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REVIEW

Adding ezetimibe to statin therapy: latest evidence and clinical implications

Marija Vavlukis MD, PhD, FESC[1], Ana Vavlukis MSc[2]

[1]University Clinic of Cardiology, Vodnjanska St. no 17, Medical Faculty, Ss' Cyril and Methodius University, 1000, Skopje, Republic of Macedonia; [2]Faculty of Pharmacy, Ss' Cyril and Methodius University, 1000, Skopje, Republic of Macedonia

Abstract

Background: Statins are the hypolipemic treatment of choice for hyperlipidemia with confirmed atherosclerotic cardiovascular disease (ASCVD) protective effect, proven even in normolipemic patients. But in rare situations, even with a high-dose treatment regimen, or maximally tolerated statin dose treatment, treatment targets of low-density lipoprotein cholesterol (LDL-C), according to the risk profile of the patient, cannot be achieved. Combination therapy with ezetimibe is an effective treatment choice, as it is one of the few hypolipemic drugs with proven ASCVD protective effect.

Aim: In this review, we address the question of therapeutic efficacy and safety of ezetimibe in combination therapy with statins, as expressed through its hypolipemic and vasoprotective effects and its potential side effects.

Methods: We conducted a literature review of English articles through PubMed, PubMed Central, and Cochrane for randomized clinical trials, retrospective analyses, meta-analyses, and review articles by using key words: ezetimibe, statins, combination therapy, adverse effects. We analyzed data on ezetimibe–statin combination therapy in terms of hypolipemic efficacy, ASCVD risk reduction, and adverse effects.

Results: Statins have been proven to be very effective in reducing ASCVD risk, with no apparent threshold at which LDL-C lowering is not associated with reduced risk. Yet, a significant on-treatment residual risk of major cardiovascular (CV) events still exists according to meta-analyses of statin trials. Findings like this point to the unmet needs of the patients on statin treatment. The unmet needs in terms of LDL-C targets and ASCVD risk reduction raise the question of statin combination therapy. Ezetimibe is a cholesterol-lowering drug from the class of cholesterol absorption inhibitors, with the potency to decrease LDL-C by about 10–18% and Apo B by 11–16%, while in combination therapy with statins, an additional LDL-C lowering of 25% or total LDL-C lowering of 34–61% is observed. The effects on LDL-C and other lipoprotein (LP) fractions are translated by ASCVD risk reduction. Ezetimibe is one of the few hypolipemic medications that leads to additional ASCVD risk reduction when added to statin therapy. Present data on ezetimibe support the existence of pleotropic anti-inflammatory and antioxidative effects, in addition to its hypolipemic effect, which are responsible for this added ASCVD risk reduction on top of statin monotherapy. Ezetimibe, in combination therapy with a maximal or maximally tolerated statin therapy, is used in patients who fail to achieve target LDL-C levels with statin monotherapy. In combination with low-to-moderate statin dose treatment, or with second- or third-line statins, ezetimibe is used in situations of statin-associated muscle symptoms. The combination therapy is relatively safe.

Conclusion: Ezetimibe add-on to statin combination therapy is an effective treatment option that leads to additional LDL-C lowering – recommended in situations where, with a maximal or maximally tolerated statin monotherapy treatment regimen, LDL-C targets cannot be achieved. It leads to additional ASCVD risk reduction, without raising significant safety concerns.

Keywords: adverse effects, cardiovascular diseases, cerebrovascular disease, diabetes, ezetimibe, hydroxymethylglutaryl-CoA reductase inhibitors, hyperlipidemias, low-density lipoprotein cholesterol, prevention, residual risk.

Citation

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Introduction

Low-density lipoprotein cholesterol (LDL-C) has a central role in the pathogenesis of atherosclerosis and atherosclerotic cardiovascular disease (ASCVD). There is an independent linear positive association between LDL-C and ASCVD risk that extends down to low LDL-C levels.[1] Statins are the cornerstone hypolipemic treatment, at the same time leading

to a reduction of ASCVD risk. Some patients cannot achieve treatment goals even after maximal statin doses and lifestyle adherence, or are intolerant to high-dose regimens, as recommended by guidelines according to patients' risk profile. In situations where the patient is on maximal or maximally tolerated statin dose and cannot reach treatment goals, he/she can benefit from an additional LDL-C lowering agent. The cholesterol absorption inhibitor, ezetimibe, is one of the nonstatin drugs that additionally reduces ASCVD risk, when added to a statin, leading to a modest reduction of LDL-C by about 20%.[2]

The aim of this review is to address the question of therapeutic efficacy, as expressed through the hypolipemic and ASCVD risk reduction effect and safety of ezetimibe in combination therapy with statins.

