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Statins plus ezetimibe in the era of proprotein convertase subtilisin/kexin type-9 inhibitors

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Abstract

Statins are first-line agents in patients with dyslipidemia, with established benefits for reducing low-density-lipoprotein cholesterol (LDL-C) levels and cardiovascular events. However, a considerable number of statin-treated patients do not achieve target LDL-C levels, even at maximally tolerated statin doses, or are intolerant to intensive statin therapy. These patients can benefit from the addition of a non-statin lipid-lowering agent, and recent cholesterol guidelines have placed increased focus on combination lipid-lowering therapy. For patients that cannot achieve target treatment goals with statin therapy alone, the addition of the cholesterol absorption inhibitor ezetimibe leads to additional LDL-C reductions with good tolerability, and reductions in cardiovascular morbidity and mortality. The more recent Proprotein Convertase Subtilisin-Like/Kexin Type 9 (PCSK-9) inhibitors can lower LDL-C by an additional 45–65% and are also well tolerated with associated cardiovascular outcome data. These complementary approaches for LDL-C lowering in statin-treated patients lower LDL-C levels beyond that achieved with statin monotherapy. As no threshold level has been established below which LDL-C lowering benefits cease to occur, an early combination treatment strategy may lead to improved cardiovascular outcomes, particularly in high-risk patients. This review will examine the rationale, advantages and potential barriers to combination lipid-lowering therapy with reference to current guideline recommendations.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains one of the leading causes of death worldwide [1], and high lifelong levels of atherogenic lipoproteins are one of the major risk factors. There are many reasons for poor cholesterol control including inappropriate use of treatment options, low patient adherence, therapeutic and physician inertia, and deficiencies in healthcare systems [2,3]. However, treatments are now available that can lower LDL cholesterol levels to below guideline recommended targets (< 55 mg/dl) in almost all patients [2,3]. Furthermore, these treatments are backed up by evidence of cardiovascular protection in large randomized controlled trials [2,3]. The focus must now be on how to optimize treatment by prescribing effective combinations as single pills and tailoring treatment to individual patients based on their ASCVD risk profile.

This review will examine the rationale and evidence for adding ezetimibe and the Proprotein Convertase Subtilisin/Kexin type 9 (PCSK-9) inhibitors as second- and third-line treatments, respectively, to statins, and in whom these agents should be prescribed in light of recent updates to international cholesterol-lowering guidelines.

The role of LDL-C reduction in cardiovascular events and the current therapeutic armamentarium

The role of elevated levels of atherogenic lipoproteins in the development of ASCVD and its clinical manifestations is firmly established. Data from epidemiological studies, genetic analyses and randomized clinical trials have provided consistent evidence that high levels of these lipids, irrespective of their underlying cause, are strongly associated with ASCVD and cardiovascular mortality and that lowering their levels reduces this risk [4]. Recent longitudinal data from several observational studies including Framingham Offspring [5], the Multinational Cardiovascular Risk Consortium [6] and the Cooper Clinic Longitudinal Study [7] have shown that life-long elevations in either low-density lipoprotein cholesterol (LDL-C)

or non-high-density lipoprotein cholesterol (non-HDL-C) are associated with significantly higher future ASCVD risk compared with individuals with low levels throughout adulthood [8].

Mendelian randomization studies have emerged as a powerful method to examine whether associations between exposures and disease outcomes are causal. Thus, for example, individuals with favourable mutations in genes such as PSCK-9 have low PCSK-9 levels and lifelong low LDL-C levels [9]. Meta-analyses of Mendelian randomization studies have demonstrated that the association between long-term exposure to lower LDL-C and the risk of ASCVD was approximately log-linear [2-4].

A causal role for atherogenic lipids in ASCVD is further implicated by the results of numerous landmark randomized clinical trials in a variety of patient populations, which have demonstrated that lowering LDL-C with a statin significantly reduces the risk of ASCVD events as well as all-cause mortality. Just as for the Mendelian randomization studies, meta-analyses of the statin trials have confirmed a dose-dependent, approximately log-linear relationship between the absolute reduction in LDL-C and the proportional reductions in the incidence of coronary and major vascular events [10]. Successive meta-analyses of statin trials by the Cholesterol Treatment Trialists' Collaborators have shown that active treatment reduces the risks of major coronary events (myocardial infarction [MI] or death from coronary heart disease [CHD]), ischemic strokes, and coronary revascularisations by about one fifth (22% - 23%) for each 1 mmol/L reduction in LDL-C [11-12]. The second CTTC meta-analysis included 26 randomized controlled trials: 21 of statin versus control and five of more versus less intensive statin regimens [12]. The results showed that additional reductions in LDL-C with more intensive therapy further reduced the incidence of these major vascular events and found no significant evidence that intensive lowering of LDL-C produced any adverse effects [12]. These results suggest that intensive lowering in high-risk patients may

produce additional benefits. However, given that high doses of some statins may be associated with a higher risk of myopathy [13,14], these benefits may be more safely achieved by combination of standard doses with other LDL-C lowering therapies.

