Ezetimibe: an update on its clinical usefulness in specific patient groups

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***Abstract*:** The aim of pharmacological lipid modification is to reduce low-density lipoprotein cholesterol (LDL-C) as a means of either secondary or primary prevention of cardiovascular disease. Statins are the first-line therapy for pharmacological lipid modification. Ezetimibe is a drug which reduces LDL-C by selectively inhibiting intestinal cholesterol absorption. This provides an alternative pharmacological approach to that of statin therapy to reduce LDL-C. Ezetimibe has been shown to significantly reduce levels of LDL-C and recently, as demonstrated in the IMPROVE-IT trial, to reduce the rate of cardiovascular events in high-risk patients. Ezetimibe therefore has an important role in pharmacological lipid modification. In this paper, we examine the body of research behind ezetimibe and assess its current clinical applications in different patient subgroups.

Keywords: cholesterol, dyslipidaemias, ezetimibe, hypercholesterolaemias, hyperlipidaemia, lipids, low-density lipoprotein

Introduction

Cardiovascular disease constitutes the leading cause of morbidity and mortality in middle- and high-income countries across the world [WHO, 2014]. Large-scale epidemiological studies including the Framingham Heart Study [Kannel *et al.* 1979] and the Seven Countries Study [Keys *et al.* 1984] have demonstrated a direct link between serum low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular events. Consequently, multiple large-scale randomized controlled trials have demonstrated that in patients with hypercholesterolaemia, both with and without established cardiovascular disease, treatment with statin therapy results in lower LDL-C levels which reduces cardiovascular events [Heart Protection Study Collaborative Group, 2002; Shepherd *et al.* 1995]. In light of this compelling evidence, statins are the first-line pharmacological agents for lipid modification in both the secondary and primary prevention of cardiovascular disease.

Trials comparing statins of differing intensities or the same statin at differing doses have demonstrated that aggressive reduction in LDL-C to the lowest possible levels result in the greatest reduction in cardiovascular events in high-risk patients [Cannon *et al.* 2004; Pedersen *et al.* 2005]. However, reduction in LDL-C to target levels is often not met in spite of statin therapy and intolerance of statins (due to their side-effect profile and publicity of this) can contribute to suboptimal LDL-C reduction. Additional drug therapies that aim to reduce LDL-C have therefore been an area of significant interest.

Ezetimibe is a drug that selectively inhibits intestinal cholesterol absorption. Early trials demonstrated an additional reduction in LDL-C levels of 12–19% when ezetimibe was taken in conjunction with a statin [Ballantyne *et al.* 2003; Davidson *et al.* 2002]. However, there has been controversy as to whether ezetimibe therapy confers an additional reduction in cardiovascular risk and little evidence of this until recently. In this article, the current evidence base for the use of ezetimibe in cardiovascular risk reduction will be examined, and this will be applied to the current recommendations regarding the use of ezetimibe in clinical practice.

Mechanism of action

Serum cholesterol is derived from two major sources: cholesterol synthesized *de novo* in the

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liver and cholesterol that has been absorbed from the gastrointestinal tract. Statins reduce serum cholesterol by reducing the synthesis of cholesterol in the liver through competitively inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyses the rate-limiting step in cholesterol production. In response to a reduction in hepatic LDL-C, there is a compensatory upregulation in hepatic LDL receptors, leading to LDL-C being taken up from the blood into the liver. Ezetimibe, however, targets gastrointestinal cholesterol absorption within the small intestine. Ezetimibe acts locally at the brush boarder of the small intestine by selectively inhibiting the cholesterol transport protein Nieman Pick C1 like 1 protein (NPC1L1), thereby preventing uptake of intestinal luminal micelles, which contain cholesterol, into enterocytes [Phan *et al.* 2012]. Ezetimibe does not appear to have an effect on the absorption of dietary lipid-soluble vitamins or drugs. Through reduced cholesterol uptake, ezetimibe causes a depletion of hepatic LDL-C stores, again resulting in upregulation of hepatic LDL receptors, causing LDL-C to be taken up by the liver from the blood. Ezetimibe is metabolized within the small intestine and the liver; it is then excreted back into the gastrointestinal tract *via* bile, where it can again inhibit cholesterol absorption. This pathway gives ezetimibe a long half life, estimated at 22 h. Ezetimibe is eventually excreted predominantly *via* faeces. In addition to reducing gastrointestinal cholesterol absorption, it is also thought that ezetimibe inhibits hepatic NPC1L1, reducing hepatic cholesterol absorption [Phan *et al.* 2012].