Methods

We conducted a literature review of English articles through PubMed, PubMed Central, and Cochrane for randomized clinical trials (RCT), retrospective analyses, meta-analyses, and review articles by using key words: ezetimibe, statins, combination therapy, adverse effects. We analyzed the ezetimibe–statin combination therapy in terms of hypolipemic efficacy, ASCVD risk reduction, and adverse effects.

Results

HMG-CoA reductase inhibitors – statins

Statins are reversible inhibitors of the microsomal enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which converts HMG-CoA to mevalonate – an early rate-limiting step in cholesterol biosynthesis. The HMG-CoA reductase inhibition decreases intracellular cholesterol biosynthesis, leading to upregulated HMG-CoA reductase production and cell surface LDL receptors. Subsequently, additional cholesterol is provided to the cell by *de novo* synthesis and by receptor-mediated uptake of LDL-C from the blood. Given the previous situation, plasma LDL-C is the main clinical variable evaluated in statin pharmacodynamic studies, which takes about 4 to 6 weeks to show a reduction after the start of treatment, with a dose-dependent relationship.[3] Even though the statin group shares a common mechanism of action, members differ in terms of their chemical structures, pharmacokinetic profiles, and lipid-modifying efficacy.[4]

The chemical structure of the statins is constituted by two components – the pharmacophore, which is a dihydroxyheptanoic acid segment, and its moiety – composed of a ring system with different substituents. The ring system is a complex hydrophobic structure involved in the binding interactions to the HMG-CoA reductase. The structure of the ring can be a partially reduced naphthalene (lovastatin, simvastatin, and pravastatin), a pyrrole (atorvastatin), an indole (fluvastatin), a pyrimidine (rosuvastatin), or a quinolone (pitavastatin). The substituents on the rings define the solubility of the statin, along with many of their pharmacological properties. Among the statins mentioned, lovastatin, simvastatin, atorvastatin, and fluvastatin are lipophilic, whereas pravastatin and rosuvastatin are more hydrophilic.[5]

Statins are administrated orally as active hydroxy acids, except for lovastatin and simvastatin, which are administrated as lactone prodrugs and then hydrolysed to hydroxy acid form. The percentage of absorption is between 30 and 98% and the time to reach peak plasma concentration (T_{max}) is within 4 hours after administration. Their bioavailability varies; pitavastatin has a bioavailability of 80%, whereas fluvastatin between 19 and 29%.[5] Statins are predominantly metabolized by the cytochrome P450 (CYP450) enzyme family. The CYP3A4 isoenzyme is responsible for the metabolism of the majority of human drugs, including lovastatin, simvastatin, and atorvastatin. A proportion of their HMG-CoA reductase inhibitory activity is attributable to their active metabolites – 2-hydroxy- and 4-hydroxy-atorvastatin acid from atorvastatin and β-hydroxy simvastatin acid and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives from simvastatin. Fluvastatin is chiefly metabolized by the CYP2C9 isoenzyme, while pravastatin, pitavastatin, and rosuvastatin do not undergo substantial metabolism by CYP450 pathways. The predominant route of elimination for the majority of statins is via the bile after metabolism by the liver. Pravastatin is eliminated by both the kidney and liver, mostly as an unchanged drug. Rosuvastatin is also eliminated, largely unchanged, by both the kidney and liver.[6]

Cholesterol absorption inhibitors – ezetimibe

Ezetimibe is a cholesterol-lowering drug from the class of cholesterol absorption inhibitors that acts at the brush border of the small intestine. It appears to bind to a critical mediator of cholesterol absorption, the Niemann-Pick C1-Like 1 (NPC1L1) transporter protein on the gastrointestinal tract epithelial cells as well as in the hepatocytes. Ezetimibe blocks the absorption of dietary and biliary cholesterol and plant sterols resulting in intracellular cholesterol depletion.[7,8]