More recent meta-analyses have also included non-statin lipid-lowering therapies including diet, bile acid sequestrants, ileal bypass surgery, ezetimibe and PCSK-9 inhibitors [15-17]. In a meta-analysis of 49 clinical trials of over 312 000 participants, Silverman et al showed that each 1 mmol (38.7 mg/dL) reduction in LDL-C was associated with reductions in risk of major vascular events of 23% for statins and 25% for the non-statin interventions [15]. The Silverman et al meta-analysis investigated the entire statin class, without distinguishing the different types and doses of statin therapy administered. This has been addressed by Koskinas et al, who compared the clinical impact of more intensive versus less intensive LDL-C lowering by statin or non-statin medications for secondary prevention in a meta-analysis of 19 randomized controlled trials including over 152 000 patients [16]. More intensive lowering was associated with a 19% greater reduction in major vascular events across the different treatments and was more pronounced for statin vs. no statin when compared with either statin intensification or addition of a non-statin agent. These findings support current guidelines recommending statins (up-titrated to the highest tolerable doses) as first-line treatment for LDL-C lowering in patients at very high risk, with the addition of ezetimibe and PCSK-9 inhibitors as valuable add-on therapies in statin-treated patients requiring additional LDL-C lowering [3,8].

Mechanisms of action and LDL-C lowering efficacy

In the 2019 ESC/EAS guidelines [3], three main options exist for the management of high cholesterol levels: statins, ezetimibe and PCSK-9 inhibitors, with the intensity of the intervention depending on the individual’s level of cardiovascular risk.

Statins reduce the synthesis of cholesterol in the liver by competitively inhibiting the enzyme HMG-CoA reductase (Figure 1). This promotes upregulation of hepatic LDL receptor expression, thereby decreasing plasma concentrations of LDL-C as well as other ApoB-containing lipoproteins. Statins have clinically relevant differences in efficacy and choice of individual agent should be dictated by the level of LDL-C reduction required. The following range of LDL-C reductions has been reported for the individual statins as monotherapy: rosuvastatin, 45-63% (5-40 mg daily); atorvastatin, 26-60% (10-80 mg daily); simvastatin, 26-47% (10-80 ng daily); lovastatin, 21-42% (10-80 mg daily); Fluvastatin, 22-36% (10-20 mg daily); pitavastatin, 32-43% (1-4 mg daily); and pravastatin, 22-34% (10-80 mg daily). Each doubling of the statin dose yields an additional 6% reduction on average in LDL-C [18]. Ezetimibe is a first-in-class selective cholesterol absorption inhibitor that blocks cholesterol absorption at the level of the brush border of the intestine without affecting the absorption of fat-soluble nutrients (Figure 1) [19]. This reduces the amount of cholesterol delivered to the liver, which responds by upregulating LDL receptor expression resulting in increased clearance of LDL-C from the blood. Ezetimibe monotherapy is associated with LDL-C reductions of approximately 20%. The mechanisms of action of statins and ezetimibe are complementary and their coadministration leads to substantial additional reductions in LDL-C compared with statin monotherapy. This facilitates the attainment of LDL-C goals and may reduce the need for higher statin doses in those patients requiring more rigorous LDL-C reductions.

PCSK-9 inhibitors are human monoclonal antibodies that bind human PCSK-9 with high affinity that reduce LDL-C concentrations by decreasing the degradation of LDL receptors available for recycling at the hepatocyte cell surface (Figure 1) [20]. Two PCSK-9 inhibitors, evolocumab and alirocumab, have been approved for primary and secondary prevention, and both substantially reduce LDL-C levels by approximately 50% to 60% [20].

The importance of a statin/ezetimibe association

For high-risk individuals requiring secondary prevention with cholesterol-lowering therapy, current guidelines recommend first-line treatment with a high-intensity statin prescribed up to the highest tolerated dose [2,3,8]. However, a large proportion of high-risk patients does not achieve LDL-C targets even on maximum tolerated dose [21], and around 10%-20% of patients on statins suffer some degree of intolerance and require a dose adjustment [22,23]. For patients who fail to achieve their LDL-C target with a maximum tolerated statin dose, combination with ezetimibe is recommended as second-line treatment based on the rationale that inhibiting the two main sources of cholesterol – synthesis and uptake – will produce more effective lipid lowering than targeting synthesis alone.

Ezetimibe, indeed, acts by interfering with the gastrointestinal cholesterol absorption through the inhibition of the Niemann-Pick C1-Like 1 (NPC1L1) [24], a key protein involved in cholesterol absorption that is abundantly expressed in the small intestine and liver. Ezetimibe in response of the inhibition of NPC1L1 of cholesterol absorption causes a homeostatic upregulation of LDL receptors in the liver thus leading to increased clearance of cholesterol from the blood [25].