Fundamental trials

Early trials focused on establishing whether ezetimibe was able to significantly reduce serum LDL-C levels. Ezetimibe used as monotherapy for patients with hypercholesterolaemia was shown to significantly reduce serum LDL-C levels as evidenced by meta-analysis of eight randomized, double-blind, placebo-controlled trials, demonstrating ezetimibe monotherapy produces a statistically significant mean reduction in LDL-C of 18.58% compared with placebo [Pandor *et al.* 2009].

The use of ezetimibe in conjunction with a statin therapy has been found to be a potent combination in reducing serum LDL-C levels. Numerous trials demonstrated that statin and ezetimibe therapy produced a superior reduction in LDL-C compared with statin monotherapy, with a subsequent meta-analysis of 27 trials covering over 21,000 patients, demonstrating a 15.1% greater reduction in LDL-C in patients treated with statin and ezetimibe in combination when compared with statin alone [Morrone *et al.* 2012].

Having demonstrated its efficacy in reducing serum LDL-C, questions remained as to the clinical outcomes of ezetimibe treatment. Two major approaches were utilized to answer this question. The first approach sought to directly assess the effect of ezetimibe therapy on atherosclerotic plaque burden, using this as a surrogate predictor of future cardiovascular events. The second approach followed a group of patients with a high cardiovascular risk profile and directly assessed the impact of ezetimibe therapy against a placebo on the rate of cardiovascular events, when taken in conjunction with a statin.

The ENHANCE trial was a double-blind, randomized, 24-month trial assessing whether the addition of ezetimibe to simvastatin 80 mg produced a significant reduction in intima-media thickness in carotid and femoral arteries of patients with familial hypercholesterolaemia. This trial concluded that in spite of decreased LDL-C levels in the simvastatin/ezetimibe arm, there was no significant reduction in intima-media thickness in this group compared with the simvastatin monotherapy arm [Kastelein *et al.* 2008]. However, this trial assessed a group of patients with familial hypercholesterolaemia, the majority of whom would have been treated for many years on statin therapy prior to entering the trial, it is unclear whether intima-media changes in this group are representative of other patient groups without familial hypercholesterolaemia. Moreover the ENHANCE trial lacked actual meaningful clinical outcomes data.

The PRECISE-IVUS trial assessed patients with coronary artery disease, adopting a different approach to assess the effect of ezetimibe on atherosclerotic plaque burden. This randomized, controlled, prospective study compared ezetimibe in combination with atorvastatin with atorvastatin monotherapy, utilizing serial volumetric intravascular ultrasound studies to assess and compare coronary plaque burden and subsequent plaque regression between the two treatment arms at baseline, 9- and 12-month intervals after commencing treatment. There was a superior absolute change in percent atheroma volume (PAV) in the

atorvastatin/ezetimibe arm compared with the atorvastatin monotherapy arm [−1.4%, 95% confidence interval (CI) −3.4 to −0.1 *versus* −0.3%, 95% CI −1.9% to 0.9% with atorvastatin monotherapy; $p = 0.001$]. For PAV, a significantly greater percentage of patients in the atorvastain/ezetimibe arm showed coronary plaque regression (78% *versus* 58%; $p = 0.004$) [Tsujita *et al.* 2015]. This study therefore demonstrated that ezetimibe in combination with atorvastatin induced greater coronary plaque regression than atorvastatin monotherapy in patients with coronary artery disease.

