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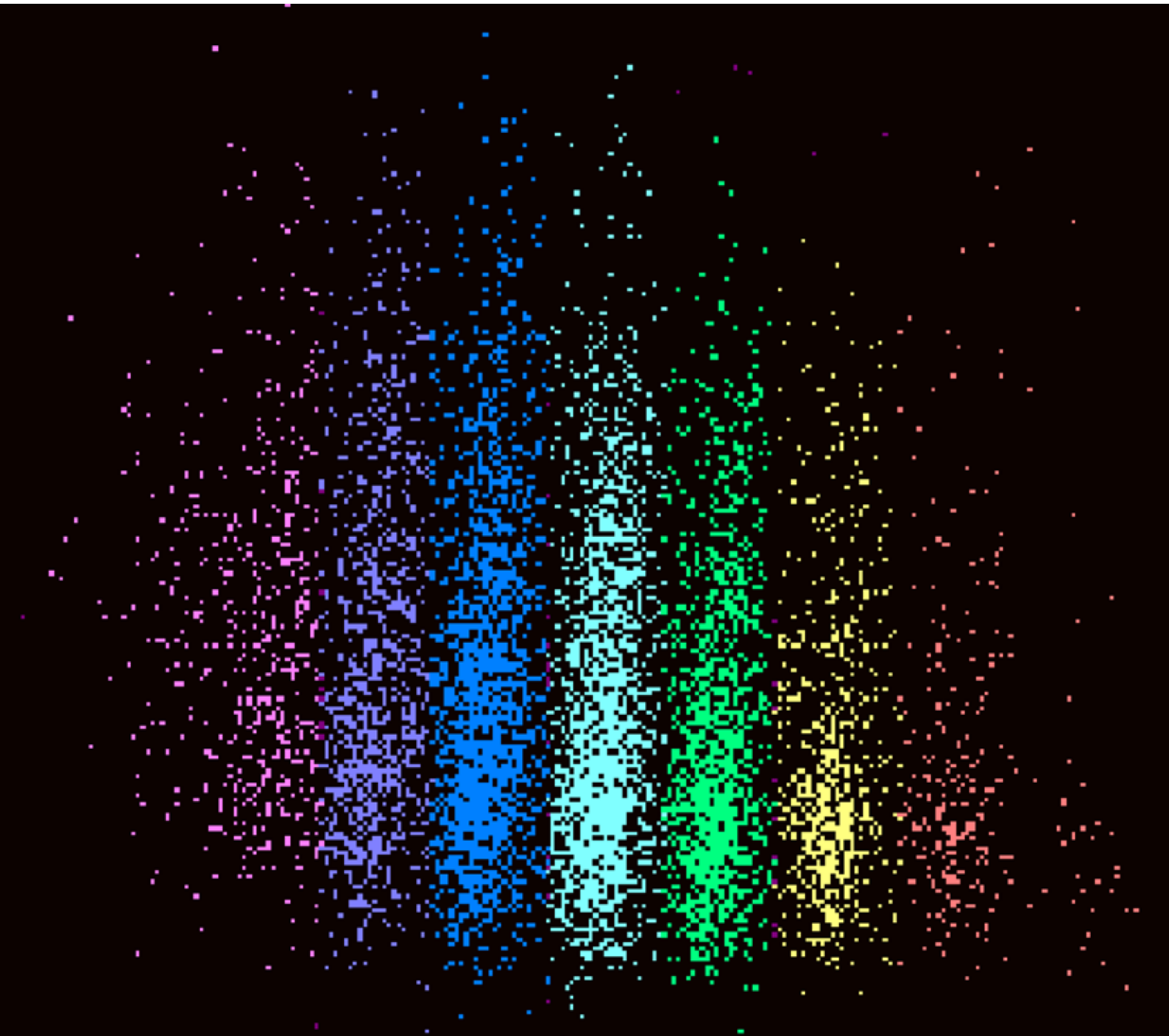

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Contents

European Atherosclerosis Journal is an international, peer-reviewed, fully open access, four-monthly journal covering all topics within atherosclerosis and cardiovascular disease areas. The European Atherosclerosis Journal is an official journal of SITeCS (Società Italiana di Terapia Clinica e Sperimentale - Italian Society for Experimental and Clinical Therapeutics).

European Atherosclerosis Journal

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Figure/Table number	6	5	3	2
References	100	60	30	15

Flexibility on word count may be offered after discussion with the Editor-in-Chief.

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General information. Prepare the manuscript text using a Word processing package and submit it in this format. Do not submit your manuscript as a PDF. Indicate on the title page the word count and the number of figures and/or tables included in the paper. Submitted manuscripts must not exceed 6000 words for Original paper, 5000 words for Reviews, 3000 words for Methodology papers, and 1500 for other article categories, excluding references, tables, and figures. Oxford English spelling should be used.

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Abstract. The abstract should not exceed 250 words (150 words for Methodology papers).

Keywords. A maximum of 6 keywords should be submitted.

Main text. The manuscript must contain the following sections: Introduction, Methods, Results, Discussion, Conflict of interest (mandatory), Funding (if applicable), Author contribution (mandatory), Acknowledgements (if applicable), References. Abbreviations must be defined when first used in the text.

Tables. Tables must be submitted as Word files, with titles and legends. Tables can be included in the same file as the main text or in a separate file. All tables must have a title and be numbered consecutively and in the order they appear in the text.

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All manuscripts submitted to European Atherosclerosis Journal will be evaluated by the Editorial Board. Manuscripts will be returned to authors if they do not meet submission requirements. Manuscripts that pass the first stage will undergo a regular peer review process.

After acceptance, the corresponding author will be contacted by the editorial office. Page proofs will be sent by e-mail to the corresponding author, who should check carefully for any changes or typographic errors. Corrected proofs must be returned to the editorial office within 3 working days.

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Welcome to *European Atherosclerosis Journal*, a new Open Access Journal

Alberto Corsini

Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milan, Italy

EDITORIAL

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As the Editor-in-Chief, I am pleased to introduce *European Atherosclerosis Journal*, a new open access journal, which is conceived to publish peer-reviewed articles covering all topics within atherosclerosis and cardiovascular disease area. Why a new journal in this area?

Atherosclerosis and related cardiovascular diseases represent a hot topic in the field of human health. Despite the development and approval of several new effective and safe drugs in the last years, cardiovascular disease still represents a major cause of mortality and morbidity all over the world, including low-income countries, in which the prevalence of cardiovascular risk factors has been increasing significantly in recent years. These observations further support the need to continue to deepen the knowledge of genetic and molecular mechanisms causing atherosclerosis, as well as the impact of lifestyle and behaviour of both single individuals and the population, and the role of pharmacological interventions in the control and prevention of this disease. Understanding the mechanisms underlying the onset and progression of atherosclerosis makes possible the conception of new drugs that specifically target causal genes or proteins.

The continuous progress of available methodologies allows an ever deeper understanding of the multiple, interconnected mechanisms that govern the complex process of atherosclerosis. This is crucial for the development of new pharmacological approaches, but also paves the way for a personalized medicine based on the specific characteristics of each single patient.

All aspects related to atherosclerotic-related cardiovascular diseases lie within the scope of *European Atherosclerosis Journal*. The journal is meant to encourage the submission of research papers that may shed further lights in this field, but also fosters thematic issues and featured articles dealing with specific hot topics.

European Atherosclerosis Journal publishes original research papers, reviews, methodology papers, editorials, letters to the Editor, viewpoints, congress/conference reports. Papers will be rapidly processed, with a rigorous revision process by expert reviewers, and published on line as soon as accepted. As an open access journal, papers will be immediately and freely available for all researchers and institutions interested in these topics.

European Atherosclerosis Journal is supported by a qualified international Editorial Board, which includes renowned scientists who embrace different aspects in the field of atherosclerosis and related cardiovascular diseases. Their expertise will ensure that all articles published in European Atherosclerosis Journal satisfy the highest scientific standard.

Conflicts of Interest

The author declares no conflict of interest.

Corresponding Author
Alberto Corsini: alberto.corsini@unimi.it

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The pharmacology of cholesterol-lowering drugs

Christie M. Ballantyne[1], Alberico L. Catapano[2]

[1]*Department of Medicine, Baylor College of Medicine, Houston, TX, USA*

[2]*Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, and Center for the Study of Dyslipidaemias IRCCS MultiMedica, Sesto S. Giovanni, Milan, Italy*

Keywords
Cholesterol-lowering drugs;
LDL cholesterol;
Statins;
Ezetimibe;
PCSK9 inhibitors

ABSTRACT

The causal role of low-density lipoprotein cholesterol LDL-C in atherosclerotic-related cardiovascular disease (ASCVD) has been undoubtedly established over the last decades, and lowering plasma LDL-C levels represents the main approach to reduce the risk of cardiovascular (CV) events. A large number of observations has definitely proven that the protective effect is independent of the drug used to lower LDL-C, with a continuous linear reduction of CV risk with further LDL-C reductions. Although high-intensity statin therapy may significantly reduce CV event incidence, frequently statins are insufficient to achieve the large reductions recommended by current guidelines for high and very high risk patients.