Following oral administration, ezetimibe is rapidly absorbed and extensively metabolized (>80%) to the pharmacologically active ezetimibe glucuronide. Total ezetimibe (sum of 'parent' ezetimibe plus ezetimibe glucuronide) concentrations reach a maximum 1–2 hours post-administration. The estimated half-life of ezetimibe and ezetimibe glucuronide is approximately 22 hours. The major metabolic pathway for ezetimibe is glucuronidation of the 4-hydroxyphenyl group by uridine 5′-diphosphate-glucuronosyltransferase isoenzymes to form ezetimibe glucuronide in the intestine and liver. Approximately 78% of the dose is excreted in the feces, predominantly as ezetimibe. Overall, ezetimibe has a favourable drug–drug interaction profile, as evidenced by the lack of clinically

relevant interactions between ezetimibe and a variety of drugs commonly used in patients with hypercholesterolemia, such as statins, except for fibrates and cyclosporine. Described adverse effects are also rare, as monotherapy – upper respiratory tract infection, diarrhea, arthralgia, sinusitis, and pain in extremity – or in combination with statins – nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, and diarrhea.[9–11]

The recommended ezetimibe dosage is 10 mg daily, with or without food, taken either 2 hours before or 4 hours after bile acid sequestrants (BAS) if used in combination.[11,12] When administered as monotherapy or coadministered with statins, timing of administration has no effect on their potency. This was confirmed by the study of Hyung Sik Yoon, who tested the therapeutic efficacy and safety of a fixed-dose combination of ezetimibe 10 mg and simvastatin 20 mg, in terms of morning versus evening administration. Morning administration was reported to be noninferior to evening administration.[13]

Ezetimibe has a potency to decrease LDL-C by 10–18% and Apo B by 11–16%, while in combination therapy with statins, an additional LDL-C lowering of 25% or total reduction of 34–61% is observed. In combination with fenofibrate, a 20–22% LDL-C and 25–26% Apo B lowering can be achieved, with an increase of high-density lipoprotein cholesterol (HDL-C) as well.[8,11,14]

Effects of statins

Statins have been proven to be very effective in reducing ASCVD risk, with no apparent threshold at which LDL-C lowering is not associated with reduced risk. The Atherosclerosis Risk in Communities (ARIC) study, performed on 13,342 individuals, provided evidence that protection against ASCVD happens in a graded fashion with LDL-C level, and a meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration on statin, suggested that a 1.0 mmol/L LDL-C reduction is associated with a 10% reduction of all-cause mortality, 24% reduction of major adverse cardiac events (MACE), and 15% stroke reduction. These benefits are irrespective of baseline cholesterol concentration[1] and in direct proportion to the magnitude of LDL-C lowering. High-intensity statin treatment (atorvastatin 80 mg) in the Treating to New Targets (TNT) trial, the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial, and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, demonstrated an additional 11 to 23% relative risk reduction of major cardiovascular disease (CVD) events when compared with moderate-intensity statin therapy (atorvastatin 10 mg, simvastatin 20 to 40 mg, or pravastatin 40 mg). Nonetheless, the atorvastatin 80 mg treated patients still experienced a major CVD event during the trials (ranging from 4 to 11% per year). Mean LDL-C levels in the atorvastatin 80 mg groups ranged from 1.6 to 2.1 mmol/L. This data suggest that further reductions in LDL-C may be justified.[14,15]

The question of residual risk

A significant on-treatment residual risk of major CV events still exists. The meta-analysis of statin trials shows a significant 22% relative risk for 5-year major CV events among individuals with prior CVD and 10% among those without prior disease. Even with LDL-C levels < 2 mmol/L, there is still a residual CVD event risk. The aforementioned TNT trial, conducted on patients with stable coronary artery disease (CAD), described an 8.7% incidence of a major event over 5 years in patients receiving atorvastatin 80 mg, with on-treatment LDL-C concentrations of 1.8–2.6 mmol/L.[1]