Ezetimibe is rapidly glucuronidated in the intestines, and the glucuronide undergoes enterohepatic recirculation which causes the long duration of action (22 hours) [26]. Ezetimibe is not metabolized by cytochrome P450 enzymes and has a low potential for causing clinically significant drug interactions when co-administered with all currently available statins [19]. Pooled safety data from four similarly designed trials of ezetimibe (10 mg) co-administered with statins (10-80 mg) in 2 382 patients with primary hypercholesterolemia reported no significant differences in the incidences of laboratory (elevated ALT/AST and CK levels) and clinical adverse events including hepatic, muscle, hepatitis-, gastrointestinal-, gallbladder-related, and allergic reaction/rash adverse events

compared with statin monotherapy [27]. A 2008 meta-analysis of 18 randomized clinical trials (n = 14 497) in which combination ezetimibe and statin therapy was compared with statin monotherapy confirmed these findings [28].

Two other issues strongly support the combination therapy: 1) the extreme variability in LDL cholesterol lowering response by monotherapy either statins [29] or ezetimibe [30] as compared to the lower relative variability in patients treated with statins + ezetimibe [31]; and 2) The complementary mechanisms of action of statins + ezetimibe which provides a powerful approach to prevent and treat atherosclerosis [32].

Numerous randomized controlled studies have confirmed that the combination of a statin with add-on ezetimibe has greater cholesterol-lowering efficacy than statin monotherapy, due to the synergistic additive effect of simultaneously inhibiting both cholesterol synthesis and absorption. A pooled analysis of four similarly designed trials of ezetimibe co-administered with a statin (atorvastatin, simvastatin, pravastatin or lovastatin) in 2 382 patients with primary hypercholesterolemia showed that ezetimibe combined with the lowest dose of a statin was as effective at lowering LDL-C as the highest dose of statin monotherapy [27]. These findings have also been confirmed by real-world data from a large retrospective study of a US managed-care database, which demonstrated greater efficacy of ezetimibe added to simvastatin, atorvastatin, or rosuvastatin monotherapy compared with up-titration of the statin monotherapy [33].

The clinical significance of ezetimibe an add-on to statin therapy was first demonstrated in the SHARP trial conducted in 9 270 patients with chronic kidney disease treated with the combination of ezetimibe 10 mg plus simvastatin 20 mg [34]. The results of the trial have clearly shown that the combination simvastatin – ezetimibe reduced LDL-C by 33 mg/dL (0.85 mmol/L) associated with a significant 17% reduction in major atherosclerotic events [34].

A second trial IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) evaluated the efficacy of ezetimibe 10 mg/simvastatin 40 mg versus simvastatin 40 mg/placebo for reducing risk of cardiovascular morbidity and mortality in patients hospitalized within the preceding 10 days for an acute coronary syndrome (ACS), a group at high risk of recurrent cardiovascular events [35]. It was the first study powered for clinical outcomes to show a benefit with a non-statin agent when added to a statin. A total of 18 144 patients from 39 countries were randomized: 9 067 to the combination and 9 077 to simvastatin alone. Patients were required to have an LDL-C of 50-125 mg/dL (50-100 mg/dL if on prior lipid-lowering therapy) [35]. Exclusions were failure to meet ACS stability criteria, current statin treatment more potent than simvastatin 40 mg, creatinine clearance < 30 ml/min and active liver disease. The study continued until each patient had been followed up for a minimum of 2.5 years and until the target number of events (5 250) was reached. Baseline characteristics were similar between the two arms: mean age was 64 years, 25% were female, around 27% had type 2 diabetes and 21% a history of prior MI. Over the course of the study, up-titration to 80 mg simvastatin was required in 6% of the combination arm and 27% of the monotherapy arm. Baseline LDL-C levels were 95 mg/dL in both arms. Reductions in LDL-C were observed as early as 1 month and sustained, with mean levels of 54 mg/dL and 70 mg/dL achieved in the ezetimibe/simvastatin and simvastatin arms, respectively, over a median follow-up of 6 years [35].

The primary efficacy endpoint, a composite of CVD death, major adverse cardiac event (nonfatal MI, unstable angina leading to hospitalization, coronary revascularization after day 30), or nonfatal stroke, was significantly lower in the ezetimibe/simvastatin compared with simvastatin arm over the duration of follow-up (32.7% vs. 34.7%, P = 0.02) [35]. Other endpoints including MI, stroke, and a composite of cardiovascular death/MI/stroke were all significantly lower in the ezetimibe/simvastatin arm; no differences were noted for all-cause

mortality, cardiovascular mortality, and need for coronary revascularization [35]. Prespecified secondary analyses of IMPROVE-IT have confirmed the benefits of adding ezetimibe to simvastatin in both men and women [36], patients with diabetes [37] and the elderly [38], as well as the long-term safety and efficacy of achieving very low LDL-C levels (< 30 mg/dL) 1 month after an ACS [39].