Several non-statin drugs, having mechanisms of action complementary to that of statins, are now available, and include ezetimibe, monoclonal antibodies targeting PCSK9, and, more recently, inclisiran, bempedoic acid, and evinacumab. Combining these drugs based on the recommendations by current and future guidelines should be considered for optimal risk reduction, although several gaps in clinical practice remain to be filled.

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Introduction

Since the discovery of statins, the landscape of cardiovascular disease (CVD) management has changed drastically, having shown unequivocally that reducing low-density lipoprotein cholesterol (LDL-C) levels results in a reduced incidence of CV events. The causality of LDL-C in the aetiology of atherosclerotic-related CVDs (ASCVDs) has been clearly established over the last decades (1, 2), with concordant observations from a variety of sources spanning from basic research, to genetic and clinical studies, further strengthening the evidence that the pharmacological control of plasma LDL-C levels is the major route to prevent CV outcomes, independently of the drug used to lower LDL-C (3, 4). Another major finding arising from clinical trials is that therapy intensification, either as statin dose/type or combination therapy, associates with significant reduction of CV event incidence in high and very high risk patients. Altogether these observations have led to intensify the research of new non-statin drugs having mechanisms of action that can "complement" the effect of statins; as a result, several alternative approaches for the treatment of hypercholesterolemia became available for therapy with unprecedented speed, thus enriching the tools for therapy to lower LDL-C.

In this context, statins still represent the cornerstone for the treatment of hypercholesterolemia, having shown approximately a 20% reduction in the risk of CV events per each mmol/L LDL-C reduction (5). Despite that, this approach might not be enough to reach the recommended goals in all individuals, especially when taking into consideration the lower LDL-C goals introduced by the most recent guidelines for the management of hypercholesterolemia (6). The need of additional approaches, together with the observation that, while there is no evidence of detrimental health effects associated with very low LDL-C-levels, there is a continuous linear reduction of CV risk (7), led to the development of other cholesterol-lowering drugs, including ezetimibe, monoclonal antibodies targeting PCSK9, and, more recently, inclisiran, bempedoic acid, and evinacumab.

The pharmacology of statins

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase(HMG-CoAR), the rate-limiting enzyme of cholesterol synthesis pathway. The inhibition of this enzyme results in the reduction of intracellular cholesterol synthesis, which, in turn, upregulates the hepatic surface expression of low-density lipopro-

Corresponding Authors
Christie M. Ballantyne: cmb@bcm.edu | Alberico L. Catapano: alberico.catapano@unimi.it

tein receptor (LDLR), increases the uptake of LDL particle and reduces plasma LDL-C levels. A large number of randomized clinical trials have shown that statin-induced LDL-C lowering translates into a clinical benefit, with reduction of cardiovascular morbidity and mortality, in primary as well as secondary prevention (5, 8-13). More specifically, statin therapy reduces the risk of major atherosclerotic vascular events by ~20% per mmol/l (~39 mg/dL) absolute reduction in LDL-C (5), with the absolute benefit being determined by the individual CV risk. Compared with less intensive regimens, more intensive statin regimens were associated with a further 15% reduction in major cardiovascular events (MACE), the first demonstration that greater reductions in LDL-C produce further reductions in the incidence of MACE (**Figure 1**) (8).

Statin therapy has been shown to be effective in a wide range of patient categories. First of all, the proportional effects of statins on MACE is comparable in women and men having equivalent baseline risk of cardiovascular disease, as shown by a meta-analysis of data from 174,000 participants in 27 RCTs (14). This represents a relevant finding, as previous clinical trials and meta-analyses generated uncertainty about the effects of statin therapy in women, largely due to the lower number of women among participants in clinical trials. Statin therapy is effective among patients with diabetes, a condition conferring an increased CV risk: statin-treated diabetic patients show a significant 21% proportional reduction in MACE per mmol/l reduction in LDL-C (comparable to that observed in non-diabetic individuals) (15), but, being the absolute risk of CV events and death much higher compared to nondiabetic subjects, the same absolute reduction in LDL-C will result in a greater absolute CV risk reduction. In addition, the benefit of statin therapy applies both to high CV risk and low CV risk patients: the analysis of participants in 22 RCT of statins versus control, divided into categories of baseline 5-year risk of MACE, showed that the proportional reductions in MACE per 1 mmol/L LDL-C reduction in the two lowest risk categories (<5% and ≥5% to <10%) was at least as large as for higher risk participants (16). Again, people at highest risk have the highest absolute risk reduction per mmol/l LDL-C reduction, resulting in 61 MACE avoided per 1000 compared with 6 MACE avoided per 1000 in the lowest CV risk category over 5 years (16). Special consideration must be given to patients with chronic kidney disease (CKD): although statin therapy is effective in preventing coronary heart disease (CHD) and stroke in patients with mild-to-moderate CKD, in those with more advanced CKD or even on dialysis the relative reductions in MACE achieved with statin therapy became smaller as eGFR declined, with little evidence of benefit in patients on dialysis (17).

From these studies, a linear relationship between proportional reduction in the incidence of major cardiovascular events and mean absolute LDL-C reduction has been derived, indicating that the lower the LDL-C levels achieved, the greater the clinical benefit. There are, however, some challenges remain in clinical practice regarding the potential unfavourable effects related to the long-term daily use of

