coronary heart disease (CHD) (12). Ezetimibe inhibits intestinal cholesterol absorption by inhibiting NPC1L1.

Ezetimibe reduces the absorption of sterols (including cholesterol) from dietary and biliary sources by preventing the transport of cholesterol through the intestinal wall, and therefore reducing LDL-C levels. As before, NPC1L1 is also in the liver, where it mediates the reuptake of cholesterol from the bile into the liver (13) (**Figure 1**). Genetic variants in NPC1L1 associated with lower levels of LDL-C protect against ischemic vascular disease, while increasing the risk of symptomatic gallstone disease (14). However, while inhibition of hepatic NPC1L1-mediated reuptake of cholesterol may theoretically increase the risk of cholesterol gallstones, analysis from pooled clinical trial data suggest little to no difference in the risk of gallbladder-related disease with ezetimibe (15).

Pharmacokinetics and drug interactions

Following oral administration, ezetimibe is rapidly absorbed and extensively metabolised (>80%) to the pharmacologically active ezetimibe-glucuronide. Because of the extensive enterohepatic circulation, relatively low doses of ezetimibe are required to be effective, with an estimated terminal half-life of ezetimibe and ezetimibe-glucuronide of~22 hours (16). Approximately 78% of the dose is excreted in the faeces predominantly as ezetimibe, and 11% in the urine mainly as ezetimibe-glucuronide. Due to its unique pharmacokinetic properties, ezetimibe has minimal potential for significant drug-drug interaction with other co-administered medications. Ezetimibe is neither an inhibitor nor an inducer and only a minor substrate of common cytochrome P450 drug-metabolising isoenzymes, that are highly applicable for the metabolism of some statins (e.g., lovastatin, simvastatin, and atorvastatin) (16). Ezetimibe does not affect plasma levels of statins or other drugs, and concomitant administration of statins does not alter ezetimibe bioavailability (16). Ezetimibe is not significantly excreted by the kidneys and thus does not require adjustment in patients with renal disease. (Zetia prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021445s018lbl.pdf).

Coadministration of ezetimibe and cyclosporine increases the levels of each (Zetia prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021445s018lbl.pdf). The increase in exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine and ezetimibe, cyclosporine levels should be carefully monitored, and the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe.

Ezetimibe and remnant lipoproteins

Pre- or post-statin therapy, many patients remain at substantial risk for a future CVD event, sometimes attributable to persistent elevations in atherogenic remnant lipoproteins (RLPs). RLPs are formed in the circulation from enzymatic breakdown of chylomicrons and very-low-density lipoproteins (VLDL) via triglyceride lipolysis by enzymes such as lipoprotein lipase. The result is the formation of smaller VLDLs and intermediate-density lipoproteins (IDL). Circulating remnant lipoproteins are highly atherogenic via promotion

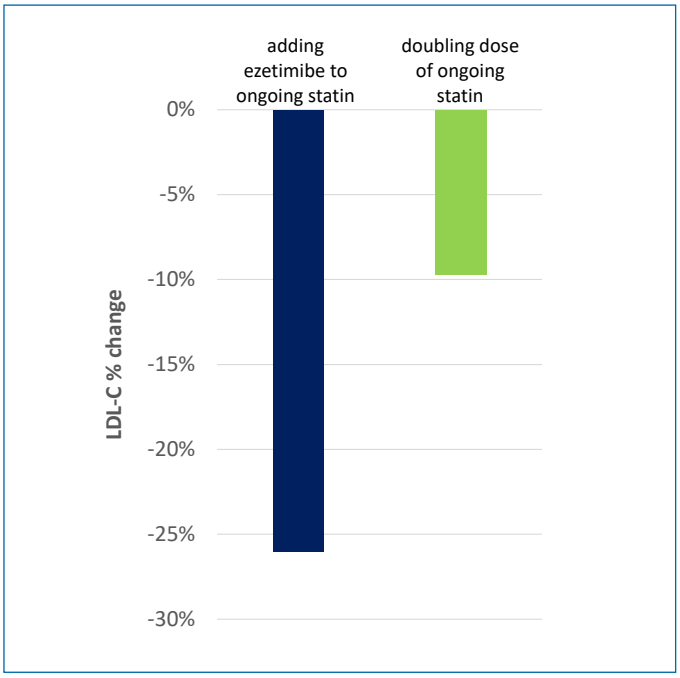

Figure 2 | Percent change from baseline in LDL-C levels in patients receiving ezetimibe added to ongoing statins or doubling the ongoing statin dose. Pooled analysis of data from 17 studies of 8667 hypercholesterolemic patients (20).
LDL-C, low-density lipoprotein cholesterol

of systemic inflammation, platelet activation, coagulation, thrombus formation, and macrophage foam cell formation (17). While different methods to measure RLP-C may not always correlate well, ezetimibe plus statins achieves greater RLP-C reductions compared to statin monotherapy (18).

Combining ezetimibe with a statin: Evidence from clinical trials

Combining a cholesterol synthesis inhibitor (a statin) with an intestinal absorption inhibitor (ezetimibe) represents utilization of two different cholesterol-lowering agents with complementary mechanisms of action that have the potential to result in additive cholesterol lowering (19). Co-administration of ezetimibe (i.e., ezetimibe is marketed only at the 10 mg dose) with a statin produces significantly greater reductions in LDL-C levels than either of the two drugs alone, resulting in higher attainment of LDL-C goals. Furthermore, statin-ezetimibe combination therapy appears to reduce the variability in LDLC-lowering response observed with statin monotherapy (4), and is more effective than doubling the dose of the ongoing statin (**Figure 2**)or switching to another statin (20, 21).