Findings like this point to the unmet needs of patients treated with statins. Several cholesterol treatment guidelines recommend a LDL-C treatment goal of <2.6 or <1.8 mmol/L, depending on the level of risk. However, in the everyday clinical practice, many high-risk patients fail to reach the LDL-C goal of <2.6 mmol/L, and/or few patients on high-intensity statin therapy achieve LDL-C levels <1.8 mmol/L.[15]

The most recent guidelines of the professional associations from both sides of the Atlantic Ocean, the 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the management of Dyslipidaemias and the 2017 Guidelines of the American Association of Clinical Endocrinologists and the American College of Endocrinology for Management of Dyslipidaemia and Prevention of Cardiovascular Disease, have recommended similar target LDL-C levels, which should provide clinicians with the confidence to aim for specific and low LDL-C targets.[10,14] This is a major difference from the risk profile treatment approach in the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guidelines.[16]

The particular developments in these guidelines are the inclusion of specific LDL-C targets and the suggestion of combination therapy (ezetimibe and proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) to achieve these targets in situations in which maximally tolerated statin monotherapy is insufficient (Table 1).[1,10]

There is one significant difference in the American Association of Clinical Endocrinologists (AACE) guidelines, where an additional 'extreme high-risk' category is defined, which is not recognized by the ESC/EAS, and an additional treatment target of LDL-C of <1.4 mmol/L is set. This 'extreme high-risk' group consists of patients with progressive disease despite an LDL-C of <1.8 mmol/L while on statin therapy. Of paramount importance is that both sets of guidelines have recommended similar target LDL-C levels that should provide clinicians with the confidence to aim for specific and low LDL-C targets.[17]

The rationale of such an approach is in the individualisation of the total CV risk reduction that can be better done if goals are defined. Treatment goals are defined and tailored to the total CV risk level of each individual patient. The 'individualized approach' may possibly result with better patient adherence to the therapy. Available evidence suggests that lowering of LDL-C beyond the guidelines-set goals may lead to further reduction

Table 1. Recommendations for treatment target goal of LDL-C.[10]

Risk profile of the patient	Treatment target goal of LDL-C	COR LOE
Very high CV risk	<1.8 mmol/L, or at least 50% reduction if the baseline LDL-C[1] is 1.8–3.5 mmol/L	I/B
High CV risk	<2.6 mmol/L, or at least 50% reduction if the baseline LDL-C is 2.6–5.2 mmol/L	I/B
Low/moderate CV risk	LDL-C goal of <3.0 mmol/L	IIa/C

[1]'Baseline LDL-C' refers to the level in a subject not taking any lipid-lowering medication.
COR, class of recommendation; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence.

of CVD events. Therefore, it seems appropriate to reduce LDL-C as low as possible, especially in patients at very high CV risk.[10]

Furthermore, the IMPROVE-IT (Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin *versus* Simvastatin) trial demonstrated that not only such low levels are safe but such levels are also beneficial, in terms of additional CV risk reduction. Current studies demonstrate LDL-C reduction as low as 0.5 mmol/L is not only therapeutically effective but also safe.[15,17,18]

Combination therapy: ezetimibe add-on to statin

Ezetimibe add-on to statin treatment

The unmet needs in terms of LDL-C targets and ASCVD protection raised the question of statin combination therapy. It only needed right clinical settings for such a combination to be defined. It was done in the 2016 ESC/EAS Guidelines for the Management of Dyslipidemias (Table 2)[10] and in the 2016 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-C lowering in the management of atherosclerotic CVD risk. This guideline is a continuation of the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, and there the role of ezetimibe is clearly positioned.[11]

Effects of ezetimibe add-on to statins on LDL-C

In clinical studies, ezetimibe as monotherapy reduces LDL-C in hyperlipidemic patients by 15–22%. Combined therapy with statins provides an incremental reduction in LDL-C levels of 15–20%, leading to the total LDL-C reduction by 34–61%, as previously mentioned.[10]

The most comprehensive data analysis for LDL-C lowering efficiency was performed by the group of Descamps, published in 2015. Twenty-seven differently designed trials (double-blind placebo and/or active controlled studies) in which statins (type of statin, statin brand, potency, or different dose) were compared with ezetimibe add-on to statin were included, with over 21,671 patients, analyzing variables such as variances (standard deviation [SD], coefficient of variation [CV], and root mean squared error [RMSE] adjusted for various factors) for percentage change from baseline in LDL-C. In this very comprehensive data analysis, ezetimibe add-on to statin was found to lead to a significantly more pronounced LDL-C lowering, as compared to statin monotherapy.[19]