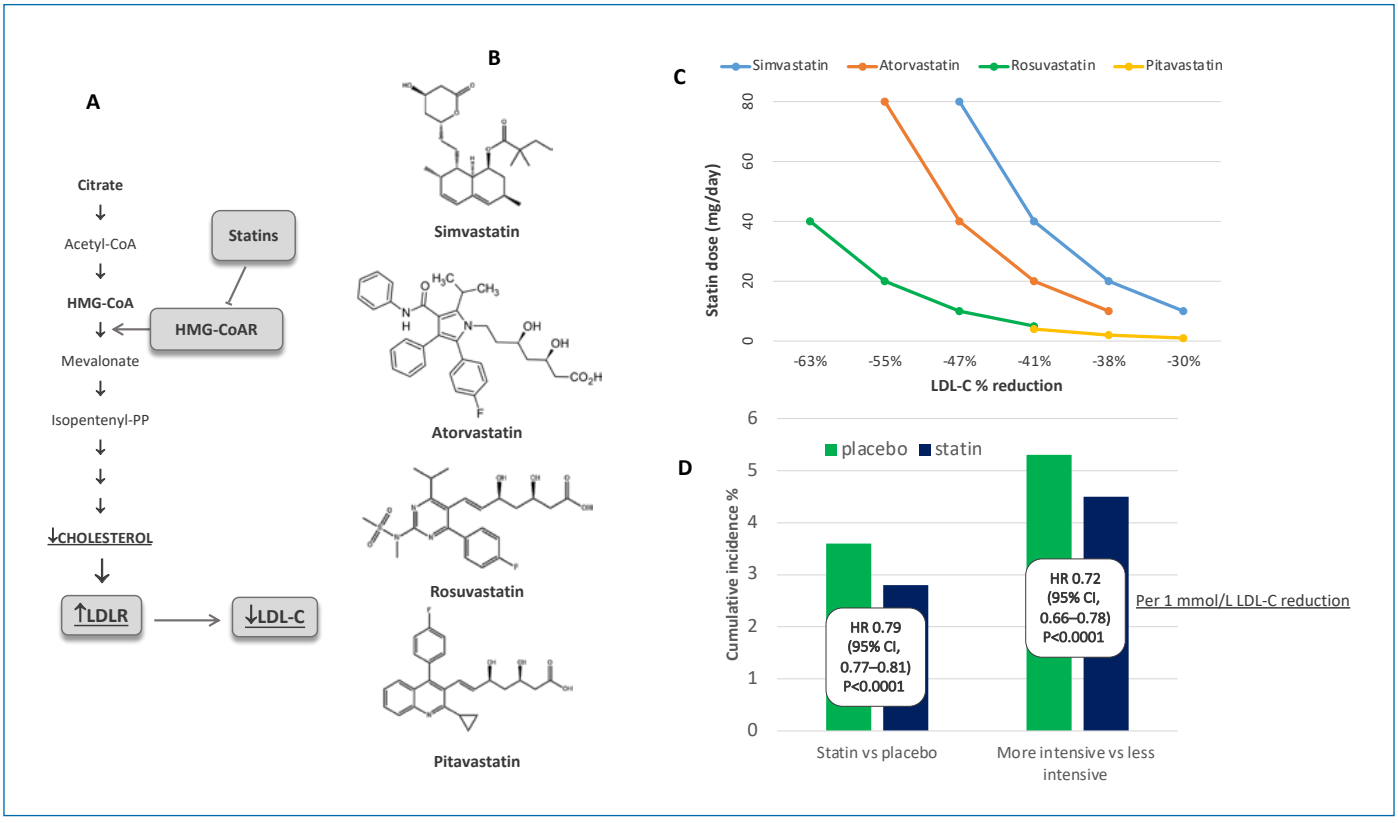

Figure 1 | Mechanism of action (A), structures (B), and LDL-C-lowering properties (C, D) of statins. (A) Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoAR), the rate-limiting enzyme of cholesterol synthesis pathway, thus reducing intracellular cholesterol synthesis and upregulating LDL-C levels. (B) Chemical structures of most commonly used statins. (C) LDL-C % reduction with different statins and doses. (D) Cardiovascular outcome incidence in patients treated with statins vs placebo or with more intensive vs less intensive statin regimens.
HMG-CoA, hydroxyl-methyl-glutaryl coenzyme A; HMG-CoAR, hydroxyl-methyl-glutaryl coenzyme A reductase; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

statins. Among these potentially negative effects, the most commonly studied is the occurrence of muscle-related adverse events and an increased incidence of new-onset diabetes. Statin-intolerance is referred as the inability to tolerate an effective dose of statin due to the occurrence of muscular symptoms while taking statin (18); such adverse events limit the effectiveness of statin therapy, and commonly lower the adherence to therapy or drug discontinuation, an effect that is more frequently observed in the everyday clinical practice rather than in clinical trials. Although a true statin intolerance condition is much rarer than reported, due to a "nocebo effect" (19), it represents a relevant issue as it places patients at high risk for CV events (20). Furthermore, a link between statin therapy (and in particular high intensity statin dose) and an increased risk in new-onset diabetes has been reported in several clinical trials and meta-analyses (21-25); such an increased risk, however, is modest and emerges mostly in patients with insulin resistance or prediabetes (26), and the clinical benefit in terms of CV event risk reduction largely exceeds this risk. This observation is supported by the results of a mendelian randomization analysis showing that variants in *HMGCR* (the gene encoding HMG-CoAR) associated with low LDL-C levels and a reduced risk of CV events also associate with an increased risk of diabetes (13% for each 10 mg/dL decrease in LDL-C) in patients with impaired fasting glucose (≥100 mg/dL), but not in those with normal fasting glucose (27).

The pharmacology of ezetimibe

Niemann-Pick C1L1 (NPC1L1) protein is a sterol transporter highly expressed in intestinal epithelial cells and involved in the intestinal absorption of cholesterol (**Figure 2A**), thus contributing to the regulation of cholesterol plasma levels.(28, 29) Subjects carrying inactivating mutations in *NPC1L1* have lower LDL-C levels compared with noncarriers, and a 53% reduction in the risk of CHD, suggesting this protein as a pharmacological target (30).

Ezetimibe, by interfering with the activity of NPC1L1, inhibits the absorption of biliary and dietary cholesterol. This drug exhibit a complementary mechanism of action as compared to statins, and their combination results in an LDL-C reduction greater than those observed using these two drugs in monotherapy, due to their mechanisms of action. In fact, statins, by inhibiting cholesterol synthesis pathway, produce the upregulation of hepatic LDLR and increase the uptake of LDL from the circulation. In turn, this causes a feedback mechanism resulting in an increased intestinal cholesterol absorption and a partially reduced efficacy of statin therapy. On the other hand, ezetimibe, by inhibiting intestinal cholesterol absorption, induces a compensatory mechanism increasing cholesterol synthesis in the intestine and the liver (31). When statins are combined with ezetimibe, both cholesterol synthesis and absorption are reduced, resulting in a further 15–20% LDL-C level decrease,(32-34) and adding ezetimibe to a statin is much more effective than doubling the dose of the statin, which only provides an additional 5-6% reduction in LDL-C (35, 36). The efficacy of this combination has been proved also in diabetic patients, who achieved greater LDL-C reductions compared with those observed in patients doubling the statin dose (37, 38), and in patients with familial hypercholesterolemia (FH) showing a residual LDLR activity (39-41).

The first demonstration that this combination has also a clinical benefit derived from the IMPROVE-IT trial, that compared the effect of a 6-year administration of ezetimibe+simvastatin or simvastatin alone in patients with a recent acute coronary syndrome (42). LDL-C level was further reduced by 24% with the combination therapy compared with simvastatin alone, translating into a significant 6.4% reduced risk of the primary composite endpoint (**Figure 2B, 2C**) (42). A secondary analysis of this trial showed an even higher benefit in specific subgroups of patients, such as women, aged people, and diabetic patients (43-45).

At present, the combination statin+ezetimibe represents a main approach for the treatment of hypercholesterolemia, and guidelines indicate that the combination will be used as a second step when patients cannot reach the recommended goals (or cannot tolerate an effective dose of statin). For a more detailed description of findings from clinical trials using ezetimibe, please see the paper by H. Bays in this issue.

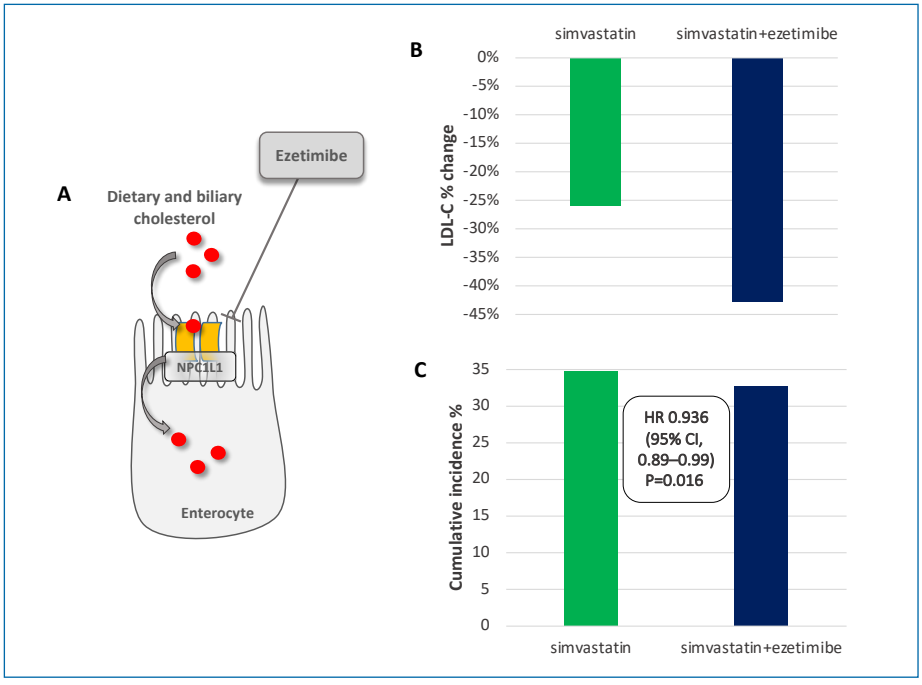

Figure 2 | Mechanism of action of ezetimibe (A) and results from the IMPROVE-IT (B, C). (A) NPC1L1 is localized on the brush border of the enterocytes and mediates the uptake of dietary and biliary cholesterol. Ezetimibe inhibits the activity of NPC1L1. (B) LDL-C percent change and incidence of cardiovascular events in patients receiving simvastatin monotherapy or the combination ezetimibe+simvastatin (IMPROVE-IT trial). NPC1L1, Niemann-Pick C1-Like 1; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

The pharmacology of PCSK9 inhibitors

Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease highly expressed in the liver, intestine, kidney, and brain (46); it plays a crucial role in regulating the expression of hepatic LDLR by targeting it to degradation and, as a consequence, modulates plasma LDL-C levels (**Figure 3A**) (47-49). Individuals carrying loss-of-function mutations in *PCSK9* associated with lower levels of LDL-C also have a significantly reduced CV risk (50-54), whereas genetic gain of function variants associated with higher levels of LDL-C confer an increased risk of premature cardiovascular disease and are a cause of FH (55-57). These observations have suggested PCSK9 as a pharmacological target for the control of dyslipidaemia, and great research efforts have generated two monoclonal antibodies targeting circulating PCSK9 and, more recently, a gene silencing approach able to control more efficiently the production of PCSK9 only in the liver. In fact, despite PCSK9 is produced mainly by the liver, which contributes for circulating PCSK9 levels, other tissues express this protein, raising uncertainties on the potentially harmful effects of the pharmacological inhibition of PCSK9 in extrahepatic tissues.

