REVIEW ARTICLE

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

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ABSTRACT
Statins are first-line agents used in patients with dyslipidemia, which show established benefits in reducing low-density lipoprotein cholesterol (LDL-C) levels and decreasing the rate of cardiovascular events. However, a considerable number of patients on statins 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 nonstatin lipid-lowering agent, and recent cholesterol guidelines have put greater focus on combination lipid-lowering therapy. In patients who cannot achieve target treatment goals with statin therapy alone, the addition of a cholesterol absorption inhibitor, ezetimibe, leads to further LDL-C reduction with good tolerability and decreases cardiovascular morbidity and mortality. The more recent proprotein convertase subtilisin-like / kexin type 9 (PCSK-9) inhibitors can lower LDL-C by additional 45% to 65% and are also well tolerated. These complementary approaches for LDL-C lowering in patients treated with statins decrease LDL-C levels more effectively than statin monotherapy. As no threshold level has been established below which LDL-C lowering benefits disappear, the early application of a combination treatment strategy may lead to improved cardiovascular outcomes, particularly in high-risk patients. This review examines the rationale, advantages, and potential barriers to combination lipid-lowering therapy with reference to the current guideline recommendations.

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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 for this condition. 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 low-density lipoprotein cholesterol (LDL-C) levels below guideline recommended targets (below 55 mg/dl) in almost all patients.[2,3] Furthermore, these treatments are backed up by the evidence of cardiovascular protection in large randomized controlled trials.[2,3] The focus must now be put on how to optimize treatment by prescribing effective combination therapies in the form of single pills and tailoring treatment to individual patients based on their ASCVD risk profile.

This review examines the rationale and evidence with regard to adding ezetimibe and proprotein convertase subtilisin / kexin type 9 (PCSK-9) inhibitors as second- and third-line treatments, respectively, to statins, and to analyze in whom these agents should be prescribed in light of recent updates to international guidelines on cholesterol lowering.

The role of low-density lipoprotein cholesterol reduction in cardiovascular events and the current therapeutic armamentarium

The role of elevated atherogenic lipoprotein levels 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 the Framingham Offspring,[5] the Multinational Cardiovascular Risk Consortium,[6] and the Cooper Clinic Longitudinal Study[7] have shown that individuals presenting lifelong elevations in either LDL-C or non–high-density lipoprotein cholesterol (non–HDL-C) levels were at significantly higher future ASCVD risk compared with those with low levels throughout adulthood.[8]

Mendelian randomization studies have emerged as a powerful method to examine the causality of associations between exposure and disease outcomes. Thus, for example, individuals with favorable mutations in genes such as *PSCK-9* have low PCSK-9 levels and low lifelong 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 of 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 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' Collaboration have shown that active treatment reduces the risk of major coronary events (myocardial infarction [MI] or death from coronary heart disease [CHD]), ischemic stroke, and coronary revascularization by about one fifth (22%–23%) for each 1-mmol/l reduction in LDL-C.[11-12] The second Cholesterol Treatment Trialists' Collaboration meta-analysis included 26 randomized controlled trials: 21 of statin versus control and 5 of more versus less intensive statin regimens.[12] The results showed that additional reductions in LDL-C with more intensive therapy further decreased the incidence of these major vascular events and did not provide significant evidence that intensive LDL-C lowering caused any adverse effects.[12] These results suggest that intensive LDL-C lowering in high-risk patients may have 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 using a combination of standard doses with other LDL-C lowering therapies.

More recent meta-analyses have also focused on nonstatin 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[15] showed that each 1-mmol (38.7-mg/dl) reduction in LDL-C was associated with a decrease in the risk of major vascular events of 23% for statins and 25% for nonstatin interventions.[15] In their meta-analysis, Silverman et al[15] investigated the entire statin class, without distinguishing various types and doses of statins administered. This has been addressed by Koskinas et al,[16] who compared the clinical impact of more intensive versus less intensive LDL-C lowering by statin or nonstatin medications for secondary prevention in a meta-analysis of 19 randomized controlled trials including over 152 000 patients. More intensive lowering was associated with a 19% greater reduction in major vascular events across various treatments and was more pronounced for statin versus no statin when compared with either statin intensification or addition of a nonstatin agent. These findings support the current guidelines recommending statins (uptitrated 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 patients on statins requiring additional LDL-C lowering.[3,8]

Mechanisms of action and efficacy of low-density lipoprotein cholesterol lowering

In the 2019 European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) guidelines,[3] 3 main options are recommended for the management of high cholesterol levels: statins, ezetimibe, and PCSK-9 inhibitors, at doses adjusted to an individual's cardiovascular risk.