Prespecified safety endpoints included abnormal elevations of liver enzyme and creatine kinase levels, myopathy, rhabdomyolysis, adverse hepatobiliary events, and cancer. The rates of these adverse events were low in IMPROVE-IT and ezetimibe did not increase myopathy or transaminitis compared with placebo. There was no increase in the incidence of cancer or new-onset type 2 diabetes, and no increase in study-drug discontinuation rates. Importantly, in IMPROVE-IT median trial follow-up was 6 years, a duration that is more than adequate to identify low frequency adverse events or those appearing after long-term exposure. Over this period, the 971 patients who achieved an LDL-C of ≤ 30 mg/dL at 1 month had no excess safety concerns, including hemorrhagic stroke or cataract-related adverse events [39].

In all the trials, the effect of combination with ezetimibe + statin treatment on cholesterol levels was more pronounced in patients with type 2 diabetes than in those without, whereas the effect of statin alone did not differ between those with and without type 2 diabetes [35,40-42].

Compared with standard statin monotherapy, the combination of statin plus ezetimibe showed greater coronary plaque regression, which might be attributed to cholesterol absorption inhibition–induced aggressive lipid lowering [43]. This difference translated into a reduced risk of ASCVD events in both individual trials [37] and a meta-analysis of randomized controlled trials with a statin control arm, which showed that an ezetimibe/statin combination was associated with a greater reduction of major adverse cardiovascular events in patients with diabetes than in those without [44].

Available fixed-dose combinations with ezetimibe

Based on the above premises, in order to simplify dosing and improve adherence for patients taking both agents [45], single-pill formulations (SPC) have been developed for ezetimibe combinations with simvastatin, atorvastatin and rosuvastatin. Different formulations of fixed combination rosuvastatin/ezetimibe have been developed from a hard gelatine capsule containing two unique tablets of the two separate active ingredients to tablet [42]. Pharmacokinetics studies for both formulations have demonstrated their bioequivalence in terms of AUC and Cmax to concurrent administration of each corresponding individual drugs thus supporting their potential clinical use [46].

Each of the individual component used in these different combinations has well-characterized efficacy and safety profiles that have been studied in randomized controlled trials across different comorbid conditions, ages and geographic regions. In Europe, all three combinations are indicated as adjunctive therapy to diet for use in patients with homozygous familial hypercholesterolemia, and in patients with primary hypercholesterolemia or mixed hyperlipidemia, when appropriate.

The respective lipid-lowering efficacy, in terms of mean percent changes total cholesterol and LDL-C levels, of the three combinations is illustrated in Table 1.

Finally, among newer agents, the prodrug bempedoic acid, when metabolized to the active form in the liver, is responsible for the inhibition of ATP citrate lyase (ACL) leading to a reduced production of cytosolic acetyl-coenzyme-A, a precursor of the mevalonate pathway of cholesterol biosynthesis [47]. Recent studies have demonstrated that bempedoic acid is a safe and effective lipid-lowering agent and may be a suitable alternative in statin-intolerant patients [48]. Fixed combination of bempedoic acid with ezetimibe reduced LDL-C up to − 41% [49].

What are the benefits of adding a PCSK-9 inhibitor to a statin/ezetimibe combination?

The incremental LDL-C lowering benefit of adding ezetimibe to statins and the demonstration that there is no LDL-C threshold for clinical benefit have paved the way for the addition of further lipid-lowering agents as triple therapy to achieve even greater reductions in LDL-C. This has come in the form of the anti-PCSK-9 monoclonal antibodies (PCSK9-inhibitors) evolocumab and alirocumab, which have a mode of action complementary to statin and ezetimibe.

Two large-scale randomized cardiovascular outcomes trials with these agents have recently been published: FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) with evolocumab [50] and ODYSSEY OUTCOMES with alirocumab [51]. Both trials enrolled high-risk groups with established ASCVD and LDL-C levels ≥ 70 mg/dL on optimal statin therapy [50,51]. Ezetimibe was used infrequently at baseline (3–5% of patients in both trials). The study design of the two trials is shown in Table 2. In the FOURIER trial, 27 564 patients with stable ASCVD were randomized to double-blinded subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or placebo [50]. In the ODYSSEY Outcomes trial, 18 924 early post-ACS patients were randomized to twice monthly injections of alirocumab (75 or 150 mg) or placebo [51]. Median baseline LDL-C levels in both trials were similar (92 mg/dL in FOURIER and 87 mg/dL in ODYSSEY OUTCOMES), and in both trials a reduction of at least 50% in LDL-C levels was achieved [50,51].