Two monoclonal antibodies (evolocumab and alirocumab) have been developed and approved for the treatment of hypercholesterolemia, and are recommended by guidelines as an add-on to current lipid-lowering therapy when patients with high or very high CV risk cannot achieve the recommended goals with maximally tolerated dose of statin with or without ezetimibe; this recommendation stems on the results of randomized clinical trials having shown a substantial cholesterol-lowering efficacy (50%-60%) and a consequent clinical benefit. The development of an additional antibody (bococizumab) was halted due to the production of anti-drug antibodies that reduced the efficacy of the treatment.

Evolocumab. Evolocumab was evaluated in several phase 2 clinical trials, showing a cholesterol-lowering efficacy either as monotherapy or as add-on to ongoing lipid-lowering therapy (LLT) in different groups of patients (58-60). The evolocumab clinical trial program **PROFICIO** included phase 3 clinical trials that assessed the effectiveness of evolocumab in comparison with placebo or ezetimibe across a wide range of patient categories. Evolocumab alone was more effective than placebo or ezetimibe in reducing LDL-C levels (61), and adding evolocumab to the ongoing LLT resulted in a greater reduction in LDL-C (60%-65%) than adding ezetimibe (15%-20%) or placebo (62). Evolocumab was shown to be effective in statin-intolerant patients (63, 64), and in patients with heterozygous FH (65), whereas in HoFH patients the reduction was smaller (20-30%) and strictly related to the presence of a residual LDLR activity (as for all drugs acting by increasing LDLR expression) (60, 66, 67). The evaluation of the long-term effects of evolocumab showed a persistent hypocholesterolemic effect up to 5 years, and an overall safe profile, with no neutralizing antibodies detected (68).

The clinical benefit of PCSK9 inhibition has been addressed in the FOURIER trial, that evaluated the effect of evolocumab or placebo added to a background of statin therapy in patients with ASCVD and LDL-C ≥70 mg/dL (69). At week 48, LDL-C levels were reduced by 59% which translated into a 15% lower risk of the primary endpoint (a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) (**Figure 3B, 3C**) and by 20% the secondary endpoint (a composite of cardiovascular death, myocardial infarction, or stroke) after

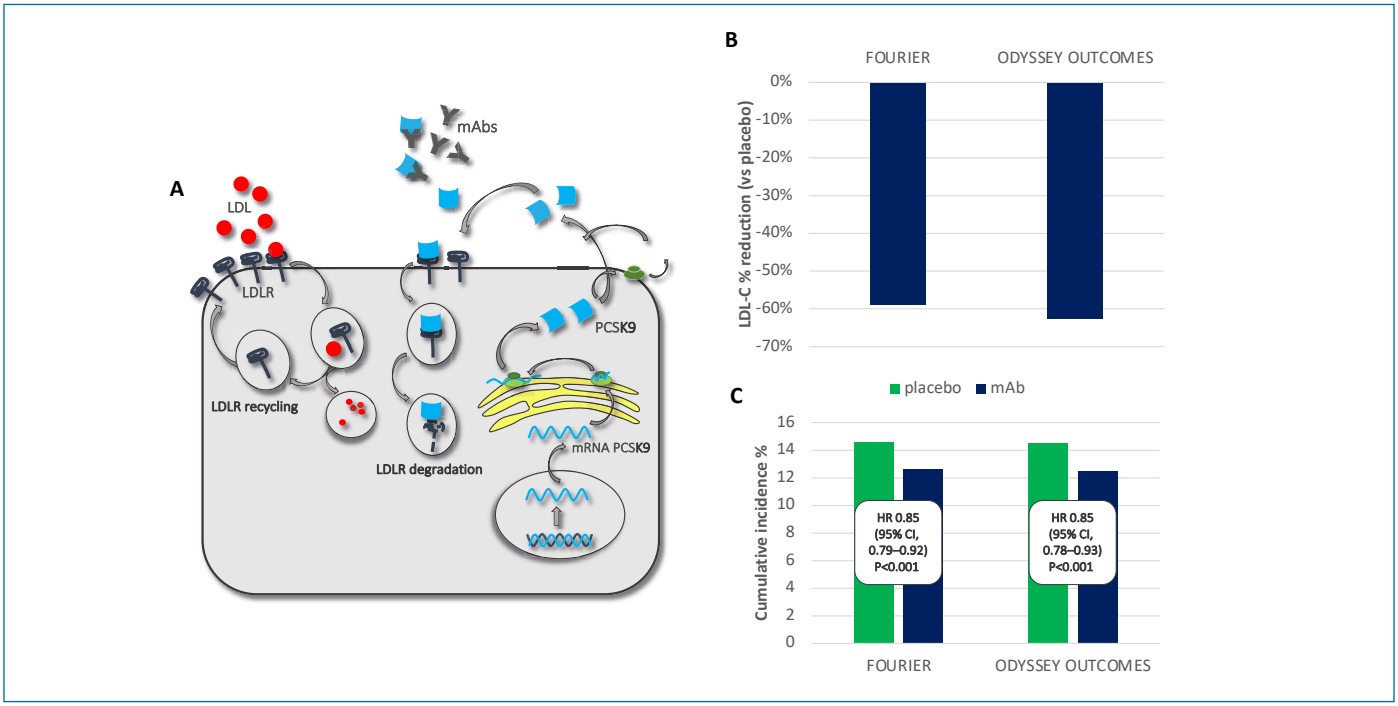

Figure 3 | Mechanism of action of mAbs to PCSK9 (A) and results from FOURIER and ODYSSEY OUTCOMES trials (B, C). (A) monoclonal antibodies to PCSK9 bind extracellular (secreted) PCSK9, thus preventing its binding to LDLR and the subsequent degradation of LDLR. LDL-C percent change (B) and incidence of cardiovascular events (C) with evolocumab (FOURIER) and alirocumab (ODYSSEY OUTCOMES).
LDL, low density lipoprotein; LDLR, low-density lipoprotein receptor; mAbs, monoclonal antibodies; PCSK9, proprotein convertase subtilisin kexin 9; HR, hazard ratio.

a median follow-up of 2.2 years (69). Relative risk reductions were comparable across patient categories, but larger absolute risk reductions were observed among patients at higher baseline risk, such as patients with diabetes (70), peripheral artery disease (71), advanced chronic kidney disease (72), recent MI (<2y), multiple prior MIs, or residual multivessel coronary artery disease (73), or elevated polygenic risk score (74). The use of monoclonal antibodies targeting PCSK9, for the first time, allowed patients to achieve very low LDL-C levels (<0.5 mmol/L (<~20 mg/dL), without specific safety concerns related to the low levels of LDL cholesterol achieved (75), and further supported the hypothesis of a linear relationship between LDL-C levels and CV outcomes even for very low LDL-C levels (1). Of note, no adverse cognitive effects were reported among patients treated with evolocumab over a median of 19 months (76), neither in those who achieved very low LDL-C levels (75).

Alirocumab. Based on the results obtained in phase 2 trials, suggesting substantial reductions in LDL-C levels in alirocumab-treated patients, ranging from 40% to 73% (77-80), the **ODYSSEY** program was started to assess the efficacy and safety of alirocumab alone or in combination with other LLT across different subgroups of hypercholesterolemic patients. The administration of alirocumab 75 mg Q2W or ezetimibe 10 mg/day showed that LDL-C levels were reduced in both groups compared with placebo, but the reduction observed among alirocumab-treated patients was higher than that observed among ezetimibe-treated patients (47.2% vs 15.6%) (81). The higher LDL-C-lowering efficacy of alirocumab has been shown also when given in combination with the ongoing therapy (maximum tolerated statin±other LLT) in high CV risk populations, when compared with either placebo (82, 83) or ezetimibe (84). Furthermore, adding alirocumab to atorvastatin or rosuvastatin was more effective than adding ezetimibe, or doubling the statin dose (85, 86). Finally, alirocumab can represent a valuable approach to reduce significantly hypercholesterolemia in specific groups of patients, such as statin-intolerant patients, in whom alirocumab reduced LDL-C levels substantially more than ezetimibe (45% and 14.6% at week 24, respectively) (87), and in FH (83, 88, 89).