Combination ezetimibe+simvastatin: focus on IMPROVE-IT

The cardiovascular benefit of adding ezetimibe to a statin was evaluated by the IMPROVE-IT trial (22). In this study, 18,144 patients hospitalized for an acute coronary syndrome were randomized to receive the combination ezetimibe+simvastatin 40 mg or simvastatin 40 mg alone for a median follow-up of 6 years (22). Patients treated with the combination had an additional 24% reduction in LDL-C levels and a 2.0% absolute cardiovascular risk reduction compared with patients treated with simvastatin monotherapy (22) (**Figure 3**). The relatively low absolute risk reduction found with the IMPROVE-IT trial was potentially affected by misinterpretation of interim data of a surrogate marker study by influencers and the press, resulting in premature discontinuation of ezetimibe during participation in the IMPROVE-IT trial (as well as discontinuation of ezetimibe among patients in clinical practice). The lesson learned was that: "characterization of clinical outcomes regarding lipid-altering agents based on surrogate biomarker studies not designed to assess CVD outcomes may be misleading, potentially placing patients at increased CVD risk" (23).

When patients were stratified based on the LDL-C levels achieved at 1 month after ACS, those achieving LDL-C <30 mg/dL had a safe-

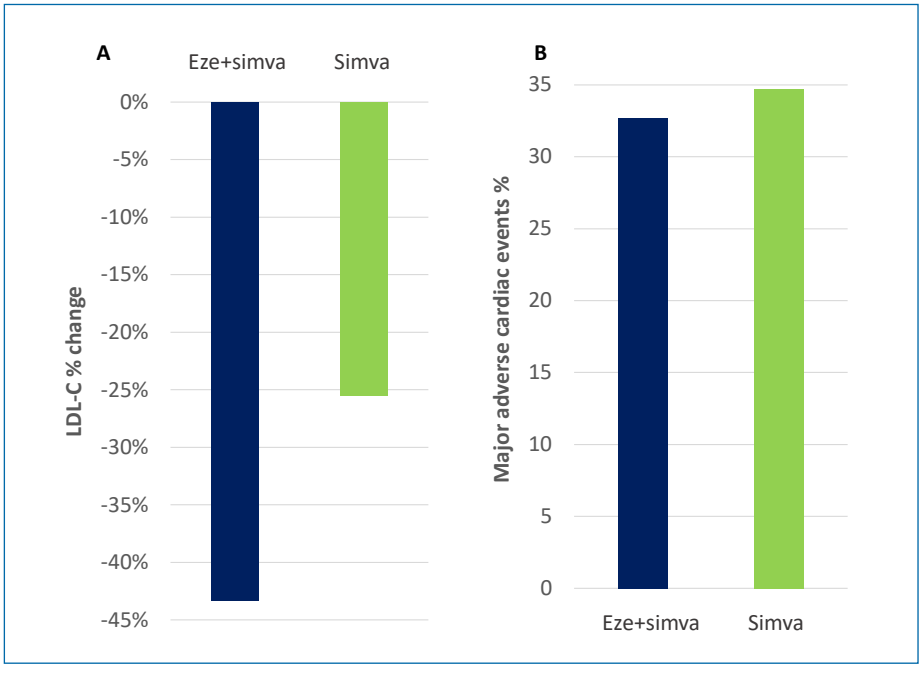

Figure 3 | The IMPROVE-IT trial. Percent change from baseline in LDL-C levels (A) and incidence of the primary end point (B) in patients receiving ezetimibe 10 mg + simvastatin 40 mg per day or simvastatin 40 mg per day alone (22). Absolute risk reduction with ezetimibe + simvastatin vs simvastatin alone was 2% with a relative risk reduction of 6% (P=0.016).
LDL-C, low-density lipoprotein cholesterol; eze, ezetimibe; simva, simvastatin.

ty profile similar to those of patients achieving higher LDL-C levels, but a lower rate of CV events (24). The addition of ezetimibe to a statin appears to reduce the risk of CV events in post-ACS patients independently of their baseline LDL-C levels, and appears to be effective also in patients with lower baseline levels (25). The results of the IMPROVE-IT are supported by a Mendelian randomization study showing that the effect of lower LDL-C levels on the risk of CHD determined by genetic variants in *NPC1L1* (as a proxy for ezetimibe treatment) or *HMGCR* (as a proxy for statin treatment) is similar per unit lower LDL-C levels; the combination combination of both *NPC1L1* and *HMGCR* variants is associated with a linearly additive effect on plasma LDL-C levels and a log-linearly additive effect on CHD risk (26).

Based on the results of the IMPROVE-IT trial, European guidelines for the treatment of dyslipidaemias recommend the addition of ezetimibe to the ongoing therapy in patients who are unable to achieve the LDL-C goals with maximally tolerated statins in monotherapy (1). Guidelines from the American College of Cardiology/American Heart Association suggest as reasonable to add ezetimibe to statin therapy in very high-risk ASCVD patients with LDL-C ≥ 70 mg/dL (≥1.8 mmol/L) while on maximally tolerated statin therapy, in adult patients with LDL-C ≥190 mg/dL (≥4.9 mmol/L) who achieve <50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of ≥100 mg/dL (≥2.6 mmol/L), or in adults with diabetes and a 10-year ASCVD risk ≥20% taking maximally tolerated statin therapy to reduce LDL-C levels by ≥50% (3).