The FOURIER primary composite endpoint was incidence of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization, and occurred in 9.8% of the evolocumab group and 11.3% of the placebo group over a median follow-up of 2.2 years, a 15% reduction ($P < 0.001$) [50]. There was also a statistically significant 20% reduction in the key secondary endpoint, a composite of cardiovascular death,

myocardial infarction, or stroke, which occurred in 5.9% and 7.4% of patients in the evolocumab and placebo groups, respectively ($P < 0.001$). No significant differences were observed in the risk of cardiovascular or all-cause mortality, but the study was not designed to detect such a difference and follow-up was relatively short [50].

The ODYSSEY OUTCOMES primary endpoint was a composite of death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or hospitalization for unstable angina and occurred in 9.5% patients in the alirocumab group and 11.1% in the placebo group ($P < 0.001$), a 15% reduction over a median follow-up of 2.8 years [51]. In this trial, all components of the primary endpoint were significantly reduced except death by CHD. In both studies, the PCSK-9 inhibitors were well tolerated with no adverse safety concerns even among individuals who achieved very low LDL-C levels [51].

Despite some differences in the design of the two trials (stable ASCVD, 80% of patients with previous MI, and single evolocumab dose in FOURIER, versus early post-ACS, 19% of patients with previous MI, and two doses of alirocumab in ODYSSEY OUTCOMES), both trials confirmed there is no LDL-C threshold for clinical benefit [50,51].

The addition of the PCSK-9 inhibitors to the lipid-lowering armamentarium provides an alternative, complementary, and aggressive mechanism of action for lipid lowering that will modify the share of other LDL-lowering agents on the market. Following the publication of results from the ezetimibe and PCSK-9 inhibitor cardiovascular outcome trials, European and US society task forces were convened to develop clinical guidance on when to use these non-statin therapies, including in which patients, in which situations, and in which order [2,52]. In patients with clinical ASCVD, the recommended first approach to the management of elevated LDL-C levels was to intensify statin therapy. Based on the benefits on ASCVD outcomes and demonstrated safety of ezetimibe in patients with ACS in IMPROVE-IT, ezetimibe 10 mg was recommended as the first non-statin agent to be added. However, it was

recognized that while the addition of ezetimibe provides a further reduction in LDL-C levels, this may not be sufficient to achieve the ≥ 50% reduction in LDL-C levels required by very high risk ASCVD patients to attain treatment goals. In these patients, further lipid lowering with the addition of a PCSK-9 inhibitor may be required.

These recommendations have subsequently been incorporated into respective ESC/EAS and ACC cholesterol-lowering guidelines [3,8], both of which stratify patients by level of CVD risk. First-line therapy is with a high potency statin at the highest recommended/tolerable dose to reach the LDL-C goal. If the target is not achieved after 4–6 weeks despite lifestyle modification and maximally tolerated statin therapy, add-on therapy with ezetimibe and thereafter a PCSK-9 inhibitor is recommended. For secondary prevention in patients at very high CVD risk, ESC/EAS 2019 guidelines recommend lowering LDL-C to < 1.4 mmol/L (55 mg/dL) and an LDL-C reduction of ≥ 50% from baseline [3]. PCSK-9 inhibitor use should be considered in patients with clinical ASCVD treated with maximal tolerated statin therapy and/or ezetimibe, but still showing LDL-C > 3.6 mmol/L (140 mg/dL). US ACC guidelines also recommend a ≥ 50% reduction from baseline, but have an LDL-C threshold of 1.8 mmol/L (70 mg/dL) for the addition of a non-statin medication, first ezetimibe and then PCSK-9 inhibitors if LDL-C remains ≥ 70 mg/dL [8].

Prescriptive barriers and possible solutions

First approved for the management of cholesterol levels in patients with homozygous familial hypercholesterolemia, the EMA extended the indication for PCSK-9 inhibitors in 2018 to include secondary prevention in the high-risk group of patients with ASCVD**.** The latter in association with a statin at maximal tolerated dose with or without other lipid-lowering agents, or as monotherapy or in association with other non-statin therapies in patients intolerant of statins or in whom statins are contraindicated. However, the high cost of these medications has meant that they are not available for secondary prevention in all member

states, and others regulatory authorities in other countries have defined criteria for their use in clinical practice.

An analysis of a prospective Swiss cohort of 2023 patients hospitalized for ACS with available data for LDL-C and lipid-lowering therapy illustrated how different guideline criteria are able to influence the proportion of individuals eligible for treatment [53]. In the United States, the 2016 ACC expert consensus threshold for consideration of therapy with PCSK-9 inhibitors was 2.6 mmol/L versus 3.6 mmol/L in the ESC/EAS statement, with an even lower LDL-C threshold (1.8 mmol/L) among patients with comorbidities or rapidly progressive ASCVD. In the Swiss cohort analysis, the use of a statin was 98.5% at discharge and 94.3% at 1 year. After modelling, the effect of ezetimibe in all patients not already receiving ezetimibe at 1 year, 13.4% would have been eligible for PCSK-9 inhibitors according to ACC guidelines, but only 2.7% of patients according to ESC/EAS guidelines [53].