The clinical benefit of alirocumab-based therapy was tested in an outcome trial (ODYSSEY OUTCOMES) that recruited patients with a recent acute coronary syndrome and LDL-C levels not at target despite high-intensity statin therapy (90). Alirocumab reduced LDL-C levels by 62.7% at 4 months and 54.7% at 48 months (90). After a median follow-up of 2.8 years, the risk of the primary endpoint (a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was significantly reduced by 15% in alirocumab treated patients (**Figure 3B, 3C**); individuals with the highest baseline LDL-C levels (≥100 mg/dL) achieved the highest absolute risk reduction (90). Among participants in this study, those who did not receive background statin therapy had higher baseline LDL-C levels and were at higher risk of recurrent events, but also experienced a greater absolute LDL-C reduction and absolute MACE risk reduction (91). The beneficial effect of alirocumab was independent of patient age, but, because the higher absolute risk in older individuals, the absolute benefit deriving from alirocumab treatment increased with advancing age (92). An analysis of the ODYSSEY OUTCOMES trial using a polygenic risk score (PRS) for CAD showed that patients having a high PRS have a higher incidence of MACE than those with lower PRS, but also derive a larger absolute and relative risk reduction when treated with alirocumab (93), suggesting the potential of using PRS to stratify patients and identify those who may benefit more from a more intensive cholesterol-lowering approach.

Altogether, the results obtained in RCTs have substantiated PCSK9 inhibitors as an effective and safe approach to further reduce the CV risk in several groups of patients, thanks to a remarkable and sustained reduction of LDL-C levels beyond that obtained with statins±other LLT, with patients at increased CV risk having the greatest absolute benefit. As per the safety a major concern in statin therapy is the increased risk of new-onset diabetes. Although the mechanism by which anti-PCSK9 mAbs increase LDLR differs from that of statins, it is well established that LDLR plays a role in cholesterol metabolism in pancreatic beta cells (94) and indeed PCSK9 deficiency has been associated with an increased risk of new onset diabetes both in animal models and humans (27, 95). To date, results from an experimental model suggest that locally produced rather than circulating PCSK9 plays a role in the homeostasis of cholesterol in beta cells, and thus the inhibition of PCSK9 by mAbs should not affect this pathway; accordingly, evolocumab and alirocumab treatments do not appear to increase the risk of new-onset diabetes and do not worsen glycaemia (70, 96-100).

New cholesterol-lowering drugs

Inclisiran. Over the last few years, gene-based approaches targeting key players in the metabolism of lipids, and in particular LDL, led to the development and approval of inclisiran (101). Inclisiran is a small interfering RNA (siRNA) targeting PCSK9 mRNA thus inhibiting the intracellular production of PCSK9 (**Figure 4A**), in contrast with monoclonal antibodies against PCSK9 which bind and inhibit extracellular, circulating PCSK9.

Different experimental models have shown a rapid, durable, and reversible reduction in circulating PCSK9 and LDL-C levels with a single dose of a siRNA targeting PCSK9 (a precursor of inclisiran) (102); next, healthy volunteers who received a single intravenous dose of this siRNA showed a mean 70% reduction in circulating PCSK9 plasma levels and a 40% reduction in LDL-C levels (103). The N-acetylgalactosamine (GalNAc) modification of the double-stranded molecule, leveraging on the asialoglycoprotein receptor for its uptake, ensures a prompt and specific uptake by the liver, where this receptor is abundantly expressed (while only minimally expressed in extrahepatic tissues). The introduction of modifications that have led to the development of the GalNAc-siRNA conjugate (inclisiran) has largely improved the administration, increased the potency of the drug (allowing the use of lower doses), and reduced the potential for side effects. Following the demonstration of a dose-dependent reduction of plasma PCSK9 levels (up to 83.8%) and LDL-C levels (up to 59.7%) in healthy volunteers, inclisiran has been evaluated in the ORION clinical program that includes phase 2 and 3 clinical trials, some of which are still ongoing (**Figure 4A**). The phase 2 trial ORION-1 showed for the first time that inclisiran given as a single dose or two doses (at days 1 and 90) was effective in reducing LDL-C levels in hypercholesterolemic patients at high CV risk (104). Reduced levels of PCSK9 and LDL-C were maintained up to day 240 in inclisiran-treated patients (104), and one year after administration of either a single dose or two doses of inclisiran LDL-C were persistently low, with a 50% LDL-C reduction being maintained for at least 6 months after 2 doses of 300mg inclisiran (105). The rate of adverse events was similar in inclisiran and placebo groups, and injection-site reactions were rare and similar to those reported with monoclonal antibodies (104, 106). The ongoing open-label extension study of ORION-1 (ORION-3) is comparing the long-term effect inclisiran 300 mg administered on day 1 and every 180 day thereafter or evolocumab 140 mg every 2 weeks for up to 4 years (NCT03060577); the trial is expected to be completed in 2022. An interim analysis at ~22 months reported a 51% reduction

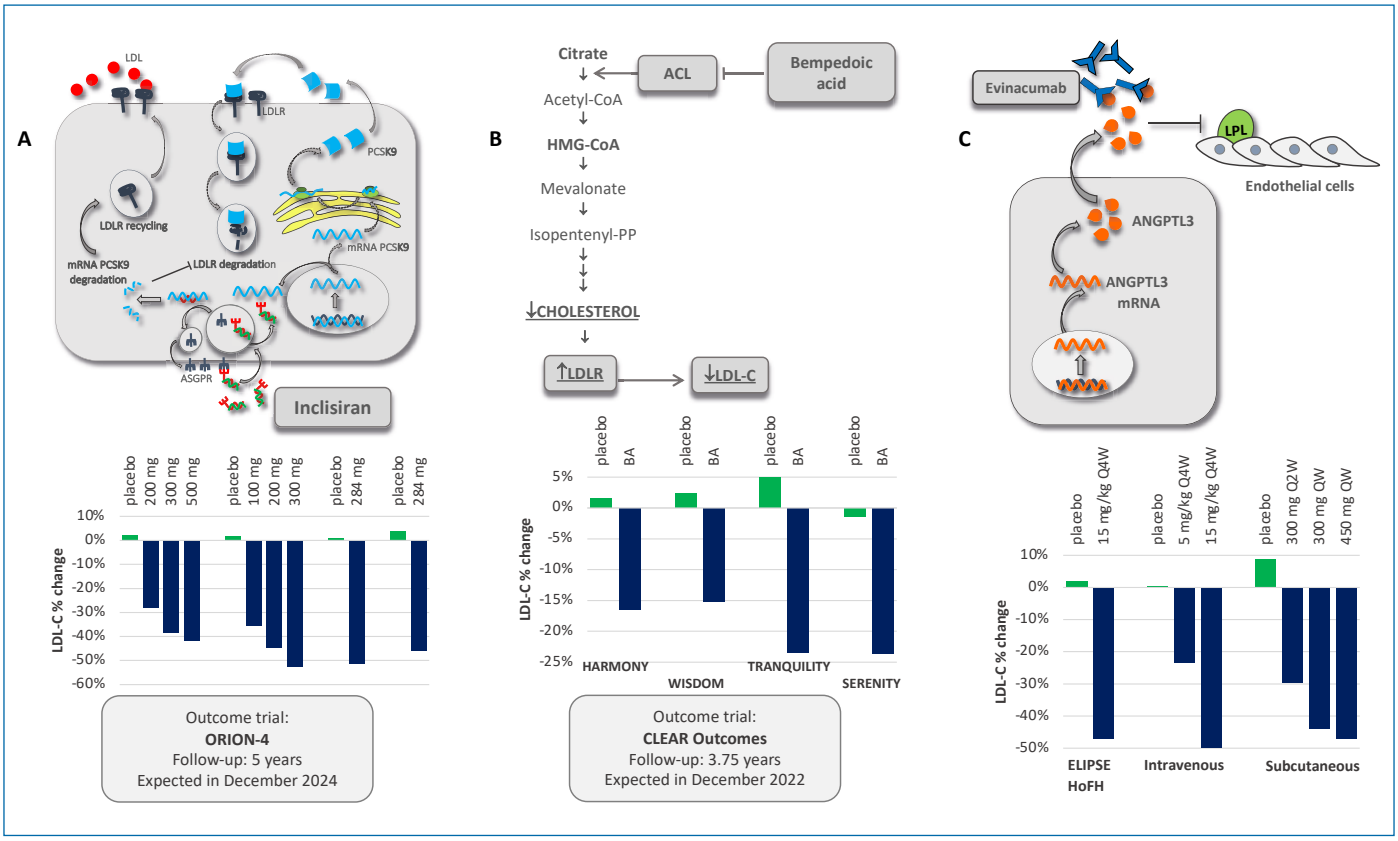

Figure 4 | New LDL-C-lowering drugs. Mechanism of action and LDL-C-lowering properties of inclisiran (A), bempedoic acid (B), evinacumab (C). LDL-C, low density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin kexin 9; ACL, adenosine triphosphate-citrate lyase; BA, bempedoic acid; ANGPTL3, angiopoietin-like 3; LPL, lipoprotein lipase; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

in LDL-C levels in all patients, with a time-averaged lowering of ~60 mg/dL, and a good safety profile (107).