Statins reduce the synthesis of cholesterol in the liver by competitively inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (FIGURE 1). This promotes upregulation of hepatic LDL receptor expression, thereby decreasing plasma concentrations of LDL-C as well as other apolipoprotein B–containing lipoproteins. Statins show clinically relevant differences in efficacy, and the choice of an individual agent should be determined by the degree of LDL-C reduction required. The following ranges of LDL-C reductions have been reported for individual statins as monotherapy: rosuvastatin, 45%–63% (5–40 mg/d); atorvastatin, 26%–60% (10–80 mg/d); simvastatin, 26%–47% (10–80 mg/d); lovastatin, 21%–42% (10–80 mg/d); fluvastatin, 22%–36% (10–20 mg/d); pitavastatin, 32%–43% (1–4 mg/d); and pravastatin, 22%–34% (10–80 mg/d). Each

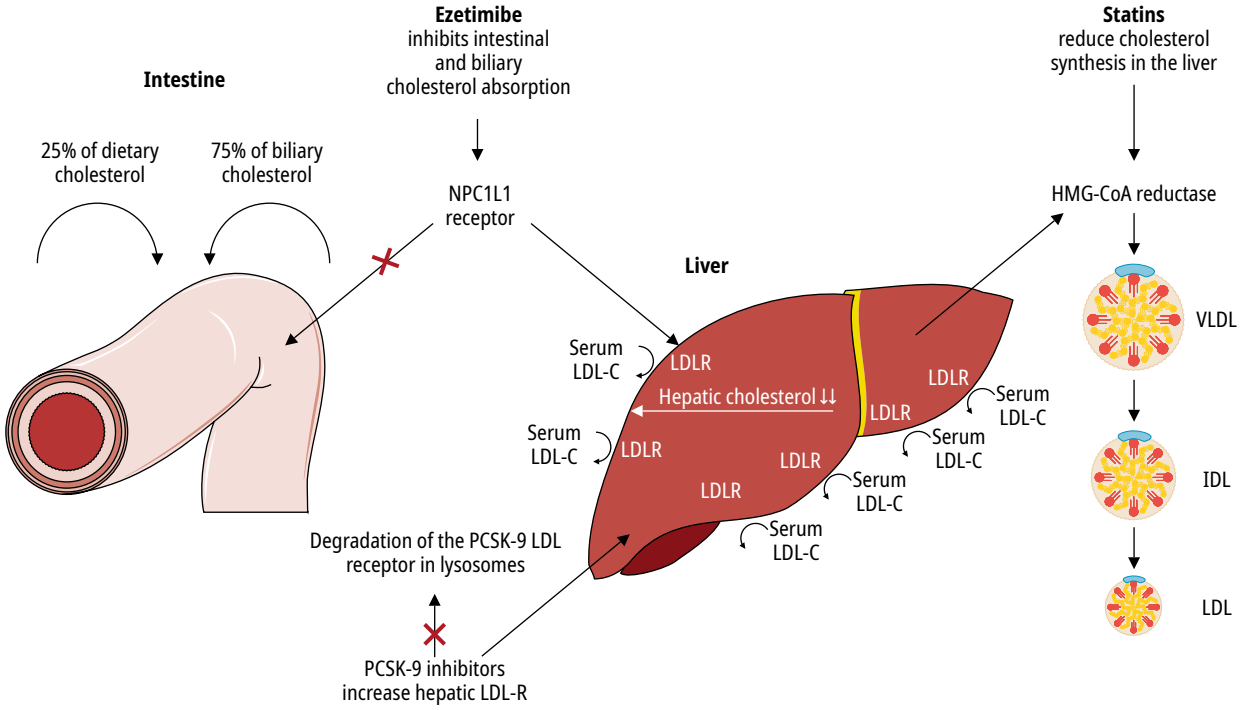

FIGURE 1 Lipid-lowering mechanisms of action for statins, ezetimibe, and proprotein convertase subtilisin-like / kexin type 9 inhibitors
Abbreviations: ↓↓, decrease; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDL-R, low-density lipoprotein receptor; NPC1L1, Niemann-Pick C1-Like 1; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; PCSK-9, proprotein convertase subtilisin-like / kexin type 9; VLDL, very low–density lipoprotein

doubling of the statin dose yields an additional 6% reduction in LDL-C on average.[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 reduction of approximately 20%. The mechanisms of action of statins and ezetimibe are complementary and their coadministration leads to substantial additional reduction 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 patients requiring more rigorous LDL-C reductions.