A separate analysis considered PCSK-9 eligibility according to ESC/EAS and Agenzia Italiana del Farmaco (AIFA) regulatory agency criteria using data from two Italian, nationwide, prospective, real-world registries of patients with stable CAD [54]. Similar to the ACC, AIFA criteria consider post-MI patients eligible for PCSK-9 inhibitors if they have LDL-C > 100 mg/dL despite treatment with high potency statins plus ezetimibe, or ezetimibe alone in the presence of a well-documented condition of statin intolerance. Despite ESC/EAS guideline recommendations to treat LDL-C in post-MI patients to a target level of < 70 mg/dL using high-intensity statin therapy in combination with ezetimibe, if needed, the analysis revealed that many patients were undertreated with conventional lipid-lowering therapies [54]. A low-dose statin was prescribed in 9.3% of patients, and a high dose in 61.4%; statin plus ezetimibe therapy was used in less than 18% of cases. In the 3 074 post-MI patients with LDL-C data available, a target level of < 70 mg/dL was achieved in only 1186 (38.6%)

patients and around a quarter (24%) had an LDL-C ≥ 100 mg/dL. Statins were prescribed to 97.1% of patients with LDL-C levels < 70 mg/dL, 96.2% of those with LDL-C in the range 70 to 99 mg/dL, and 90.8% in those with LDL-C levels ≥ 100 mg/dL. In the overall post-MI cohort treated with statins and/or ezetimibe (n=2 977), 293 (9.8%) and 450 (22.2%) would have been eligible for PCSK-9 inhibitors, according to ESC/EAS and AIFA criteria, respectively [54].

While ESC/EAS recommendations are more conservative than those of the ACC or AIFA, there must be a balance between setting levels too high that exclude a significant proportion of very high-risk patients that would gain clinical benefit from PCSK-9 inhibitors, and lower levels that are not sustainable for healthcare systems. Standard practice in ACS management is the initiation of a high-intensity statin during the acute phase, which is a particularly high-risk period for recurrent events. This practice has a Class IA recommendation in the guidelines based on published evidence that it results in a significantly reduced rate of the composite of death, MI, or rehospitalization for ACS within 30 days, compared with a less aggressive approach to LDL cholesterol lowering [3].

A small-scale trial has recently evaluated the benefit of the PCSK-9 inhibitors in this high-risk patient group. EVOPACS (Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients With Acute Coronary Syndromes) randomized 308 patients hospitalized for ACS with elevated LDL-C levels to evolocumab 420 mg (n=155) or placebo (n=153) initiated in hospital and then every 4 weeks [55]. All patients received atorvastatin 40 mg and most patients (78.2%) had not been on statin treatment previously. At 8 weeks, mean LDL-C levels had decreased from 3.6 mmol/L (140 mg/dL) to 0.8 mmol/L (31 mg/dL) with evolocumab and from 3.4 mmol/L (132 mg/dL) to 2.1 mmol/L (80 mg/dL) with placebo. LDL-C levels < 1.8 mmol/L were achieved at week 8 by 96% of patients in the atorvastatin/evolocumab group versus 38% of those on high-intensity statin plus placebo injection. Furthermore, 90% of the

dual-therapy group had achieved the new ESC/EAS guideline-recommended target of an LDL-C level < 55 mg/dL, compared with 11% of patients randomized to high-intensity atorvastatin at 40 mg/day plus placebo injections [55].

The EVOPACS findings highlight the importance of starting early aggressive lipid-lowering therapy for rapid reductions in LDL-C in very high-risk patients. The clinical impact of very early LDL-C lowering with PCSK-9 inhibitors initiated in the acute ACS setting now warrants further investigation in a dedicated cardiovascular outcomes trial. The results of such a trial may help further define the population of high-risk patients who would benefit from the addition of PCSK-9 inhibitors to high-intensity statins and ezetimibe.

Final considerations

Dyslipidemia continues to be a central and modifiable causal risk factor in the development of ASCVD, and a major focus of intervention remains lowering plasma LDL-C levels, foremost with the use of high-intensity statins with the aim of reducing LDL-C by at least 50%. Current cholesterol guidelines have lowered LDL-C goals in patients at high ASCVD risk, but recent real-world data show that only a minority of patients using lipid-lowering drugs reach desirable LDL-C levels (< 70 mg/dL) [21,56,57].