Ezetimibe+atorvastatin

Several studies have compared the efficacy and safety of the combination ezetimibe+atorvastatin with atorvastatin monotherapy (**Figure 4**). In a double-blind study, 628 patients with hypercholesterolemia (LDL-C 145-250 mg/dL) were randomized to ezetimibe 10 mg, atorvastatin (10, 20, 40, or 80 mg), ezetimibe+atorvastatin (10, 20, 40, or 80 mg/d), or placebo; compared to atorvastatin alone, the combination of ezetimibe + atorvastatin provided a significant 12% additional reduction in LDL-C levels (pooled data 56.3% vs 44.2%) and also provided a greater reduciton in hs-CRP (pooled data 41% vs 31%). Ezetimibe alone reduced LDL-C levels 20% (27). In a subsequent study, 1,547 hypercholesterolemic patients at high CV risk and with elevated LDL-C (100-160 mg/dL) while taking atorvastatin 10 mg entered a randomized clinical trial consisting of two study periods (28). At the end of period I, during which patients added ezetimibe to atorvastatin 10 mg, or doubled the atorvastatin dose to 20 mg, or switched to rosuvastatin 10 mg, LDL-C were significantly lower among patients taking the combination therapy (22.2% vs 9.5% or 13.0%, respectively, p <0.001) (28). During the period II, patients in atorvastatin 20 mg in period I had ezetimibe added to atorvastatin 20 mg, or uptitrated atorvastatin to 40 mg, whereas patients on rosuvastatin 10 mg during period I switched to atorvastatin 20 mg plus ezetimibe or uptitrated rosuvastatin to 20 mg. Adding ezetimibe allowed greater reductions in LDL-C levels than doubling atorvastatin or switching to (or doubling) rosuvastatin at the compared doses, with adverse events being generally similar among groups (28). The higher favourable effect of the combination ezetimibe+atorvastatin was also observed in patients with heterozygous familial hypercholesterolemia (HeFH), CHD, or multiple CV risk factors and a severe hypercholesterolemia (~186 mg/dL at baseline while on atorvastatin 10 mg): at week 14, LDL-C were reduced by 23.8% with ezetimibe+atorvastatin 10 mg and by 9.0% with atorvastatin 20 mg (treatment difference: 14.8%), with greater beneficial effects on other lipid parameters (29). When tested in patients with diabetes mellitus, metabolic syndrome or neither, the combination ezetimibe+atorvastatin was more effective in reducing LDL-C levels than doubling the dose of atorvastatin in all three groups (~27% vs ~12%), and the proportion of patients reaching LDL-C <70 mg/dl was substantially greater among those taking the combination therapy in all three groups (30). Also reductions in non-HDL-C, TC, TG, and apoB were greater with the combination therapy compared with doubling the atorvastatin dose, and comparable across groups (30). Patients at high CV risk, having CHD or CHD risk equivalents and elevated LDL-C (100-160 mg/dL) receiving atorvastatin 40 mg were randomized to receive ezetimibe+atorvastatin 40 mg or atorvastatin 80 mg; after 6 weeks, LDL-C was reduced by 27% in the combination therapy group and by 11% in atorvastatin 80 mg group (treatment difference 16%), and significantly more patients taking the combination reached LDL-C <70 mg/dL (74% vs 32% with atorvastatin 80 mg).(31) All other measured lipid parameters were reduced more with the combination therapy (31).

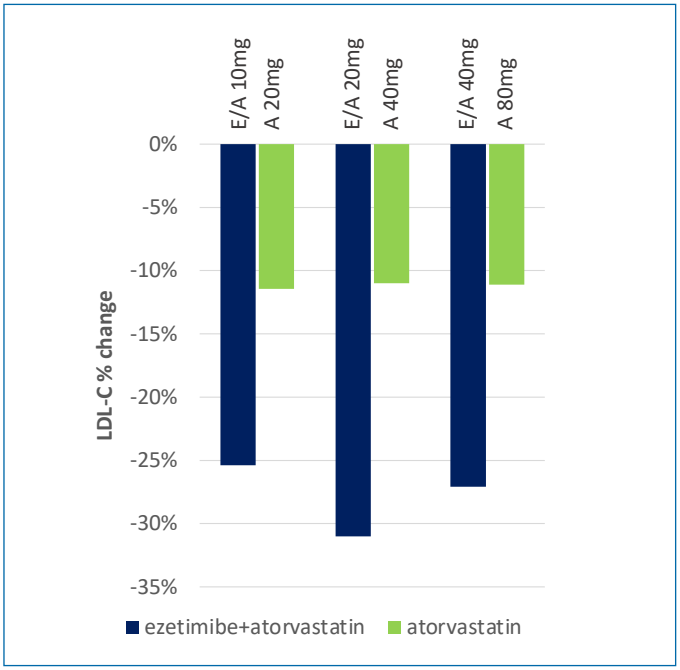

Figure 4 | Percent change from baseline in LDL-C levels in patients treated with baseline atorvastatin, comparing the addition of ezetimibe versus doubling dose of atorvastatin monotherapy. Data derives from studies included in the meta-analysis by Ai et al. (32).
LDL-C, low-density lipoprotein cholesterol; E, ezetimibe; A, atorvastatin.

A meta-analysis of available randomized clinical trials showed that combination therapy of ezetimibe and atorvastatin lowered LDL-C levels much more than atorvastatin monotherapy among all the four doses comparison (E10+A10 vs A10; E10+A10 vs A20; E10+A20 vs A40; E10+A40 vs A80), with a mean difference between treatments of 15.4%; greater reductions were also observed in TC (mean difference: 9.5%) and TG (mean difference: 6.4%) (32).