Proprotein convertase subtilisin / kexin type 9 inhibitors are human monoclonal antibodies that bind human PCSK-9 with high affinity and 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 cardiovascular prevention. Both agents substantially reduce LDL-C levels by approximately 50% to 60%.[20]

The significance of the statin / ezetimibe association In high-risk individuals requiring secondary prevention with cholesterol-lowering therapy, current guidelines recommend first-line treatment with a high-intensity statin prescribed at 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 the maximum tolerated dose,[21] and around 10% to 20% of patients on statins suffer from some degree of intolerance and require dose adjustment.[22,23] In patients who fail to achieve their LDL-C target with a maximum tolerated statin dose, a combination with ezetimibe is recommended as second-line treatment based on the rationale that inhibiting the 2 main sources of cholesterol, synthesis and uptake, will produce more effective lipid lowering than targeting synthesis alone.

Ezetimibe, indeed, acts by interfering with gastrointestinal cholesterol absorption through the inhibition of Niemann-Pick C1-Like 1,[24] a key protein involved in cholesterol absorption, which is abundantly expressed in the small intestine and the liver. Ezetimibe, as a result of Niemann-Pick C1-Like inhibition and reduced cholesterol absorption, causes 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, causing long drug

activity (22 hours).[26] Ezetimibe is not metabolized by cytochrome P450 enzymes and has a low potential for inducing clinically significant drug interactions when coadministered with all currently available statins.[19] Pooled safety data from 4 similarly designed trials of ezetimibe (10 mg) coadministered with statins (10–80 mg) in 2382 patients with primary hypercholesterolemia showed no significant differences in the occurrence of laboratory (elevated alanine aminotransferase / aspartate aminotransferase and creatine kinase levels) and clinical adverse events including hepatic, muscular, hepatitis-related, gastrointestinal, and gallbladder-related events as well as allergic reaction or rash, as compared with statin monotherapy.[27] A 2008 meta-analysis of 18 randomized clinical trials (including a total of 14 497 patients) in which ezetimibe and statin combination therapy was compared with statin monotherapy confirmed these findings.[28]

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

Numerous randomized controlled trials have confirmed that the combination of a statin with add-on ezetimibe has greater cholesterol-lowering efficacy than statin monotherapy, which is due to the synergistic additive effect of simultaneously inhibiting both cholesterol synthesis and absorption. A pooled analysis of 4 similarly designed trials of ezetimibe coadministered with a statin (atorvastatin, simvastatin, pravastatin, or lovastatin) in 2382 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 United States managed care database, which demonstrated greater efficacy of ezetimibe added to simvastatin, atorvastatin, or rosuvastatin monotherapy compared with uptitration of the statin monotherapy.[33]

The clinical significance of ezetimibe as an add-on to statin therapy was first demonstrated in the SHARP (Study of Heart and Renal Protection) trial conducted in 9270 patients with chronic kidney disease treated with the combination of ezetimibe 10 mg and simvastatin 20 mg.[34] The results of the trial have clearly shown that the combination of simvastatin and ezetimibe reduced LDL-C by 33 mg/dl (0.85 mmol/l) and was associated with a significant 17% reduction in major atherosclerotic events.[34]

A second IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study 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 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 nonstatin agent when added to a statin. A total of 18 144 patients from 39 countries were randomized: 9067 to combination therapy and 9077 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] Exclusion criteria were failure to meet ACS stability criteria, current statin treatment more potent than simvastatin 40 mg, creatinine clearance below 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 (5250) was reached. Baseline characteristics were similar between the 2 study arms: the mean age was 64 years, 25% of the study patients were female, around 27% had type 2 diabetes, and 21% had a history of MI. Over the course of the study, uptitration to 80 mg of simvastatin was required in 6% of the combination arm and 27% of the monotherapy arm patients. Baseline LDL-C levels were 95 mg/dl in both arms. Reduction in LDL-C was observed as early as at 1 month and sustained, with the mean levels of 54 mg/dl and 70 mg/dl achieved in the ezetimibe / simvastatin and simvastatin arms, respectively, during a median follow-up of 6 years.[35]