When treating patients with high cholesterol, a one size fits all approach is not appropriate. When evaluating patients in clinic, there are two main groups of secondary prevention patients for whom the addition of ezetimibe and subsequently a PCSK-9 inhibitor to maximally tolerated statin may be appropriate. The first comprises patients with ASCVD and above goal LDL-C levels despite treatment with maximally tolerated statin, particularly if they have experienced recurrent events, and the second group comprises those who are statin intolerant, in whom the addition of ezetimibe and or a PCSK9-inhibitor may allow a lower statin dose to be used. In both instances the first non-statin therapy to be added should be ezetimibe from both an economical perspective and because the PCSK-9 inhibitors have not

been evaluated in any ongoing trial without patients being on maximally tolerated statins or maximally tolerated statin plus ezetimibe. Coadministration of ezetimibe with the starting dose (10 mg) of atorvastatin has been shown to provide a 50% reduction in LDL-C, comparable to the 51% reduction obtained with high-dose (80 mg) atorvastatin [58]. In clinical practice, ezetimibe co-administered with maximally tolerated statin may enable more patients to achieve recommended target LDL-C levels by offering greater LDL-C lowering with fewer dose titrations as well as a well-tolerated alternative for patients in whom maximal dose statin monotherapy is inadequate.

The PCSK-9 inhibitors lower LDL-C by 55% to 60% whether as monotherapy or when added to other lipid-lowering therapy. When used in combination, the LDL-C reductions are additive and therefore much greater lipid-lowering is achieved. As the tolerability profile of ezetimibe and the PCSK-9 inhibitors in combination with a statin is similar to statin monotherapy and as no study has yet lowered LDL-C levels to a point where they are harmful, current recommendations advocate their use in combination beginning with the addition of ezetimibe to maximally tolerated statin, and followed by the addition of a PCSK-9 inhibitor. The eligibility for PCSK-9 inhibitors depends strongly on pre-treatment with ezetimibe in combination with a maximally tolerated statin. For maximum benefit, the addition of ezetimibe should be initiated early, particularly for patients at very high risk in whom a statin/ezetimibe combination should ideally be prescribed during the index hospitalization to allow rapid attainment of LDL-C targets and early prescription of PCSK-9 inhibitors if required.

Despite the efficacy of the above treatments, their benefits will only be replicated in real-life if patients adhere and comply with the prescribed treatment regimen. In this light, it is recognized that the real-life effectiveness of the statins is significantly compromised by poor adherence and compliance [59]. To improve patient adherence, SPC of ezetimibe and some

statins are available. Ezetimibe has an acceptable and well-established tolerability profile over many years of clinical use. In addition, its use in combination with a statin may allow a reduction in statin dose.

The decision to add non-statin lipid-lowering agents in the clinic is strongly dependent on costs versus health benefits. The costs of any new drug that reaches the market are likely to be high, and therefore efforts to individualize cardiovascular care are essential so that treatments reach those most in need and who will have the greatest benefit. As the statins and ezetimibe are available as generic treatments, a regimen of intense statin therapy with ezetimibe in all ASCVD patients should be implemented wherever possible. In some very high-risk patients such as those in EVOPACS this may still be insufficient, and the addition of a PCSK-9 inhibitor may be required. Recent price reductions of the PCSK-9 inhibitors combined with targeting higher risk groups would limit the number of patients eligible for therapy and improve the economic impact of adopting these new therapies.

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Table 1. Mean percent change of total cholesterol and LDL-C from untreated baseline of the single-pill combination of ezetimibe/simvastatin, ezetimibe/atorvastatin and ezetimibe/rosuvastatin in patients with primary hypercholesterolemia.

Treatment	N	Total-C	LDL-C
Ezetimibe/simvastatin			
Pooled data (all ezetimibe/simvastatin doses)	609	-38	-53
Pooled data (all simvastatin doses)	622	-28	-39
Ezetimibe/simvastatin by dose			
10/10	152	-31	-45
10/20	156	-36	-52
10/40	147	-39	-55
10/80	154	-43	-60
Simvastatin by dose			
10	158	-23	-33
20	150	-24	-34
40	156	-29	-41
80	158	-35	-49
Ezetimibe/atorvastatin			
Pooled data (all ezetimibe/atorvastatin doses)	255	-41	-56
Pooled data (all atorvastatin doses)	248	-32	-44
Ezetimibe/atorvastatin by dose			
10/10	65	-38	-53
10/20	62	-39	-54
10/40	65	-42	-56
10/80	63	-46	-61
Atorvastatin by dose			
10	60	-26	-37
20	60	-30	-42
40	66	-32	-45
80	62	-40	-54
Ezetimibe/rosuvastatin			
Pooled data (all ezetimibe/ rosuvastatin doses)	195	-39	-57
Pooled data (all rosuvastatin doses)	194	-30	-44
Ezetimibe/rosuvastatin by dose			
10/5	65	-35	-52
10/10	66	-39	-57
10/20	64	-45	-64
Rosuvastatin by dose			
5	65	-29	-40
10	65	-31	-46
20	64	-35	-49

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Table 2. FOURIER and ODYSSEY OUTCOMES study design.