Data from a large retrospective observational study (more than 27,000 patients), published in 2014 by Toth, demonstrate a more pronounced LDL-C lowering effect of ezetimibe add-on to statin therapy and higher percentage of goal attainment (with respect to the risk profile of the patients), with one third of the patients not being able to attain the recommended LDL-C goal of <1.8 mmol/L. However, it was realized that there is a low prescription frequency of high-dose statins. Half of the patients (50.9%) remained on the same statin monotherapy, irrespective of the achievement of treatment goal.[20] The significance of this study is even bigger given that it is a real-life situation, and not a randomized study with strictly predefined inclusion criteria, study population, and so forth.

The amount of LDL-C reduction that was achieved in the large randomized study IMPROVE-IT, including 18,144 patients, was about 24%.[21] In the I-ROSETTE study (The Compare the Efficacy and Safety of a Combination Therapy of Ezetimibe and Rosuvastatin Versus Monotherapy of Rosuvastatin in Hypercholesterolemia Patients), the effect of ezetimibe add-on to rosuvastatin was analyzed in 396 patients. During the 8 weeks' treatment period, six treatment regiments were compared (5, 10, and 20 mg rosuvastatin monotherapy *versus* same-dose regimens rosuvastatin add-on 10 mg ezetimibe). The percentage change from baseline in adjusted mean LDL-C level after 8 weeks treatment was −57.0% (2.1%) and −44.4% (2.1%) in the total ezetimibe/rosuvastatin and total rosuvastatin groups, respectively ($p<0.001$). The LDL-C-lowering efficacy of each of the ezetimibe/rosuvastatin combinations was superior to that of each of the respective doses of rosuvastatin.[22]

The pleiotropic properties of ezetimibe have been confirmed in several clinical trials in addition to the beneficial effect on the lipid profile. A small-scale Japanese study by Uemura and colleagues in 39 patients, compared two arm regimens: 10 mg atorvastatin plus 10 mg ezetimibe *versus* 20 mg atorvastatin in high-risk patients with CAD and type 2 diabetes mellitus (T2DM). Besides a statistically significantly more pronounced improvement of the lipid profile in terms of total cholesterol, LDL-C, and HDL-C

Table 2. Recommendations for statin add-on ezetimibe combination therapy.[10]

Clinical setting	COR LOE	Treatment target goal of LDL-C	COR LOE
Hypercholesterolemia If the goal is not reached with statins add-on ezetimibe	IIa/B	Depends on the risk profile of the individual patient	I/A
FH Intense-dose statin, often in combination with ezetimibe	I/C	<2.6 mmol/L, or <1.8 mmol/L in presence of CVD	IIa/C
ASC If the goal is not reached with the highest tolerable statin dose, use ezetimibe add-on in post-ACS patients	IIa/B	<1.8 mmol/L, or a reduction of at least 50% if the baseline LDL-C[1] is 1.8–3.5 mmol/L	
CKD stages 3–5 These include high or very high CV risk patients. The use of statins or ezetimibe add-on to statin is indicated in nondialysis dependent patients	I/A	Depends on the risk profile of the individual patient	I/A

[1]'Baseline LDL-C' refers to the level in a subject not taking any lipid-lowering medication.
ACS, acute coronary syndrome; CKD, chronic kidney disease; COR, class of recommendation; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence.