The primary efficacy endpoint—a composite of cardiovascular death, major adverse cardiac event (nonfatal MI, unstable angina leading to hospitalization, and coronary revascularization after day 30), or nonfatal stroke—was significantly lower in the ezetimibe / simvastatin arm compared with the simvastatin arm at follow-up (32.7% vs 34.7%; $P = 0.02$).[35] Other endpoints including MI, stroke, and a composite of cardiovascular death, MI, and 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 the IMPROVE-IT study 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 (below 30 mg/dl) 1 month after 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

the IMPROVE-IT study, 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 or in study drug discontinuation rates. Importantly, in the IMPROVE-IT study, the median trial follow-up was 6 years, a time interval that is more than adequate to identify low-frequency adverse events or those appearing after long-term exposure. Over this period of time, the 971 patients who achieved an LDL-C lower than or equal to 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 a combination with ezetimibe plus statin treatment on cholesterol levels was more pronounced in patients with type 2 diabetes than in those without, whereas the effect of statins alone did not differ between those with and without type 2 diabetes.[35,40-42]

Compared with standard statin monotherapy, the combination of a statin + ezetimibe showed greater coronary plaque regression, which might be attributed to aggressive lipid lowering induced by cholesterol absorption inhibition.[43] This difference translated into a reduced risk of ASCVD events in both single trials[37] and a meta-analysis of randomized controlled trials with a statin control arm, which showed that the 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 in patients taking both agents,[45] single-pill formulations have been developed for ezetimibe combinations with simvastatin, atorvastatin, and rosuvastatin. Different formulations of the fixed rosuvastatin / ezetimibe combination have been developed from a hard gelatin capsule containing 2 unique tablets of the 2 separate active ingredients to a single tablet.[42] Pharmacokinetics studies of both formulations have demonstrated their bioequivalence in terms of the area under the curve and maximum concentration to concurrent administration of each corresponding individual drug, thus, supporting their potential clinical use.[46]

Each of the individual components used in these different combinations has well-characterized efficacy and safety profiles that have been studied in randomized controlled trials across various comorbidities, age groups, and geographic regions. In Europe, all 3 combinations are indicated as adjunctive therapy to diet for use in patients with homozygous familial hypercholesterolemia and in those with primary hypercholesterolemia or mixed hyperlipidemia, if appropriate.

The respective lipid-lowering efficacy, in terms of mean percentage changes in total cholesterol and LDL-C levels, of the 3 combinations is illustrated in TABLE 1.

Finally, among newer agents, bempedoic acid, a prodrug, when metabolized to the active form in the liver, is responsible for the inhibition of adenosine triphosphate–citrate lyase and reduces 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] A fixed combination of bempedoic acid with ezetimibe reduced LDL-C levels up to 41%.[49]

What are the benefits of adding a proprotein convertase subtilisin / kexin type 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 an even greater reduction in LDL-C levels. This has come in the form of anti-PCSK-9 monoclonal antibodies (PCSK9 inhibitors), evolocumab and alirocumab, which show a mode of action complementary to statins and ezetimibe.

The results of 2 large-scale randomized cardiovascular trials of 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 (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab) with alirocumab.[51] Both trials enrolled high-risk patients with established ASCVD and LDL-C levels higher than or equal to 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 2 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 injections of alirocumab (75 mg or 150 mg) or placebo administered twice monthly.[51] Median baseline LDL-C levels in both trials were similar (92 mg/dl in the FOURIER trial and 87 mg/dl in the ODYSSEY OUTCOMES trial), and in both trials a reduction of at least 50% in LDL-C levels was achieved.[50,51]

The FOURIER primary composite endpoint was defined as the incidence of cardiovascular death, nonfatal MI, nonfatal stroke,