The first major trial assessing the impact of ezetimibe on cardiovascular outcomes was the SHARP trial [Baigent *et al.* 2011]. This double-blind, randomized trial assessed a group of patients with chronic kidney disease, investigating whether treatment with simvastatin 20 mg daily plus ezetimibe 10 mg daily had an impact on the incidence of major cardiovascular events compared with placebo. The study confirmed simvastatin/ezetimibe therapy significantly reduced both the LDL-C levels and the rate of cardiovascular events. The weakness of this study, however, was that it was unclear how much of this beneficial effect could be attributed to ezetimibe *versus* simvastatin.

IMPROVE-IT [Cannon *et al.* 2015] was the landmark trial, spanning a 10-year period, which assessed the impact of ezetimibe therapy in conjunction with simvastatin compared with simvastatin monotherapy on the rate of major cardiovascular events in high-risk patients who already had low LDL-C levels [<125 mg/dl (3.2 mmol/liter)]. As there is a proven morbidity and mortality benefit of statin therapy in patients with a high cardiovascular risk factor profile, it is not feasible to conduct a placebo-controlled trial assessing the impact of ezetimibe therapy *versus* a placebo without concomitant statin treatment. In the IMPROVE-IT trial, patients within 10 days of a myocardial infarction or acute coronary syndrome, who had a low LDL-C, were randomized to receive either simvastatin 40 mg daily or simvastatin 40 mg daily with ezetimibe 10 mg daily. The patients were followed for a median of 6 years during which time they were assessed for major cardiovascular events, assessed as cardiovascular death, nonfatal myocardial infarction, unstable angina requiring hospital admission, coronary revascularization (⩾30 days after randomization), or nonfatal stroke. The study found that the addition of ezetimibe to simvastatin resulted in a significant reduction of the LDL-C [53.7 mg/dl (1.4 mmol/liter) *versus* 69.5 mg/dl (1.8 mmol/liter); $p < 0.001$] and that the cardiovascular event rate at 7 years was 32.7% in the simvastatin/ezetimibe group compared with 34.7% in the simvastatin monotherapy group (absolute risk reduction 2.0%; hazard ratio 0.936; 95% CI 0.89–0.99; $p = 0.016$). This reduction in serious adverse outcomes was against a control group already demonstrating a very well treated lipid profile with a mean LDL-C of 69.5 mg/dl (1.8 mmol/liter), which is well below current target guidelines. Adverse effects were similar in the two groups, demonstrating the safety profile of ezetimibe. This provided compelling evidence that ezetimibe conferred a protective benefit against major cardiovascular events when used in addition to a statin in high-risk patients through further reducing serum LDL-C levels [Banach *et al.* 2016]. Subanalysis of the results of the IMPROVE-IT trial demonstrated greater reduction in LDL-C amongst patients with diabetes within the first year of the trial [43 mg/dl (1.1 mmol/liter) reduction in simvastatin/ezetimibe arm *versus* 23 mg/dl (0.6 mmol/liter) reduction in the simvastatin monotherapy arm]. Kaplan–Meier estimates at 7 years demonstrated a 5.5% absolute risk reduction in major cardiovascular events in patients with diabetes taking simvastatin with ezetimibe *versus* simvastatin monotherapy (hazard ratio 0.86; 95% CI 0.78–0.94). This indicates a specific protective benefit conferred by the addition of ezetimibe for high-risk patients with diabetes [Giugliano, 2015]. Subgroup analysis further identified particular benefit of ezetimibe in patients aged at least 75 (hazard ratio 0.80; 95% CI 0.70–0.90) [Cannon *et al.* 2015].

The significance of the IMPROVE-IT trial is twofold. First, it supports the theory of 'lower is better' in terms of LDL-C levels and cardiovascular risk. Second, it is the first trial to show a significant reduction in cardiovascular events when ezetimibe is added to statin therapy, demonstrating a significant add-on effect of ezetimibe to statins in terms of both LDL-C reduction and reduction of cardiovascular events. The applications of these significant findings to clinical practice are evolving.