	FOURIER	**ODYSSEY OUTCOMES**
Enrolled population (*N*)	27 564	18 924
Age entry criteria (years)	≥40 and ≤85	≥40
Inclusion criteria	Prior MI, stroke or symptomatic PAD plus additional high-risk features	Prior ACS (between 1 and 12 months)
Lipid entry criteria	LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL	LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL or ApoB ≥80 mg/dL
Primary endpoint	CV death, fatal and non-fatal MI, stroke (all), unstable angina or coronary revascularization	CHD death, non-fatal MI, unstable angina or stroke (ischemic)
Therapy down-titration when LDL-C low	No	Yes

ACS, acute coronary syndrome. ApoB, apolipoprotein B. CHD, coronary heart disease. CV, cardiovascular. HDL-C, high-density lipoprotein cholesterol. LDL-C, low-density lipoprotein cholesterol. MI, myocardial infarction. PAD, peripheral artery disease.

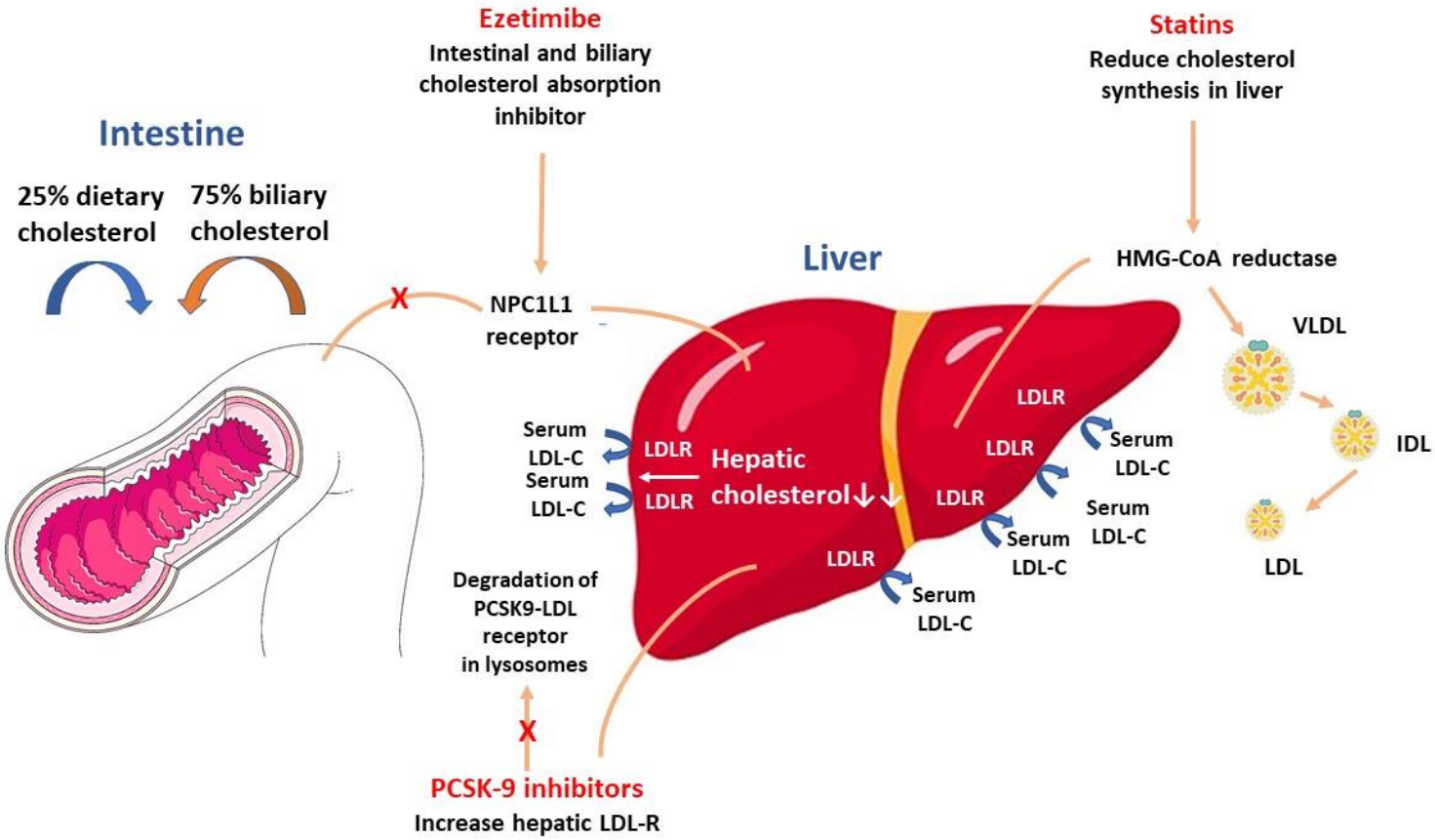

Figure 1. Lipid-lowering mechanisms of action for statins, ezetimibe, and PCSK-9 inhibtors.