Three phase 3 trials have reported a significant efficacy of inclisiran in patients with HeFH (108), ASCVD, or an ASCVD risk equivalent taking a stable LLT (109). HeFH patients showed a ~40% reduction in LDL-C levels with inclisiran 300 mg injected on days 1, 90, 270, and 450 (compared with a 8.2% increase with placebo, with a between-group difference of -47.9%) (108). Similar reductions were achieved in the ORION-10 and -11 trials (52.3% and 53.8% between-group differences, respectively), independently of the gender, age, intensity of statin treatment, and underlying co-morbidities (109). Based on the observation that inclisiran significantly reduces PCSK9 levels also in 4 patients with HoFH in the ORION-2 pilot study, but lowers LDL-C levels at an extent related to the type of causative mutation (110), the ORION-5 trial (NCT03851705) has evaluated the effect of the administration of inclisiran or placebo in 45 HoFH patients in a 6-month double blind period, after which all patients have received inclisiran for an 18-month open-label follow-up period; the results of this study are now expected. The ongoing ORION-4 trial will establish whether inclisiran 300 mg may safely reduce the risk of major atherosclerotic cardiovascular events in ≥15,000 patients with pre-existing ASCVD during a median treatment duration of 5 years (NCT03705234). Estimated primary completion date is December 2024.

Bempedoic acid. Bempedoic acid is a recently developed lipid-lowering drug that inhibits adenosine triphosphate-citrate lyase (ACL), an enzyme involved in cholesterol biosynthesis (**Figure 4B**). The activity of this drug produces an upregulation of hepatic LDLR expression, leading to a reduction of circulating LDL-C levels (111). The potential clinical benefit of bempedoic acid therapy is suggested by the observation that genetic variants in *ACLY* (the gene encoding ACL) associated with lower LDL-C levels predict a reduced risk of cardiovascular disease (112). Being a pro-drug, bempedoic acid needs to be converted into the active form by very-long chain acyl-CoA synthetase (ACSVL1), an enzyme highly expressed in hepatocytes but not detectable in skeletal muscles. This represents an advantageous characteristic of bempedoic acid, as it should avoid any muscle-related adverse effects, which are instead frequently reported with statin therapy, conferring to this drug a potential role for use in patients who cannot tolerate an effective dose of statin.

Phase 2 clinical trials have shown that bempedoic acid significantly reduces LDL-C levels either in monotherapy or in combination with a statin or ezetimibe. When given alone, bempedoic acid dose-dependently reduced LDL-C levels (form 17.9% up to 26.6%) and improved lipid profile (113). Maximum LDL-C lowering was achieved after 2 weeks and was maintained for the course of the trial. CRP was significantly reduced among patients treated with bempedoic acid (~20% at all doses), but the reduction was more marked in individuals with higher CRP at baseline (≥2 mg/l), who reported reductions from 43% to 63.5% (compared to 7.0% reduction with placebo) (113). In patients with hypercholesterolemia and diabetes mellitus bempedoic acid determined an even greater reduction

in LDL-C levels (43% vs 4% reduction with placebo); CRP was reduced by 41% and no worsening of glycaemic control was observed (114). The addition of bempedoic acid to a background statin therapy resulted in greater LDL-C reductions compared with placebo (115, 116). The triple combination of bempedoic acid, ezetimibe, and atorvastatin has been evaluated in patients with hypercholesterolemia, showing a 63.6% reduction in LDL-C levels compared with a 3.1% reduction with placebo at week 6; 95% of patients had their LDL-C levels halved following the triple therapy, and 90% achieved levels <70 mg/dL (117). Also CRP was significantly lowered by 47.7% (vs 2.7% reduction with placebo) (117). Bempedoic acid was effective in reducing LDL-C also in patients with a history of statin intolerance (118, 119). In all these studies, a good safety profile of bempedoic acid was observed, without specific concerns. A modest, fully reversible increase in uric acid levels has been reported among patients treated with bempedoic acid, likely related to the drug-mediated inhibition of a specific transporter (organic anion transporter 2) (120).

The CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen) program of bempedoic acid includes 5 phase 3 studies, 4 of which have been completed (**Figure 4B**). Two of these studies have evaluated the effect of bempedoic acid or placebo in patients with ASCVD, HeFH, or both and with persistent hypercholesterolemia despite maximally tolerated LLT: LDL-C were reduced similarly in both studies (placebo corrected differences: -18.1% and -17.4%), with an overall improvement of lipid profile and significant reductions in CRP levels (placebo-corrected differences: -21.5% and -8.7%) (121, 122). The other two studies were performed in statin intolerant patients, in which bempedoic acid therapy was even more effective in reducing both LDL-C (placebo-corrected differences: -28.5% and -21.4%) and CRP (-32.5% and -24.3%) (123, 124). The ongoing CLEAR Outcomes study will evaluate the effect of bempedoic acid or placebo on cardiovascular outcomes in statin intolerant patients with, or at high risk for, cardiovascular disease.

Evinacumab. Angiopoietin-like 3 (ANGPTL3) is a physiological inhibitor of two enzymes crucially involved in lipoprotein metabolism, namely lipoprotein lipase (LPL) and endothelial lipase (EL) (125). Complete ANGPTL3 deficiency is associated with very low plasma lipid levels and no evidence of coronary atherosclerosis (126); heterozygous carriers of *ANGPTL3* LOF mutations had approximately 50% lower ANGPTL3 levels than noncarriers, lower levels of TG (-17%, -27%) and LDL-C (-12%, -9%), associated with a substantially reduced risk of CAD (-34%, -39%) (126, 127). Despite the reasons for the reduction in LDL-C are still not completely elucidated, these observations suggested ANGPTL3 as a potential target for the pharmacological control of hypercholesterolemia, and the evidence of LDLR-independent mechanism(s) advocated a potential suitability for patients with HoFH, particularly those carrying null *LDLR* mutations (128). A fully human monoclonal antibody targeting ANGPTL3, evinacumab (**Figure 4C**), was shown to reduce dose-dependently LDL-C (up to 23%) and TG (up to 76%) levels in healthy volunteers (127). When tested in an a single-group, open-label study involving nine HoFH patients, evinacumab added to their background lipid-lowering therapy (which included statins, ezetimibe, lomitapide, PCSK9 mAbs, or a portacaval shunt) reduced LDL-C level by a mean of 49%, but with a wide range of variability among patients; three patients with null/null mutations (2 homozygotes and 1 compound heterozygote) had significant, although different, responses to evinacumab (26%, 42%, and 44%, respectively) (129). A subsequent phase 3 trial in 65 HoFH patients (ELIPSE HoFH) reported similar results, with patients treated with evinacumab achieving a 47.1% reduction in LDL-C from baseline (compared with a 1.9% increase reported in the placebo group) (**Figure 4C**) (130). Evinacumab was effective both in patients with non-null mutations (having a residual LDLR activity) and patients with null/null variants (130), and recently it was shown to induce a profound plaque regression in two severely affected young FH patients (131). This represents a worthwhile observation, as HoFH patients with null/null variants have the highest CV risk and the lowest response to pharmacological approaches with either conventional or new cholesterol-lowering drugs acting through LDLR upregulation in the liver. It appears that inactivation of ANGPTL3 decreases the production rate of VLDL-apoB (132), suggesting the possibility that the reduction in LDL-C levels observed in HoFH patients treated with evinacumab could be the consequence of a reduced production of lipoproteins. A recent small study in 4 HoFH patients examined apoB (apolipoprotein B) containing lipoprotein kinetic parameters before and after treatment with evinacumab and observed that ANGPTL3 inhibition was associated with an increase in the fractional catabolic rate of IDL-apoB and LDL-apoB (133), suggesting that evinacumab lowers LDL-cholesterol predominantly by increasing apoB-containing lipoprotein clearance from the circulation.

Current gaps in therapy and evolving approaches to address gaps, improve adherence – real world data on current practice

Randomized clinical trials have unequivocally established the cholesterol-lowering effectiveness of newly developed drugs, although for some of them, including inclisiran, bempedoic acid, and evinacumab the clinical efficacy is currently under evaluation. Despite this, both inclisiran and bempedoic acid have been approved based on their LDL-C-lowering effect, that is expected to translate into a clinical benefit.

Nevertheless, the everyday clinical practice shows unmet needs and gaps that hinder the achievement of lipid goals related to the prevention of CV outcomes. Two major issues deserving a more in-depth discussion relate to 1) the relationship between the cost and efficacy of cholesterol-lowering drugs and 2) the adherence to cholesterol-lowering therapies.