Major clinical applications of ezetimibe

There is a wealth of evidence that ezetimibe reduces serum LDL-C levels. However, as detailed above, the evidence regarding its effect on

cardiovascular events is relatively new. This is at odds with statin therapy, for which the evidence base for both reducing LDL-C and reducing cardiovascular events is plentiful and well established. For this reason, statin therapy remains the first-line therapy for pharmacological LDL-C reduction, both in the context of secondary and primary prevention of cardiovascular disease.

Pharmacological lipid modification therapy is indicated for secondary prevention in patients who have proven cardiovascular disease. However, pharmacological lipid modification is only indicated for primary prevention when the patient is deemed to have a significant 10-year risk of developing cardiovascular disease. In the UK the threshold is set at a 10-year risk of cardiovascular disease of 10% or greater [NICE, 2014]. In the USA, the threshold is lower at a 10-year risk of cardiovascular disease of 7.5% or greater [Stone *et al.* 2014]. Modelling algorithms such as QRISK2 are routinely used as an assessment tool for predicting 10-year risk of cardiovascular disease.

In the IMPROVE-IT trial, there were very strict inclusion criteria, which included myocardial infarction or acute coronary syndrome within the past 10 days, already low LDL-C [50–125 mg/dl (1.3–3.2 mmol/liter)] and no use of statins more potent than simvastatin 40 mg. In this setting, the trial proved the additional use of ezetimibe in conjunction with simvastatin reduced major cardiovascular events [Cannon *et al.* 2015]. Clearly limiting the use of ezetimibe to patients who only fulfil IMPROVE-IT's strict inclusion criteria would not only limit its use to a relatively small subset of patients with cardiovascular disease, but it would also potentially limit the potential benefit of the drug in reducing cardiovascular events.

In the UK, the National Institute of Care and Clinical Excellence (NICE) released a new guideline in February 2016 entitled *Ezetimibe for Treating Primary Heterozygous-Familial and Non-Familial Hypercholesterolaemia* [NICE, 2016]. This guideline sought to provide formalized guidance on the use of ezetimibe in light of the evidence from the IMPROVE-IT trial, extending this beyond its application to the small subset of patients meeting the IMPROVE-IT trial's inclusion criteria. The guideline made recommendations regarding both the use of ezetimibe in conjunction with a statin and for the use of ezetimibe as monotherapy. Ezetimibe in combination with a statin was recommended for patients with primary (heterozygous familial and nonfamilial) hypercholesterolaemia who had previously been started on statin therapy and total or LDL cholesterol concentration was not appropriately controlled either after appropriate dose titration of initial statin therapy or dose titration was limited by intolerance of statins, or a change from an initial statin therapy was being considered. Ezetimibe monotherapy was recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and nonfamilial) in patients in whom statin therapy was contraindicated, or in patients who were unable to tolerate statin therapy. No trials have directly assessed the effect of ezetimibe without concomitant statin therapy *versus* placebo on cardiovascular events, therefore the use of ezetimibe monotherapy lacks the evidence base that its use with statin therapy has. However, given that it is well established that reducing LDL-C reduces cardiovascular events, and that ezetimibe reduces LDL-C levels, NICE have clearly accepted that extrapolation is appropriate as placebo-controlled trials in these groups are unlikely.

The European Society of Cardiology (ESC) produced, in conjunction with other societies on cardiovascular disease prevention, updated guidelines on cardiovascular disease prevention in June 2016. Similarly to the NICE guideline, the ESC recognizes the add-on effects of ezetimibe to statin therapy and therefore recommends its use in combination with a statin when patients fail to meet specific LDL targets. This guideline, however, suggests that, in light of the evidence base, clinicians may wish to restrict this combination to only high or very high risk patients and that there may be particular benefit of this combination in patients with concomitant diabetes mellitus. Additionally these guidelines suggest the use of ezetimibe monotherapy only when patients are intolerant of statins [Piepoli *et al.* 2016].