This greater benefit was also observed in terms of coronary atherosclerosis. The PRECISE-IVUS trial evaluated the effects of the combination ezetimibe+atorvastatin versus atorvastatin monotherapy on both lipid profile and coronary atherosclerosis in patients undergoing percutaneous coronary intervention. This trial reported a larger coronary plaque regression among patients treated with the combination therapy after 9-12 months of therapy, associated with a

greater reduction in LDL-C levels (33). Furthermore, a significantly greater percentage of patients who received the combination ezetimibe+atorvastatin experienced coronary plaque regression (78 vs. 58% with atorvastatin alone) (33). A superior effect of the dual lipid-lowering strategy on favourably affecting coronary atherosclerotic development was evident especially in the acute coronary syndrome patients (33). Of note, while statin-naïve patients showed similar plaque regression with monotherapy or combination therapy, in statin-pretreated patients the addition of ezetimibe to statin induced a stronger regression than statin dosage escalation (34). Again, this observation supports a positive effect of ezetimibe which act on the the potential compensatory increase in cholesterol absorption induced by statin treatment (which in turn may attenuate a positive effect of statins on coronary plaque regression). The incremental LDL-C-lowering obtained with the combination was associated with greater coronary plaque regression (35).

The combination ezetimibe+atorvastatin demonstrated stronger coronary plaque regression effects even in patients with chronic kidney disease (CKD) compared with atorvastatin monotherapy (36). The combination ezetimibe+atorvastatin 10 mg showed comparable LDL-C lowering and regression of coronary atherosclerosis in the intermediate lesions, compared with atorvastatin 40 mg alone, after 12 months, suggesting that ezetimibe added to a low dose atorvastatin is as effective as high dose atorvastatin alone in reducing both LDL-C levels (~39%) and the extent of coronary atherosclerosis (37).

Ezetimibe+pitavastatin

Pitavastatin has a unique chemical structure providing potent lipid-lowering efficacy, minimal metabolism through CYP, and high systemic bioavailability (38). Some evidence suggests pitavastatin may regress coronary plaque volume measured by IVUS in patients with ACS (39).

The RESEARCH (Recognized Effect of Statin and Ezetimibe therapy for achieving LDL-C Goal) trial compared the LDL-C-lowering effects of higher-dose statin versus ezetimibe+statin in type 2 diabetes mellitus patients with a wide range of clinical backgrounds (40). Patients received ezetimibe added to a low to moderate intenstiy statin statin (atorvastatin 10 mg or pitavastatin 1 mg) or intensified-dose statin (atorvastatin 20 mg or pitavastatin 2 mg); the combination therapy was more effective than higher doses of statins in monotherapy in reducing LDL-C levels and improving the atherogenic lipid profile (40). In patients with ACS, adding ezetimibe to pitavastatin produces a more significant reduction than pitavastatin alone in LDL-C levels (51.9% vs 37.2%) and more patients achieved LDL-C levels <70 mg/dL at 12 weeks; lipid absorption markers were significantly reduced by the combination therapy but not by pitavastatin monotherapy (41). When analysed based on their baseline levels of sitosterol, a low percentage of "high sterol absorber" patients achieved LDL-C<70 mg/dL when treated with pitavastatin alone, while benefiting from the combination therapy (22% vs 59%) (41). This finding was confirmed in the HIJ-PROPER (Heart Institute of Japan PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome) that investigated the effect of either ezetimibe plus pitavastatin or pitavastatin monotherapy on a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, and ischaemia-driven revascularization in patients hospitalized with ACS and hypercholesterolemia (LDL-C at baseline: ~135 mg/dL) (42). The combination therapy allowed a greater reduction in LDL-C that pitavastatin alone (51.7% vs 37.6%). Despite this different effect on LDL-C levels, the combination therapy did not provide a greater reduction in the incidence of subsequent CV events than pitavastatin monotherapy after a median follow-up of 3.86 years; however, in patients who had elevated baseline levels of sitosterol the combination therapy significantly reduced the risk of the primary endpoint compared with monotherapy (HR 0.71) (42). A further analysis in statin-naïve participants stratified by quartiles of baseline LDL-C levels showed that patients with baseline LDL-C ≥131 mg/dL treated with ezetimibe+pitavastatin had better clinical outcomes than those receiving pitavastatin monotherapy, whereas this difference was not observed among patients with baseline LDL-C <131 mg/dL (43).

Ezetimibe+rosuvastatin

Rosuvastatin is a fully synthetic drug that at 20 and 40 mg is considered a high intensity statin (44), and can provide a 46-55% reduction in LDL-C with 10-40 mg daily dose (45). Rosuvastatin is not significantly metabolized by CYP3A4 and only partially metabolized by CYP2C9; unmetabolized drug is excreted via the bile into the faeces, with a reduced potential for drug-drug interactions. As ezetimibe is not metabolized by CYP, the combination of rosuvastatin and ezetimibe is not expected to induce clinically relevant drug–drug interactions, producing a low incidence of adverse events.

Rosuvastatin alone or combined with ezetimibe. Several studies have shown that combining rosuvastatin 10-40 mg and ezetimibe 10 mg enables substantial reductions in LDL-C (up to 60-70%) (**Figure 5**) with a good safety profile in many hypercholesterolemic patient subgroups. The EXPLORER (EXamination of Potential Lipid-modifying effects Of Rosuvastatin in combination with Ezetimibe versus Rosuvastatin alone) trial showed that the combination ezetimibe/rosuvastatin 40 mg reduced LDL-C significantly more than rosuvastatin 40 mg alone in patients at high CV risk (-69.8% vs -57.1%, p<0.001), with an overall improvement of the lipid/lipoprotein profile (46). A greater reduction in hs-CRP was also reported with the combination therapy compared with rosuvastatin alone (-46.4% vs -28.6%), with patients having baseline levels >3 mg/l reaching lower levels when treated with the combination therapy (46). Adverse events were reported in both groups with similar frequency, with myalgia being the most frequent (46). In the MRS-ROZE (Multicenter Randomized Study of ROsuvastatin and eZEtimibe) study in which hypercholesterolemic patients were given fixed-dose combinations of ezetimibe+rosuvastatin 5, 10, or 20 mg/day) or rosuvastatin alone: depending on the rosuvastatin dose, fixed-combinations provided LDL-C reductions of 56%-63% (compared with 43%-54% with rosuvastatin alone) (47). The safety and tolerability were similar in the two groups (47). Patients with diabetes mellitus or metabolic syndrome benefited more from the combination therapy than non-DM and non-MetS patients (47).