Cost-effectiveness considerations. As already discussed above, current guidelines have introduced more and more stringent LDL-C goals for all risk categories; this calls for the use of more effective pharmacological approaches able to reduce LDL-C levels to <55 mg/dl in very high risk patients. Most of these patients cannot reach the recommended goal with statin monotherapy and in some instances also after ezetimibe; they would thus be eligible for the use of a PCSK9 inhibitor, as specified in the treatment algorithm, allowing a substantial percentage of patients to reach their LDL-C goals, but raising a question about the costs for the healthcare system. In fact, on one hand, PCSK9 inhibitors (but this applies also to inclisiran and other biologics) have a higher cost compared with conventional oral cholesterol-lowering agents; on the other hand, they have definitely a higher cholesterol-lowering efficacy. Starting from these considerations, which can be the role for the new oral bempedoic acid in this context? Patients can be not too far from their goal, but having LDL-C above the recommended level, they are virtually eligible for PCSK9 therapy; in these patients, the addition of bempedoic acid to the ongoing LLT might favour a further (although modest if compared with PCSK9 mAbs) LDL-C reduction, allowing to reach the goal without a PCSK9 mAb. Furthermore, statin-intolerant patients, who commonly show a poor adherence and, instead, a high discontinuation rate of statin therapy, might benefit from the use of bempedoic acid. A recent simulation study performed in a cohort

of patients with coronary heart disease showed that the introducing bempedoic acid in the algorithm will reduce substantially the percentage of patients requiring a PCSK9 inhibitor to reach their goal, thus lowering medical expenditure (134). It appears that patients with fully statin intolerance might have the greatest benefit in relation to cost (134).

Improving adherence to therapy. In spite of the clearly established clinical benefit of cholesterol-lowering therapies, the everyday clinical practice shows inadequacy in the pharmacological approach among patients with established ASCVD, with a poor attainment of LDL-C target in patients at high CV risk (135, 136). Furthermore, there is a low awareness of the danger of CV risk factors, and the occurrence of adverse events that are ascribed to the therapy easily translates into a time-decreasing adherence to therapy. This is even more evident among patients experiencing muscle-related adverse events (no matter if they are really imputable to therapy or not), or having mild-to-moderate response to the therapy (which is inevitably related to the individual response, but more likely to an inadequate approach), with an increasing percentage of patients discontinuing medications. Thus, improving adherence is crucial and every step must be taken to fill this gap. It is evident that the use of fixed-dose combination therapies, by combining in one pill two or more drugs, may make the patient more willing to take medications, with more chances to attain substantial reductions in LDL-C levels, which in turn may favour the adherence to an "effective" (from the patient point of view) treatment. It is also evident that biological cholesterol-lowering drugs (mAbs, siRNA), having administration regimens different from the oral agents that must be taken daily, together with a higher efficacy, may provide significant reductions in LDL-C with infrequent dosing (although at substantially higher costs).

Conclusions

In the last three decades since the approval of statin therapy, an extraordinary accumulation of evidence which has shown that reduction of LDL-C levels results in reduced incidence of CV events and that achieving lower levels of LDL-C leads to greater event reduction, which led to new guidelines for the treatment of high-risk and very-high-risk patients. With rapid progress in identification of treatment targets through genetic epidemiology and advances in both pharmacology and biotechnology, several options are now available in addition to statins that are highly effective in lowering LDL-C levels. However, there is currently a major gap between the evidence-based goals of treatment in the guidelines and clinical practice. Changes in approach, with earlier use of combination therapy including two agents in a single pill (137), as routinely used to treat hypertension successfully, and increased use of infrequently used therapies may provide great opportunities to improve guideline implementation in clinical practice.

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Cholesterol-lowering drugs: Focus on ezetimibe

Harold E. Bays
Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY, USA

ABSTRACT

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

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

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Introduction

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

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

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

Corresponding Author
Harold E. Bays: hbaysmd@outlook.com

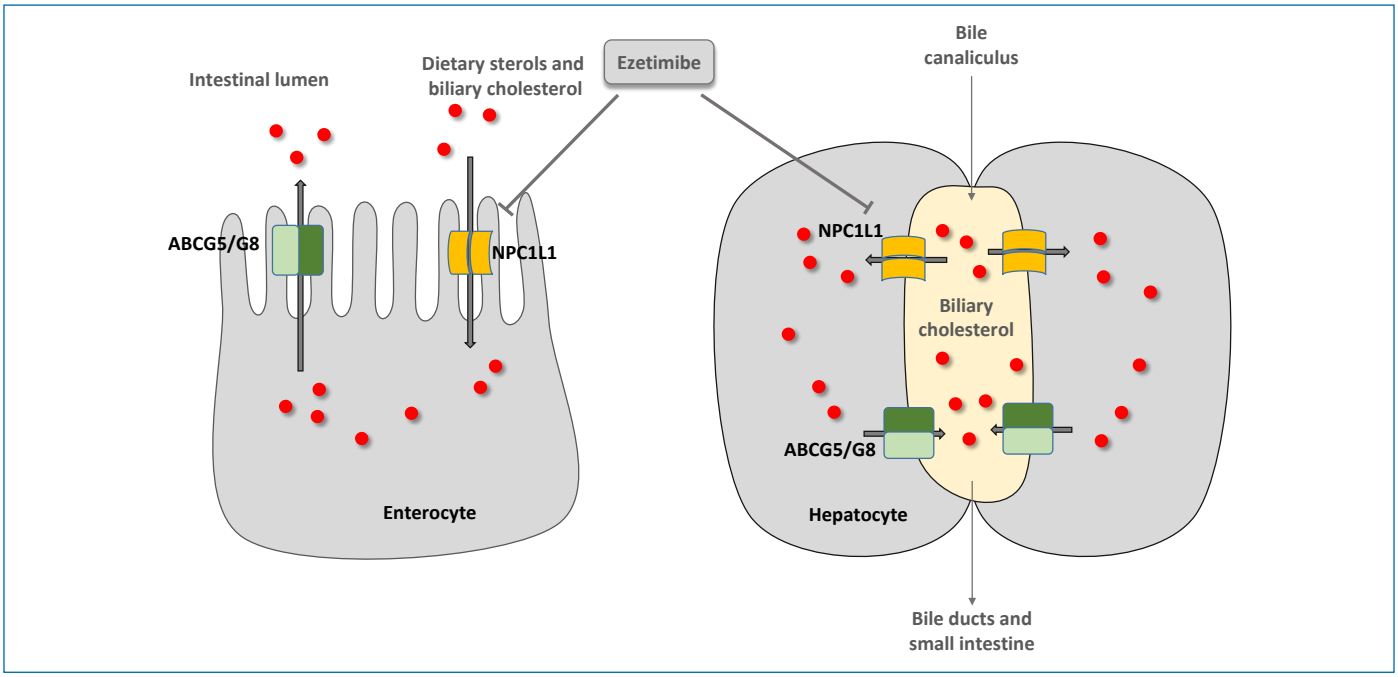

Figure 1 | NPC1L1 localization and function. NPC1L1 is localized on the brush border of the enterocytes, where it mediates the uptake of dietary and biliary cholesterol. Internalized cholesterol can be re-secreted into the lumen via the ABCG5/G8 system. NPC1L1 is expressed also at hepatocanalicular membrane,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

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

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

Pharmacokinetics and drug interactions

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

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

Ezetimibe and remnant lipoproteins

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

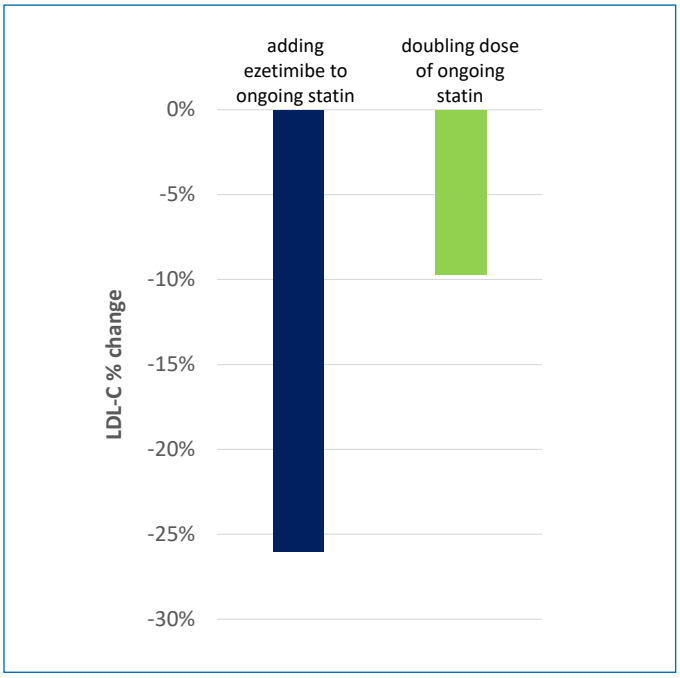

Figure 2 | Percent change from baseline in LDL-C levels in patients receiving ezetimibe added to ongoing statins or doubling the ongoing statin dose. Pooled analysis of data from 17 studies of 8667 hypercholesterolemic patients (20).
LDL-C, low-density lipoprotein cholesterol