TABLE 1 Mean percentage change in total cholesterol and low-density lipoprotein cholesterol levels compared with baseline values before treatment with the single-pill combination of ezetimibe / simvastatin, ezetimibe / atorvastatin, and ezetimibe / rosuvastatin in patients with primary hypercholesterolemia

Treatment		Patients, n	Total cholesterol, %	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 mg	152	–31	–45
	10/20 mg	156	–36	–52
	10/40 mg	147	–39	–55
	10/80 mg	154	–43	–60
Simvastatin by dose	10 mg	158	–23	–33
	20 mg	150	–24	–34
	40 mg	156	–29	–41
	80 mg	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 mg	65	–38	–53
	10/20 mg	62	–39	–54
	10/40 mg	65	–42	–56
	10/80 mg	63	–46	–61
Atorvastatin by dose	10 mg	60	–26	–37
	20 mg	60	–30	–42
	40 mg	66	–32	–45
	80 mg	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 mg	65	–35	–52
	10/10 mg	66	–39	–57
	10/20 mg	64	–45	–64
Rosuvastatin by dose	5 mg	65	–29	–40
	10 mg	65	–31	–46
	20 mg	64	–35	–49

Abbreviations: see FIGURE 1

hospitalization for unstable angina, or coronary revascularization and occurred in 9.8% of the patients in the evolocumab group and 11.3% of those in the placebo group at a median follow-up of 2.2 years—a 15% reduction (P <0.001).[50] There was also a significant 20% reduction in the key secondary endpoint, a composite of cardiovascular death, MI, 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 its follow-up was relatively short.[50]

The ODYSSEY OUTCOMES primary endpoint was regarded as a composite of death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or hospitalization for unstable angina and occurred in 9.5% of the 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 that trial, all

TABLE 2 The FOURIER and ODYSSEY OUTCOMES study design

Characteristic	FOURIER	ODYSSEY OUTCOMES
Study population, n	27 564	18 924
Age entry criteria, y	≥40 and ≤85	≥40
Inclusion criteria	Prior MI, stroke, or symptomatic PAD plus additional high-risk factors	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	Cardiovascular death, fatal and nonfatal MI, stroke (all), unstable angina, or coronary revascularization	Death from CHD, nonfatal MI, unstable angina, or stroke (ischemic)
Therapy downtitration when low LDL-C	No	Yes

Abbreviations: ACS, acute coronary syndrome; ApoB, apolipoprotein B; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; others, see FIGURE 1

components of the primary endpoint were significantly reduced except death from CHD. In both studies, PCSK-9 inhibitors were well tolerated and caused no safety concerns even among individuals who achieved very low LDL-C levels.[51]

Despite some differences in the design of the 2 trials (stable ASCVD, 80% of patients with a history of MI, and a single evolocumab dose in the FOURIER trial versus early post-ACS status, 19% of patients with a history of MI, and 2 doses of alirocumab in the ODYSSEY OUTCOMES trial), both trials confirmed that there is no LDL-C threshold for clinical benefit.[50,51]

The addition of PCSK-9 inhibitors to the lipid-lowering armamentarium provides an alternative, complementary, and aggressive mechanism of action for lipid lowering, which will modify the share of other LDL-C-lowering agents on the market. Following the publication of results from the ezetimibe and PCSK-9 inhibitor cardiovascular outcome trials, European and United States society task forces were convened to develop clinical guidance on when to use these nonstatin therapies: in which patients, in which situations, and in what order.[2,52] In patients with clinical ASCVD, the recommended first-line approach to the management of elevated LDL-C levels was to intensify statin therapy. Based on the benefits in ASCVD outcomes and demonstrated safety of ezetimibe in patients with ACS in the IMPROVE-IT trial, ezetimibe 10 mg was recommended as the first nonstatin agent to be added. However, it was found that while the addition of ezetimibe provides a further reduction in LDL-C levels, this may be insufficient to achieve a reduction in LDL-C levels greater than or equal to 50% required in ASCVD patients at very high risk in order to attain treatment goals. In that population, further lipid lowering with the addition of a PCSK-9 inhibitor may be needed.