In the I-ROSETTE (Ildong ROSuvastatin& ezETimibe for hypercholesTElolemia) trial, 396 patients received rosuvastatin (5, 10, or 20 mg) alone or in combination with ezetimibe 10 mg; after 8 weeks, the LDL-C-lowering efficacy of the combination therapy was superior to that of the corresponding dose of rosuvastatin alone (57.0% and 44.4%, respectively), with a higher number of patients achieving the LDL-C goal among those receiving the combination (92% vs 77.8% with monotherapy in patients with CHD or CHD risk equivalents) (48). Safety and tolerability of the two treatments were comparable (48).

The combination ezetimibe/rosuvastatin appears also to have a greater beneficial effect in terms of atherosclerotic plaque regression compared with rosuvastatin alone. A prospective randomized open-label study, in which 51 patients with CAD requiring percutaneous coronary intervention were treated with either rosuvastatin 5 mg alone or in combination with ezetimibe, showed greater reductions in both LDL-C levels and plaque volume (PV) among patients receiving the combination therapy than in those receiving rosuvastatin monotherapy (LDL-C: 55.8% vs 36.8%; PV: 13.2% vs 3.1%) (49).

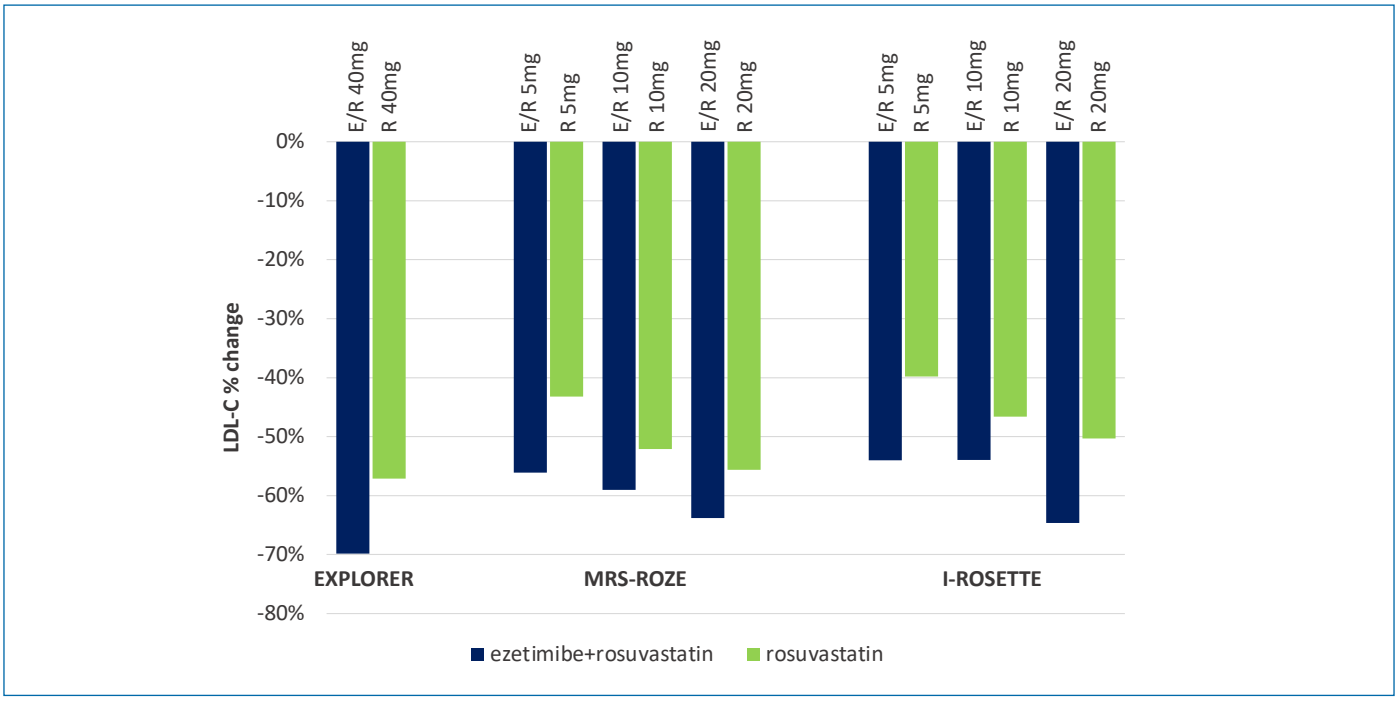

Figure 5 | Percent change from baseline in LDL-C levels in patients receiving ezetimibe plus rosuvastatin versus rosuvastatin monotherapy. Data derives from (46), (47), and (48).
LDL-C, low-density lipoprotein cholesterol; E, ezetimibe; R, rosuvastatin.

Adding ezetimibe to rosuvastatin vs doubling rosuvastatin dose. Several clinical studies have established a greater LDL-C-lowering efficacy when adding ezetimibe to current dose of rosuvastatin than doubling the rosuvastatin dose (20) . Patients at moderately high/high risk of coronary heart disease and elevated LDL-C levels received ezetimibe as add-on to stable rosuvastatin 5 or 10 mg or doubled the rosuvastatin dose to 10 or 20 mg (50). Patients taking the combination therapy achieved greater reductions in LDL-C levels compared to those who had rosuvastatin dose uptitration (between treatment difference: 15.2%), with a substantially higher percentage of patients achieving prespecified LDL-C levels (50).