Therefore current major clinical applications centre on the use of ezetimibe either in combination with a statin to achieve target LDL-C levels when suboptimally controlled with a statin alone, or on their use as monotherapy in patients intolerant of statins or in whom they are contraindicated [Serban *et al.* 2016]. Statin intolerance has been a contentious issue in recent years and there has been significant media coverage of the potential side-effect profile of statins. A recent position paper on statin intolerance has attempted to

provide a unified definition of this condition, which may provide a useful framework for diagnosing it and therefore identifying a point at which switching to ezetimibe rather than trialling other statin agents or doses may be advisable [Banach *et al.* 2015].

In spite of the recommendations of bodies including NICE and ESC, the US Food and Drug Administration (FDA) advisory committee recently voted against expanding the indications for ezetimibe, when added to statin therapy, to include reduction in cardiovascular events based on the outcomes of the IMPROVE-IT trial. The members acknowledged IMPROVE-IT as a positive trial with statistical significance, however questions remained regarding the real clinical relevance of the study. It would therefore appear further clinical trials are required before the FDA will expand the indication of the drug to include reducing cardiovascular events [Endocrinological and Metabolic Drugs Advisory Committee, 2015].

In addition to its application in familial hypercholesterolaemia, ezetimibe also has a role in the related condition sitosterolaemia. This rare autosomal recessively inherited metabolic disorder is characterized by increased absorption and reduced excretion of dietary sterols, causing hypercholesterolaemia, xanthomas and accelerated atherosclerosis. These patients do not respond to statin therapy, as their HMG-CoA reductase activity is already maximally inhibited. Ezetimibe is however effective in reducing sterol absorption in these patients and therefore has a role in the management of patients with this condition [Yoo, 2016; Tsubakio-Yamamoto *et al.* 2010].

Thus far, the indications for ezetimibe therapy have been examined principally in the context of primary hypercholesterolaemia. There may also be a role for the use of ezetimibe in reducing cholesterol in patients with secondary hypercholesterolaemia, namely patients with hypercholesterolaemia related to another disease process or drug therapy. Patients with human immunodeficiency virus (HIV) on highly active antiretroviral treatment (HAART) are at high risk of hypercholesterolaemia and have a higher risk of cardiovascular disease. Consequently the ESC recommends lipid-lowering therapy, mostly statins, in this patient group to achieve LDL-C goals defined for high-risk patients [Catapano *et al.* 2011]. However, some statins have interactions with different HAART regimes. One study successfully demonstrated that ezetimibe could be safely prescribed to patients with HIV on HARRT with hypercholesterolaemia who are unable to tolerate statin therapy and that it effectively reduces LDL-C in these patients [Wohl *et al.* 2008].

Safety of ezetimibe

The side-effect profile of statins is well described and most notable for muscle toxicity (including myalgia, myopathy and rhabdomyolysis) and deranged liver enzymes [Hu *et al.* 2012]. The IMPROVE-IT trial demonstrated that the addition of ezetimibe to simvastatin did not increase the rates of elevated liver enzymes to a level greater than three times the upper limit of normal. Similarly the trial demonstrated that the addition of ezetimibe to statin therapy did not affect the number of patients with muscle-related events (rhabdomyolysis, myopathy, myalgia or elevated creatinine kinase levels). There was no evidence of any association between ezetimibe therapy and cancer or cancer deaths [Cannon *et al.* 2015].

Future research into ezetimibe

There are some questions currently unanswered by the current body of research into ezetimibe. Research into the cardiovascular outcomes of ezetimibe as a monotherapy without concomitant statin therapy is lacking. Due to the clear proven benefits of statin therapy, it would not be acceptable to directly compare outcomes of ezetimibe against statin therapy. However, it would be possible to assess the effect of ezetimibe against a placebo on cardiovascular events for patients in whom statins are contraindicated or not tolerated, although a large-scale trial of this type is unlikely to be feasible to recruit.