These recommendations have subsequently been incorporated into the respective ESC / EAS and American College of Cardiology (ACC) guidelines on cholesterol lowering,[3,8] both of which stratify patients by the level of cardiovascular risk. First-line therapy comprises a high-potency statin at the highest recommended and tolerable dose to reach the LDL-C target level. If the goal is not achieved after 4 to 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 cardiovascular risk, the 2019 ESC / EAS guidelines recommend lowering LDL-C levels to less than 1.4 mmol/l (55 mg/dl) and advocate an LDL-C reduction greater than or equal to 50% from baseline.[3] Furthermore, 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 levels higher than 3.6 mmol/l (140 mg/dl). The United States ACC guidelines also recommend a reduction greater than or equal to 50% from baseline, but set an LDL-C threshold of 1.8 mmol/l (70 mg/dl) for the addition of a nonstatin medication, first ezetimibe and then PCSK-9 inhibitors, if LDL-C levels remain to be higher than or equal to 70 mg/dl.[8]

Prescription barriers and possible solutions

First approved for the management of cholesterol levels in patients with homozygous familial hypercholesterolemia, PCSK-9 inhibitor use was extended for secondary prevention in high-risk patients with ASCVD by the European Medicines Agency in 2018. The latter in combination with a statin at a maximum tolerated dose with or without other lipid-lowering agents, as monotherapy, or combined with other nonstatin therapies in patients intolerant of statins or in whom statins are contraindicated. However, the high cost of these medications means that they are not available for secondary prevention in all member states. Regulatory authorities in other countries have defined criteria for PCSK-9 use in clinical practice.

A prospective analysis of a Swiss cohort of 2023 patients hospitalized for ACS with available data for LDL-C and lipid-lowering therapy illustrated how various guideline criteria can 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 modeling the effect of ezetimibe in all patients not already receiving ezetimibe at 1 year, 13.4% would have been eligible for PCSK-9 inhibitor use according to the ACC guidelines, but only 2.7% of patients according to the ESC / EAS guidelines.[53]

Another analysis considered PCSK-9 eligibility according to the ESC / EAS and Agenzia Italiana del Farmaco (AIFA) regulatory agency criteria using data from 2 Italian, nationwide, prospective, real-world registries of patients with stable coronary artery disease.[54] Similar to the ACC, the AIFA criteria consider post-MI patients eligible for PCSK-9 inhibitor use if they show LDL-C levels higher than 100 mg/dl despite treatment with high-potency statins + ezetimibe, or ezetimibe alone in the presence of well-documented statin intolerance. Despite the ESC / EAS guideline recommendations to lower LDL-C levels in post-MI patients to a target level below 70 mg/dl using high-intensity statin therapy in combination with ezetimibe, if needed, the analysis revealed that numerous 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 + ezetimibe therapy was used in less than 18% of cases. In the 3074 post-MI patients with LDL-C data available, a target level below 70 mg/dl was achieved in only 1186 patients (38.6%), and around a quarter (24%) presented a LDL-C level higher than or equal to 100 mg/dl. Statins were prescribed to 97.1% of patients with LDL-C levels below 70 mg/dl, 96.2% of those with LDL-C ranging from 70 to 99 mg/dl, and 90.8% of those with LDL-C levels higher than or equal to 100 mg/dl. In the overall post-MI cohort treated with statins and / or ezetimibe (2977 patients), 293 (9.8%) and 450 (22.2%) would have been eligible for PCSK-9 inhibitor use according to the ESC / EAS and AIFA criteria, respectively.[54]

While the ESC / EAS recommendations are more conservative than those of the ACC or AIFA, there must be a balance between setting levels too high, which excludes a significant proportion of patients at very high-risk who would gain clinical benefit from PCSK-9 inhibitor use, and lower levels, which are not sustainable for healthcare systems. Standard practice in the management of ACS involves the initiation of a high-intensity statin during the acute phase, which is a particularly high-risk time for recurrent events. This strategy has a class IA recommendation in the guidelines based on published evidence and 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-C lowering.[3]