In patients with type 2 diabetes mellitus and hypercholesterolemia while taking rosuvastatin 2.5 mg daily, adding ezetimibe produced a greater LDL-C reduction than doubling rosuvastatin dose (31.1% vs 12.1%); at 12 weeks, a larger percentage of patients treated with the combination therapy reached levels <80 mg/dL compared with those who doubled the dose of rosuvastatin (61.5% vs 22.2%) (51). Similarly, patients with diabetes taking ezetimibe/rosuvastatin 5 mg showed a greater reduction in LDL-C from baseline to week 8 compared with those taking rosuvastatin 10 mg monotherapy (57.9% vs 45.1%), and a higher percentage of patients treated with combination achieved >50% reduction in LDL-C (76.5% vs 47.1% with the monotherapy) (52). Patients with CAD were treated with ezetimibe/rosuvastatin 2.5 mg or rosuvastatin 10 mg alone: the two regimens provided comparable reductions in LDL-C levels (25.4% and 23.3%, respectively) (53). Another study showed that the combination ezetimibe/rosuvastatin 5 mg and rosuvastatin 20 mg as monotherapy induced similar reduction in carotid atherosclerotic plaque inflammation (54). A randomized trial compared the effect of a fixed-dose combination of ezetimibe and rosuvastatin 2.5 mg with ezetimibe or rosuvastatin 2.5 or 5 mg monotherapies in patients with hypercholesterolemia: a greater reduction in LDL-C was observed among patients treated with the combination than in those receiving monotherapies (45.7% vs 16.7% with ezetimibe, 32.6% with rosuvastatin 2.5 mg, and 38.9% with rosuvastatin 5 mg); LDL-C goal achievement was substantially higher among patients taking the combination therapy (51.5%, 5.7%, 22.4%, and 32.9%, respectively) (55). LDL-C goals according to risk categories were attained with the combination therapy in all patients with low and moderate risk, but not in those at high or very high risk, calling for the need of a more intensive approach in higher CV risk patients (55).

The higher lipid-lowering efficacy of the combination rosuvastatin/ezetimibe appears to be higher than that of rosuvastatin monotherapy (60% vs 51%), and this is particularly evident for regimens with a lower statin dose (57.9% and 45.3%) (56); the mean LDL-C target achievement rate was 91% with the combination and 73% with monotherapy, but was more evident in the regimens with low dose rosuvastatin (94.7% ezetimibe/rosuvastatin 5 mg and 64.1% with rosuvastatin 5 mg, respectively) (56).

Comparing different regimens

The VYVA (Vytorin Versus Atorvastatin) trial was a dose-comparison study in which hypercholesterolemic patients received atorvastatin (10, 20, 40, or 80 mg) alone or the combination ezetimibe/simvastatin (10, 20, 40, or 80 mg) for 6 weeks (57) (**Figure 6**). Overall, the combination ezetimibe/simvastatin provided greater LDL-C reductions (47.1%-58.6%) than atorvastatin (36.1%-52.9%), and a substantially higher percentage of patients taking the combination therapy achieved prespecified LDL-C levels (57). At the end of treatment, the mean percentage reduction from baseline in hs-CRP levels was 24.8% for ezetimibe/simvastatin averaged across all doses and 25.1% for atorvastatin averaged across all doses (57). The GRAVITY (Gauging the lipid effects of RosuvAstatin plus ezetimibe Versus sImvastatin plus ezetimibe TherapY) study compared the efficacy