(p=0.005), a significant effect on the Apo B/Apo A-I ratio and remnant-like particle cholesterol was observed only in the atorvastatin add-on ezetimibe treatment group. However, the most powerful information obtained from this study was more pronounced effect on oxidized LDL-C [malondialdehyde-modified LDL (MDA-LDL)], a form that is responsible for the proatherogenic effects of LDL-C with the atorvastatin add-on ezetimibe treatment (p=0.0006).[23] Another Japanese study was performed by Tobaru and colleagues again on high-risk profile patients (with CAD) who remained above targeted LDL-C level after pretreatment with statins and who were subjected to ezetimibe add-on statin therapy. Besides a significant additional decrease of total cholesterol, LDL-C, remnant lipoprotein (LP) cholesterol, and LDL/HDL-C ratio, an increase of the percentage of patients who achieved target LDL-C level to 65.4% (p=0.001) in the ezetimibe add-on to statin group was also observed. Although no significant effect was achieved on high-sensitivity C-reactive protein (hsCRP) and oxidative stress markers, a significant reduction of tumor necrosis factor-α (TNF-α), 1.36 versus 0.96 (p=0.042), was observed.[24] The analysis of the data from the IMPROVE-IT trial, in which two laboratory targets were set: LDL-C (<1.8 mmol/L) and hsCRP (<2 mg/L), confirmed that ezetimibe add-on to statin treatment was far more successful in achieving both targets, and it was concluded as follows: Significantly more patients treated with ezetimibe/simvastatin met prespecified dual LDL-C and hsCRP targets, than patients treated with simvastatin alone (50 versus 29%, p<0.001). Reaching both LDL-C and hsCRP targets was associated with improved outcomes after multivariable adjustment (38.9 versus 28.0%; adjusted hazard ratio (HR), 0.73; 0.66–0.81; p<0.001).[21]

Translation of pleiotropic effect of ezetimibe when add-on statins in improved endothelial function and vascular reactivity was proven by Yunoki and colleagues, with measurement of flow-mediated dilatation (FMD) of the brachial artery in 109 patients with CAD and measurement of LP fractions as well. The significance of this study lies in the fact that triglycerides (TG) and HDL-C lipoproteins were found to be independently associated with endothelial dysfunction in CAD patients (as measured by FMD). However, the ezetimibe add-on to statin treatment (in the subgroup with high TG, irrespective of LDL-C level), significantly improved TG level and endothelial function as well.[25] This is in concordance with the fact that although LDL-C is the main treatment target, other LP fractions also contribute to atherosclerosis, and their downregulation results with improvement of endothelial function (as an early manifestation of atherosclerosis).

Effects of ezetimibe add-on to statins on ASCVD outcome

The potential benefits of adding an additional lipid-lowering agent – i.e. ezetimibe – to statin therapy for CVD prevention and risk reduction has been confirmed in several clinical trials.

The Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial evaluated the effects of ezetimibe add-on to atorvastatin *versus* atorvastatin monotherapy on the lipid profile and coronary atherosclerosis in Japanese patients who underwent percutaneous coronary intervention (PCI). The combination therapy resulted in lower LDL-C levels than atorvastatin monotherapy (1.6 *versus* 1.9 mmol/L; p<0.001) and, at the same time, coronary plaque

regression was observed in significantly higher percentage of patients (78 *versus* 58%; p=0.004).[26]

In the Study of Heart and Renal Protection (SHARP) (Simvastatin plus ezetimibe) trial, high-risk patients with diabetes and chronic kidney disease (CKD) with/without requiring dialysis constituted 23% of the study population. The combination therapy demonstrated superiority over statin monotherapy in LDL-C reduction, translated in a reduction of the primary endpoint of the first major ASCVD event – nonfatal myocardial infarction (MI) or CV death, nonhemorrhagic stroke, or any arterial revascularization procedure – over a median follow-up of 4.9 years.[10,20,27]

However, another ezetimibe add-on to statin (simvastatin) study – the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study – did not demonstrate superiority in terms of ASCVD risk reduction. The baseline hypothesis of this study was that hypolipemic medications will decrease the progression of aortic stenosis. Asymptomatic patients (1873) with mild-to-moderate aortic valvular stenosis (AS) with different LDL-C pretreatment levels were treated with ezetimibe add-on to simvastatin. In a nonprespecified *post hoc* analysis, slower progression of aortic stenosis was observed only in the patients with higher pretreatment LDL-C levels with mild aortic stenosis (0.06 m/s per year slower progression *versus* placebo in peak aortic jet velocity, 95% CI: 0.01–0.11, p=0.03), while the overall study results didn't support the hypothesis.[28]