A small-scale trial has recently evaluated the benefit of PCSK-9 inhibitor use in this high-risk population. The EVOPACS (Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients with Acute Coronary Syndromes) trial randomized 308 patients with elevated LDL-C levels who were hospitalized for ACS to evolocumab 420 mg (n = 155) or placebo (n = 153) initiated in the hospital and then administered every 4 weeks.[55] All patients received atorvastatin 40 mg and most of them (78.2%) had not been on statin treatment previously. At 8 weeks, mean LDL-C levels 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. Levels of LDL-C below 1.8 mmol/l were achieved at week 8 in 96% of the patients in the atorvastatin / evolocumab group versus 38% of those on a high-intensity statin + placebo injection. Furthermore, 90% of the dual-therapy group achieved the new ESC / EAS guideline-recommended target of an LDL-C level below 55 mg/dl compared with 11% of patients randomized to high-intensity atorvastatin at a dose of 40 mg/d + placebo injections.[55]

The EVOPACS findings highlight the significance of starting early, aggressive lipid-lowering therapy for rapid reduction in LDL-C levels in patients at very high risk. 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 outcome trial. The results of such a trial may help to better 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 lowering plasma LDL-C levels remains to be a major focus of intervention, foremost with the use of high-intensity statins, aimed at reducing LDL-C levels by at least 50%. Current cholesterol guidelines have lowered LDL-C goals in patients at high risk for ASCVD, but recent real-world data have shown that only a minority of patients using lipid-lowering drugs reach desirable LDL-C levels (below 70 mg/dl).[21,56,57]

When treating patients with high cholesterol levels, the one-size-fits-all approach is not a solution. Based on the evaluation of patients in clinics, there are 2 main groups of secondary prevention patients in whom the addition of ezetimibe and subsequently a PCSK-9 inhibitor to a maximally tolerated statin may be appropriate. The first group comprises patients with ASCVD and LDL-C levels exceeding the target value despite treatment with a maximally tolerated statin, particularly if they experienced recurrences. The second group includes those who are statin-intolerant and in whom the addition of ezetimibe and / or a PCSK-9 inhibitor may allow for use of a lower statin dose. In both instances, the first nonstatin therapy to be added should be ezetimibe. This seems reasonable both from an economical perspective and because of the fact that PCSK-9 inhibitors have not been evaluated in any ongoing trial without patients being on maximally tolerated statins or a maximally tolerated statin + ezetimibe. Coadministration of ezetimibe with the starting dose (10 mg) of atorvastatin has been shown to provide a 50% reduction in LDL-C levels, similar to a 51% reduction obtained with high-dose (80 mg) atorvastatin.[58] In clinical practice, ezetimibe coadministered with a maximally tolerated statin may enable more patients to achieve recommended target LDL-C levels by offering a greater LDL-C lowering effect with fewer dose titrations as well as a well-tolerated alternative for those in whom maximum-dose statin monotherapy is inadequate.

Proprotein convertase subtilisin-like / kexin type 9 inhibitors lower LDL-C by 55% to 60% whether as monotherapy or when added to another lipid-lowering therapy. When used in combination, the LDL-C reductions are additive and, therefore, a much greater lipid-lowering effect is achieved. As the tolerability profile of ezetimibe and PCSK-9 inhibitors in combination with a statin is similar to that of 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 a maximally tolerated statin and followed by the addition of a PCSK-9 inhibitor. The eligibility for PCSK-9 inhibitor use strongly depends on pretreatment with ezetimibe in combination with a maximally tolerated statin. For maximum benefit, the addition of ezetimibe should be initiated early, particularly in patients at very high risk, in whom a statin / ezetimibe combination should ideally be prescribed during the index hospitalization to allow for rapid attainment of LDL-C target levels 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 to and comply with the prescribed treatment regimen. In this light, the real-life effectiveness of statin use is significantly compromised by poor adherence and compliance.[59] To improve patient adherence, a single-pill combination of ezetimibe and some statins is available. Ezetimibe has had an acceptable and well-established tolerability profile over many years of clinical use. In addition, its use in combination with a statin may allow for reduction of the statin dose.

The decision to add nonstatin lipid-lowering agents in the clinic strongly depends 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 gain the greatest benefit. As statins and ezetimibe are available as generic drugs, a regimen of intense statin therapy with ezetimibe in all patients with ASCVD should be implemented wherever possible. In some very high-risk patients, such as those included in the EVOPACS trial, this may still be insufficient and the addition of a PCSK-9 inhibitor may be required. Recent reductions in the prices of PCSK-9 inhibitors combined with targeting groups being at high risk would limit the number of patients eligible for therapy and improve the economic impact of adopting these new therapies.

ARTICLE INFORMATION

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