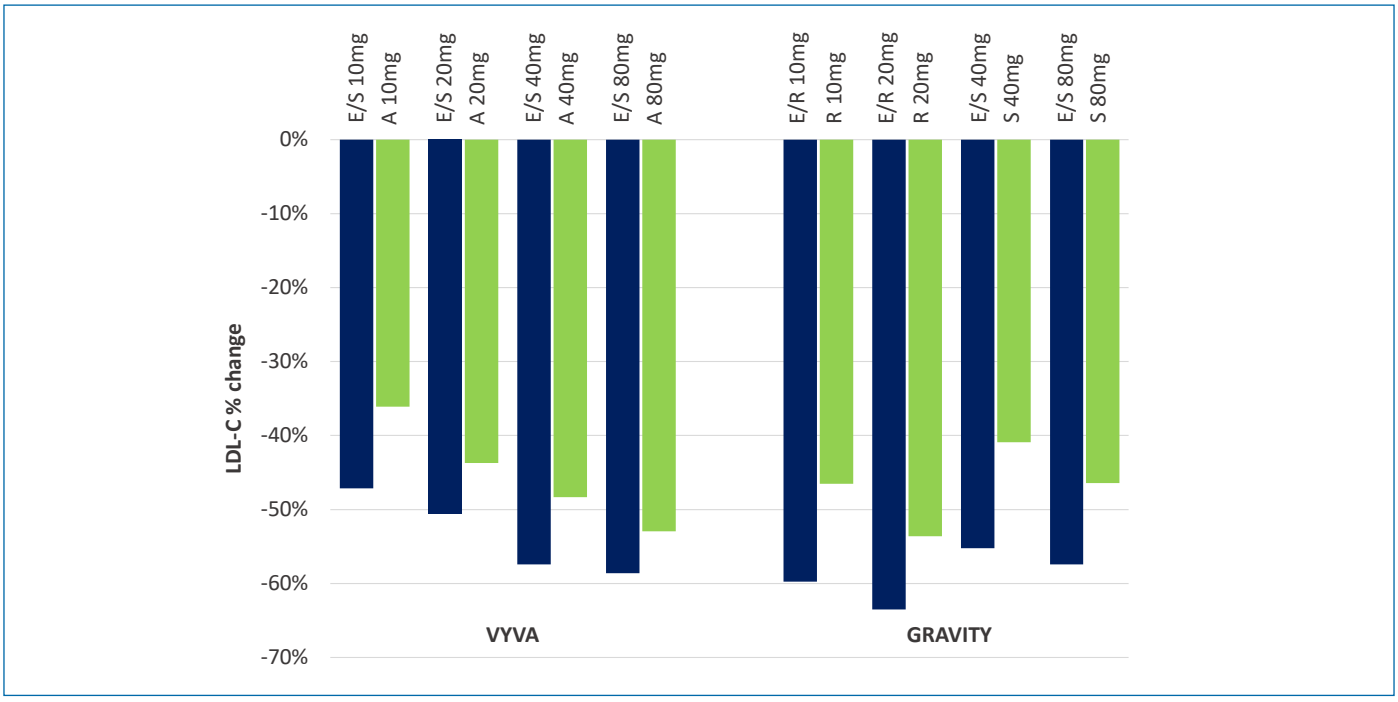

Figure 6 | Comparing the LDL-C-lowering efficacy of different regimens. The VYVA trial compared the effect of atorvastatin in monotherapy with the combination ezetimibe+simvastatin. The GRAVITY study compared the efficacy of the combinations ezetimibe/rosuvastatin and ezetimibe/simvastatin.
LDL-C, low-density lipoprotein cholesterol; E, ezetimibe; A, atorvastatin; S, simvastatin; R, rosuvastatin.

and safety of the combinations ezetimibe/rosuvastatin (10 mg or 20 mg) and ezetimibe/simvastatin (40 mg or 80 mg) in patients at high cardiovascular risk; the combination ezetimibe/rosuvastatin 20 mg was significantly more effective in reducing LDL-C than the combinations ezetimibe/simvastatin 40–80 mg (63.5% vs 55.2% with simvastatin 40 mg and 57.4% with simvastatin 80 mg) (**Figure 6**), with higher percentages of patients achieving prespecified LDL-C goals (58).

Another study compared the effects of ezetimibe/statin combination therapy (ezetimibe/simvastatin 10 mg or ezetimibe/rosuvastatin 5 mg) and statin monotherapy (rosuvastatin 10 mg or 20 mg) on carotid atherosclerotic plaque inflammation in patients with mild carotid atherosclerosis and acute coronary syndrome (59). LDL-C levels were substantially and similarly reduced in both groups at follow-up, and atherosclerotic plaque inflammation of the carotid artery and aorta evaluated decreased similarly with both treatments, which suggests that an ezetimibe/statin combination therapy may provide anti-inflammatory effects comparable to statin monotherapy at equivalent LDL-C-lowering doses(59).

Overall, evidence supports adding ezetimibe to ongoing simvastatin, atorvastatin, or rosuvastatin monotherapy provides greater reduction in LDL-C among patients at high risk of CVD than doubling the statin dose (21, 60, 61).

Ezetimibe+PCSK9 inhibitors

Ezetimibe has been evaluated in combination with a monoclonal antibody (mAb) to proprotein convertase subtilisin kexin 9 (PCSK9). The GAUSS (Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects) trial evaluated patients with statin intolerance, who received ezetimibe, or evolocumab, or the two drugs in combination for 12 weeks (62). Ezetimibe reduced LDL-C levels by an expected 15%, but <7% of patients achieved LDL-C <100 mg/dL and none achieved LDL-C <70 mg/dL; evolocumab alone provided a 50.7% reduction in LDL-C, with ~60% of patients achieving LDL-C <100 mg/dL and ~30% achieving LDL-C<70 mg/dL. When used in combination, LDL-C were reduced by 63%, and substantially larger proportions of patients achieved the prespecified LDL-C goals (90% and 62%, respectively) (62) (**Figure 7A**). Thus, combining ezetimibe with a PCSK9 inhibitor may be a useful strategy to reduce hypercholesterolemia in patients at high CV risk who may not be treated with statins.

Ezetimibe+bempedoic acid

Bempedoic acid is a synthetic drug that inhibits cholesterol synthesis by inhibiting the activity of adenosine triphosphate (ATP) citrate lyase (ACL); this inhibition induces the upregulation of LDLR and the consequent reduction of plasma LDL-C levels (63). Being a prodrug, bempedoic acid requires the conversion into its active form by very-long-chain acyl-CoA synthetase-1, an enzyme abundantly expressed in the liver, but not in skeletal muscle (63). Because it is a non-statin, bempedoic acid may represent a valuable alternative for statin-intolerant patients, possibly in combination with ezetimibe. Accordingly, some trials have evaluated the effect of this combination. Bempedoic acid 180 mg given alone or in combination with ezetimibe reduced LDL-C levels by ~30% and ~48%, respectively, compared with a ~21% reduction with ezetimibe alone, in either patients with or without statin intolerance (**Figure 7B**) (64). The result was an overall improvement of the lipid profile, and significant reduction in CRP levels (64). In the phase 3 CLEAR Tranquility trial statin-intolerant hypercholesterolemic patients received bempedoic acid or placebo added to ezetimibe for 12 weeks (65). While a 5% increase in LDL-C levels was reported among patients receiving placebo added to the ongoing ezetimibe therapy, patients who received