The landmark trial on ezetimibe plus statin combination therapy, the largest and the longest one with ezetimibe, is the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). A total of 18,144 patients with acute coronary syndrome (ACS) were randomized to ezetimibe (10 mg) or placebo, all receiving 40 mg simvastatin, which was increased to 80 mg if LDL-C on treatment was >2.04 mmol/L. The average LDL-C during the study was 1.8 mmol/L in the simvastatin group and 1.4 mmol/L in the ezetimibe add-on to simvastatin group. The event rates for the primary endpoint at 7 years were 32.7% in the simvastatin–ezetimibe group and 34.7% in the simvastatin-monotherapy group, with an absolute risk reduction of 2% (HR 0.936; 95% CI: 0.89–0.99; p=0.016). Ischemic stroke was reduced by 21% (p<0.008). Nevertheless, no benefit in reducing all-cause mortality or deaths from CV causes was observed, which was not unexpected, as prior trials of intensive-*versus* standard-dose statin therapy also did not demonstrate a benefit in terms of mortality. As elaborated by the authors, the study was not powered to detect a difference in mortality. This was the first in the row of studies that provided information on the safety of reducing LDL-C levels down to 1.4 mmol/L. Although the absolute benefit in this group of patients (already treated with statins to reach the goal) from the added ezetimibe was small, it was statistically significant and supportive for the proposition that LDL-C lowering by means other than statins is beneficial in terms of residual risk reduction and can be performed without adverse effects.[1,10,11,21,29]

The diabetic subgroup analysis in the IMPROVE-IT trial, provided the outcomes in 4933 (27%) patients with diabetes, one of the prespecified subgroups in the trial. In this patient subset, ezetimibe add-on to statin therapy decreased LDL-C at 1 year by 1.1 mmol/L, as compared to 0.6 mmol/L with statin monotherapy. Diabetic patients on ezetimibe add-on to statin therapy had a 14% relative risk reduction, or 5.5% absolute reduction, compared with a 2% absolute risk reduction for nondiabetics. The most notable reductions were seen regarding ischemic stroke (39%), MI (24%), and the composite of death due to CV causes, MI, or stroke (20%). These CV effects of ezetimibe add-on to statin therapy are a result of the more prominent reduction of LDL-C (mean 0.5 *versus* 1.4 mmol/L in simvastatin monotherapy). This substudy analysis demonstrated superiority of the ezetimibe add-on to statin therapy in CV prevention in high-risk diabetic subset of patients.[14,21]

Another significant effect of ezetimibe add-on to statin therapy is cerebrovascular protection. The 2013 ACC/AHA cholesterol guideline, as previously commented, had a risk-targeted approach.[16] In stroke patients <75 years of age, a high-intensity statin treatment was recommended in the absence of safety concerns, including a history of hemorrhagic stroke, in which, as in the cases of age >75 years, a moderate-intensity statin treatment was recommended. According to the same guidelines, if there was a need for nonstatin treatment for additional LDL-C lowering, ezetimibe is the only drug that demonstrated further reduction of ASCVD risk when added on statin therapy.[30] The problem with high-dose statin therapy in this subset of patients, as pointed out by Lovadi and colleagues, is that special precautions should be borne in mind in patients with prior intracerebral hemorrhage and ischemic cerebro-vascular insultus (CVI) that goes through hemorrhagic transformation. And again, the advantage of ezetimibe add-on to statin therapy can be expected, and it was observed in the IMPROVE-IT study. The highest risk benefit was observed in the subgroup of patients with ischemic CVI with a 21% relative reduction of ischemic stroke (p<0.008). The addition of ezetimibe as a nonstatin type drug to statin treatment contributed to further reduction of LDL-C, which translated into additional decrease in reoccurrence and mortality of/from cerebrovascular events. Achieving target values with ezetimibe add-on to statin combination allows administration of low- to moderate-dose statin, which decreases the risks of adverse effects related to high-dose statin therapy.[31]

It is obvious from trial results that the higher the risk profile of the patient, the greater is the benefit in terms of risk reduction when ezetimibe is added to statin treatment. Taken together, all of the studies support the decision to propose ezetimibe as a second-line therapy in association with statins when the therapeutic goal is not achieved at the maximal tolerated statin dose or in patients intolerant or with contraindications to these drugs.[10,11]