Another area of interest would be investigations into the role of ezetimibe in primary prevention of cardiovascular disease. The evidence base for lipid-lowering therapy in primary prevention of cardiovascular disease is all based on the use of statins and therefore the use of ezetimibe in this capacity is currently not clear. This type of trial, however, would be possible in the absence of an absolute indication for statin therapy.

A further potential area of interest for future research into the clinical applications of ezetimibe would involve its effects on patients who have high baseline cholesterol absorption. High serum levels of plant sterols and noncholesterol sterols, such as

cholestanol, are a surrogate marker for high levels of intestinal cholesterol absorption. There is evidence to suggest that in patients with high cholesterol absorption, statins are less efficacious in reducing cholesterol levels and that this results in a higher risk of cardiovascular events [Miettinen *et al.* 1998; Silbernagal *et al.* 2013]. The mechanism of action of ezetimibe may provide a preferential mechanism for reducing cholesterol in these patients by reducing intestinal absorption. The effect of ezetimibe on cardiovascular events and the relation of this to baseline cholesterol absorption is therefore a further area of interest and studies into this are ongoing [Egom, 2015]. Patients with end-stage renal failure on haemodialysis are generally 'high absorbers' of intestinal cholesterol, and statins are less efficacious at reducing cardiovascular risk in all haemodialysis patients except those with cholestenol to cholesterol ratios indicating low intestinal cholesterol absorption [Silbernagal *et al.* 2015]. Therefore, there may be an unexploited role for ezetimibe in haemodialysis patients and other subgroups of 'high cholesterol absorbers' [Baigent, 2015].

There may also be an evolving role for the use of ezetimibe in combination with pro-protein convertase subtilisin/kexin 9 (PCSK9) inhibitors. Monoclonal antibody-based PCSK9 inhibitors are a new class of drug that bind to and prevent the degradation action of PCSK9 on the LDL-C receptors, favouring lower circulating LDL-C levels. Early trials into PCSK9 inhibitors are encouraging, demonstrating significant LDL-C reductions in patients with primary hypercholesterolaemia compared with placebo and a reduction in early major cardiovascular events [Robinson *et al.* 2015]. Interestingly, the greatest reduction in LDL-C levels has been observed in patients treated with a PCSK9 inhibitor and concomitant ezetimibe compared with placebo. This reduction in LDL-C is greater than the reduction seen with either a PCSK9 inhibitor alone or ezetimibe alone [Lipinski *et al.* 2016]. However, there are presently no data on the long-term effect of this combination on cardiovascular events. The very high cost of PCSK9 inhibitors and lack of long-term outcome data are currently limiting factors to their widespread use.

Conclusion

Ezetimibe is a drug that reduces LDL-C by reducing intestinal cholesterol absorption. The IMPROVE-IT trial has demonstrated that ezetimibe significantly reduces the risk of major cardiovascular events in a group of high-risk patients with known cardiovascular disease and already low LDL-C levels, with an absolute risk reduction of 2%. Ezetimibe is safe to use and well tolerated. The clinical applications of ezetimibe are currently centred on its use in combination with a statin when total or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy, when dose titration is limited by intolerance of statins, or when a change from an initial statin therapy is being considered. Ezetimibe monotherapy is recommended for primary hypercholesterolaemia in patients in whom statin therapy is contraindicated, or in patients who are unable to tolerate statin therapy. There is significant scope for further research into the role of ezetimibe, especially its role as monotherapy and in the primary prevention of cardiovascular disease. Additional areas of interest include the role of ezetimibe in 'high cholesterol absorbers' and the combination of ezetimibe with PCSK9 inhibitors.

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Conflict of interest statement

Dr Signy is an IMPROVE-IT investigator, has been a paid speaker and a member of paid advisory boards for MSD.

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