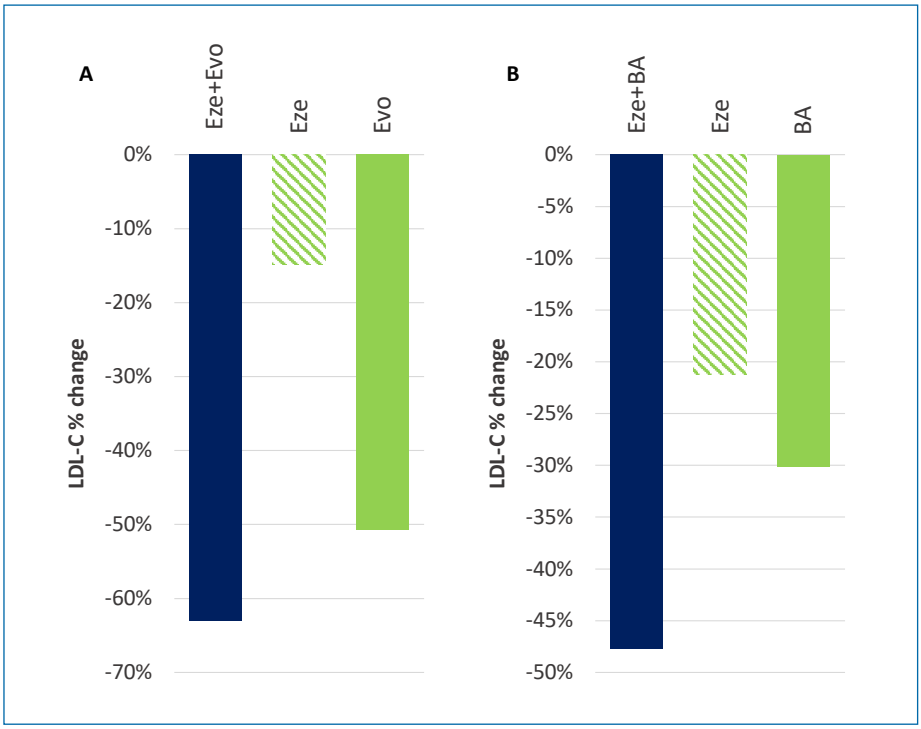

Figure 7 | Efficacy of ezetimibe addition on a PCSK9 inhibitor (A) or bempedoic acid (B). (A) LDL-C percent change in patients intolerant to statins receiving ezetimibe, evolocumab, or the combination ezetimibe+evolocumab (GAUSS trial). (B) Effect of ezetimibe and bempedoic acid alone or in combination on LDL-C levels.
LDL-C, low-density lipoprotein cholesterol; Eze, ezetimibe; evo, evolocumab; BA, bempedoic acid.

bempedoic acid reported a 23.5% reduction, together with an overall improvement of their lipid profile. Of note, the LDL-C reduction was greater among patients receiving non-statin or no background therapy (-34.7%) compared with those taking low or very low dose statin (-20.5%) (65). A fixed-dose combination of bempedoic acid and ezetimibe reduced LDL-C levels significantly more than bempedoic acid or ezetimibe alone (36.2%, 23.2%, and 17.2%, respectively, in high CV risk patients taking the maximally tolerated statin therapy (66). Other lipid parameters as well as CRP were significantly reduced among patients taking the fixed-dose combination (66). Altogether these results indicate ezetimibe and bempedoic acid in combination as a valuable strategy to either treat patients unable to tolerate statin or further reduce the CV risk in patients already on the maximally tolerated statin dose.

Use of ezetimibe in special populations

Beta-sitosterolemia is a rare autosomal recessive disorder caused by mutations in either ATP-binding cassette (ABC) subfamily G member 5 or member 8 (ABCG5 and ABCG8, respectively). Sitosterolemia may have phenotypical manifestations indistinguishable from HeFH, although a variation in phenotypic severity has been reported, likely due to its greater dependency on dietary sterol intake (67, 68). Sitosterolemia is characterized by a predisposition to hyperabsorption and accumulation of plant sterols and cholesterol in plasma, with tendinous and cutaneous xanthomas, arthritis or arthralgia, premature cardiovascular disease and atherosclerosis being the main clinical characteristics.

An accurate diagnosis of sitosterolemia is crucial to start an appropriate pharmacological approach. Patients with sitosterolemia often do not respond as well to statins, for the reason that endogenous cholesterol synthesis is already inhibited (67, 68). Ezetimibe is the only pharmacotherapy approved for treatment of sitosterolemia, which reduces the plasma levels of sterols, produces regression of xanthomas, and can alleviate potential haematological abnormalities (67, 68).

Medical nutrition therapy represents a cornerstone in the management of hypercholesterolemia. Many of those focused on management of obesity employ the use of ketogenic diets. A ketogenic diet is a very low-carbohydrate, higher fat proportion diet that may promote significant weight loss in short-term. Although carbohydrate restriction may present potential metabolic benefits in some individuals, the ketogenic diet is associated with variable alterations in blood lipid and an overall modest increase in LDL-C levels (69-72). However, in some patients, the increase in LDL-C levels may be marked (73, 74). This may be because of an increased dietary intake of saturated fats and cholesterol, as well as a potential increase in intestinal cholesterol absorption prompted by weight loss (i.e., intestinal cholesterol absorption is decreased with obesity). If enhanced intestinal cholesterol absorption is diagnosed or suspected with a ketogenic diet, then in addition to limiting dietary cholesterol and saturated fats, and starting statin therapy, ezetimibe may be recommended (75).

Conclusions

Ezetimibe is an intestinal cholesterol and sterol inhibitor that is generally well-tolerated and lowers LDL-C levels 15-25% as monotherapy or as added to statins. Guidelines recommend ezetimibe for patients who have not achieved their LDL-C treatment goals with statins alone. The IMPROVE-IT trial demonstrated ezetimibe incrementally lowering of LDL-C levels beyond that of statins, and reduced major adverse cardiac events. Ezetimibe is formulated as monotherapy, or as a fixed dose combination with statins or bempedoic acid. Finally, ezetimibe is the only pharmacotherapy approved for treatment of beta-sitosterolemia.

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Conflicts of interest

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