Safety profile of ezetimibe add-on to statins combination therapy

The relationship between lipid-lowering medications, glycemic control, insulin resistance, and new-onset diabetes has been

studied since the introduction of hypolipemic medications. We know that glycemic control is impaired not only by statin treatment but also with niacin. In contrast, BAS demonstrate moderate lipid- and glucose-lowering effects, and fibrates (particularly bezafibrate) may produce beneficial effects on glucose metabolism and insulin sensitivity. The fact that statins are the most widely used hypolipemic drugs, makes this an important issue. Statins lead to a mild elevation of glycated hemoglobin A1c (HgbA1c) and fasting plasma glycose (FPG) and increase the incidence of new-onset diabetes, an effect known to be dose and agent dependent (pravastatin and pitavastatin have less diabetogenic effect and positive impact on insulin sensitivity), and is most pronounced in patients with baseline impaired fasting blood glucose (FBG), at older age, and with metabolic syndrome. However, it has been demonstrated that the risk of new-onset diabetes is overweighed by the benefit of CV risk reduction.[10]

For a long period of time, there was a lack of clinical trials addressing the same question in ezetimibe treatment, but the data were gathered from experimental animal studies that described how ezetimibe ameliorates metabolic markers such as hepatic steatosis and insulin resistance. The process is via inhibition of intestinal cholesterol absorption, and at the hepatic level, inhibition of the NPC1L1 leads to decreased hepatic insulin resistance, improved glycemic control, and improved insulin sensitivity, especially in metabolic disorders (obesity and hepatic steatosis). A protective function to pancreatic beta cells was also found in diabetic mice. Ezetimibe treatment was shown to reduce weight gain in animals fed with diabetogenic diet. Suggested possible mechanisms at the cellular level are improved insulin signaling (evidenced by the increase in Akt phosphorylation, upregulation of SHP [small heterodimer partner], and the downregulation of sterol regulatory element binding protein-1c [SREBP-1c] expressions) in high-fat-diet–induced obese mice and possible involvement of incretin glucagon-like peptide-1 (GLP-1). This was harder to prove in humans, as ezetimibe is usually used as statin cotherapy and individual impact of ezetimibe cannot be evaluated. A recent pooled analysis of 27 randomized trials assessing efficacy and safety of ezetimibe–statin combination therapy was unable to investigate the effects of ezetimibe on glycemia due to limitations in the design of the studies. However, there are reports from several small studies in humans with ezetimibe as monotherapy that demonstrate a significant reduction of parameters of insulin resistance and fatty liver. A small study of Hiramitsy reported significant decrease of HgbA1c (−0.3%; $p<0.05$) and fasting insulin level, without significant difference in FBG, although the same results were not confirmed in other human studies.[8,32]

In a recently published systematic review of randomized clinical trials, performed by Wu and colleagues on 2440 patients, experimental data were confirmed. Ezetimibe did not cause any adverse effects in terms of increased levels of FBG and hemoglobin A1c (HbA1c). Compared with high-dose statin therapy, ezetimibe add-on to low-dose statin for more than 3 months may even have beneficial effects on glycemic control.[33]

Statin-associated muscle symptoms are a very common side effect, also known to be dose dependent. It seems that ezetimibe add-on to low-dose statin therapy is one of the possibilities to achieve good LDL-C control and CV risk reduction with lesser side effects as demonstrated with myalgia.[34] This finding found its place in the most recent guidelines – namely, in the 2016 ESC/EAS Guidelines for the Management of Dyslipidemias, ezetimibe is to be considered in combination with low-dose statin or second- or third-line statin in order to manage statin-attributed muscle symptoms.[10]

Conclusions

Ezetimibe add-on to statin combination therapy is an effective treatment that leads to additional LDL-C lowering, recommended in situations where with maximal or maximally tolerated statin monotherapy treatment, LDL-C target goals cannot be achieved. More importantly, ezetimibe add-on to statin therapy leads to a further reduction of residual risk that remains in patients already on maximal or maximally tolerated statin therapy. At the same time, the treatment is safe, with a possible beneficial effect over the adverse influence of the statin on glycemic metabolism.

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Correspondence: Marija Vavlukis, University Clinic of Cardiology, Medical Faculty, Ss' Cyril and Methodius University, 1000, Skopje, Republic of Macedonia. marija.vavlukis@gmail.com

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