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

Combining ezetimibe with a statin: Evidence from clinical trials

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

Combination ezetimibe+simvastatin: focus on IMPROVE-IT

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

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

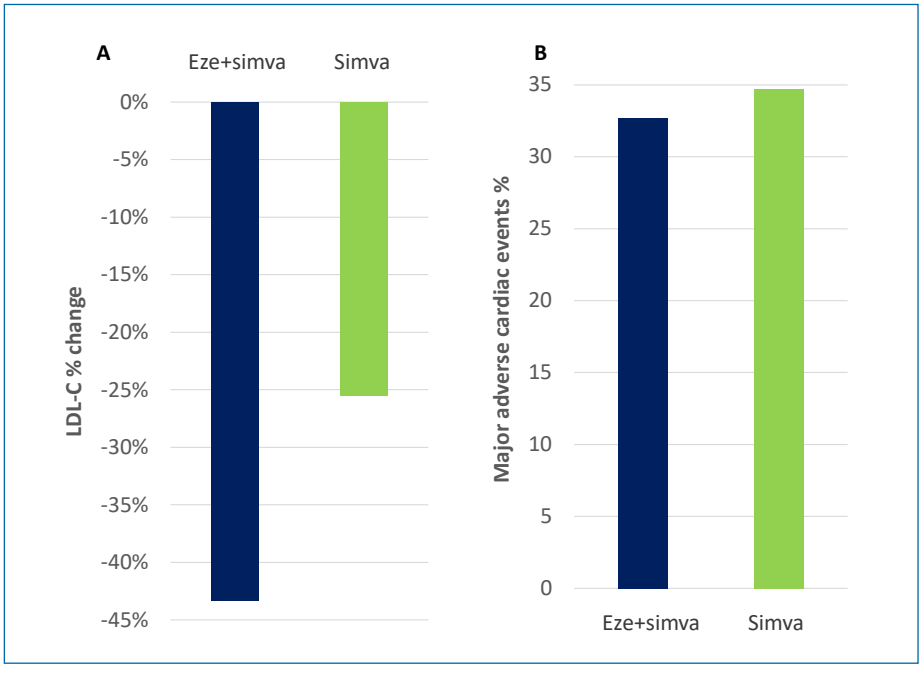

Figure 3 | The IMPROVE-IT trial. Percent change from baseline in LDL-C levels (A) and incidence of the primary end point (B) in patients receiving ezetimibe 10 mg + simvastatin 40 mg per day or simvastatin 40 mg per day alone (22). Absolute risk reduction with ezetimibe + simvastatin vs simvastatin alone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

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

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

Ezetimibe+atorvastatin

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

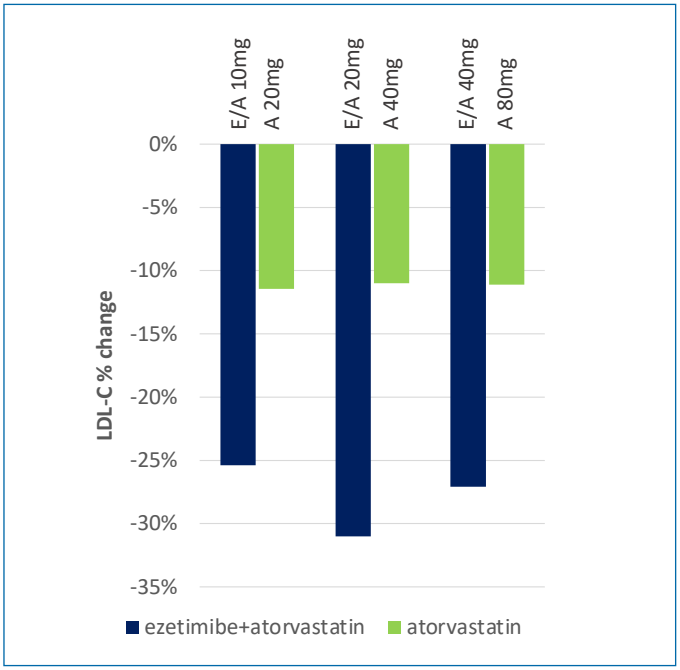

Figure 4 | Percent change from baseline in LDL-C levels in patients treated with baseline atorvastatin, comparing the addition of ezetimibe versus doubling dose of atorvastatin monotherapy. Data derives from studies included in the meta-analysis by Ai et al. (32).
LDL-C, low-density lipoprotein cholesterol;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

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

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

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

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

Ezetimibe+pitavastatin

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

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

Ezetimibe+rosuvastatin

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

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

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

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

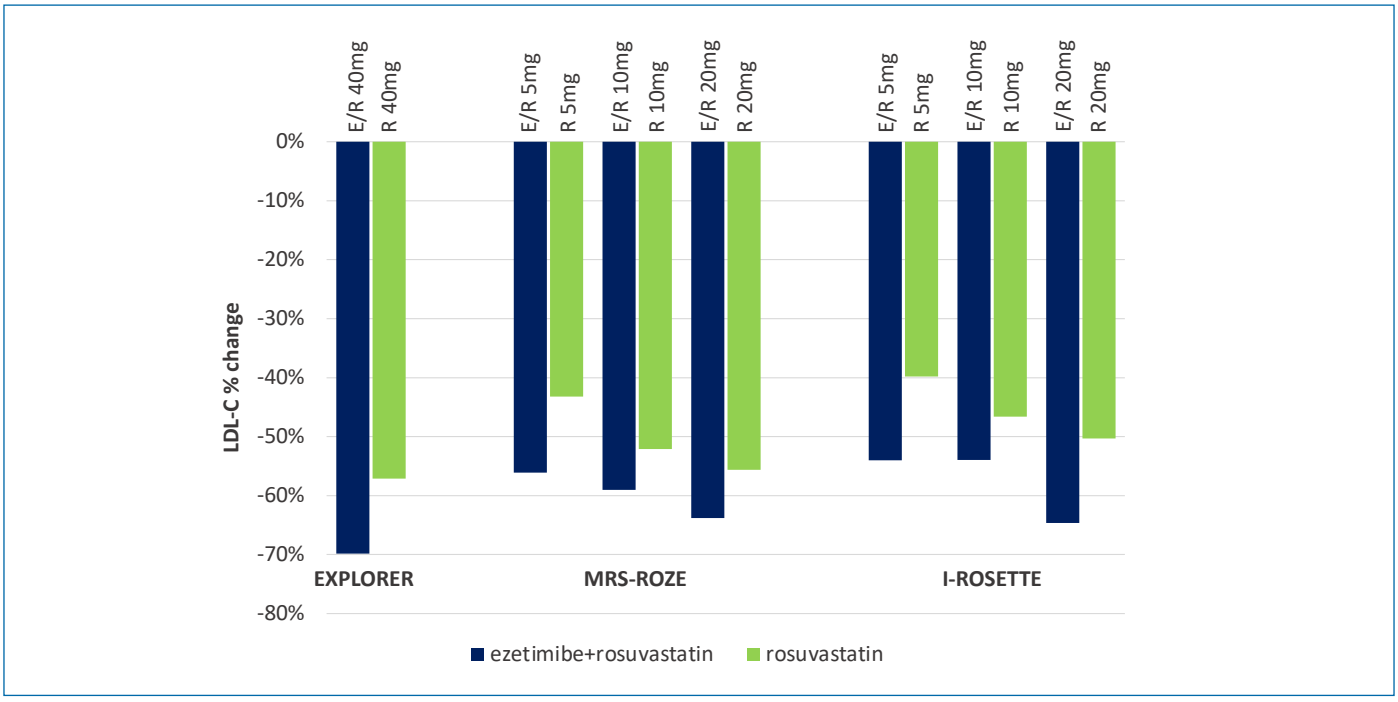

Figure 5 | Percent change from baseline in LDL-C levels in patients receiving ezetimibe plus rosuvastatin versus rosuvastatin monotherapy. Data derives from (46), (47), and (48).
LDL-C, low-density lipoprotein cholesterol; E, ezetimibe; R, rosuvastatin.

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

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

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

Comparing different regimens

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

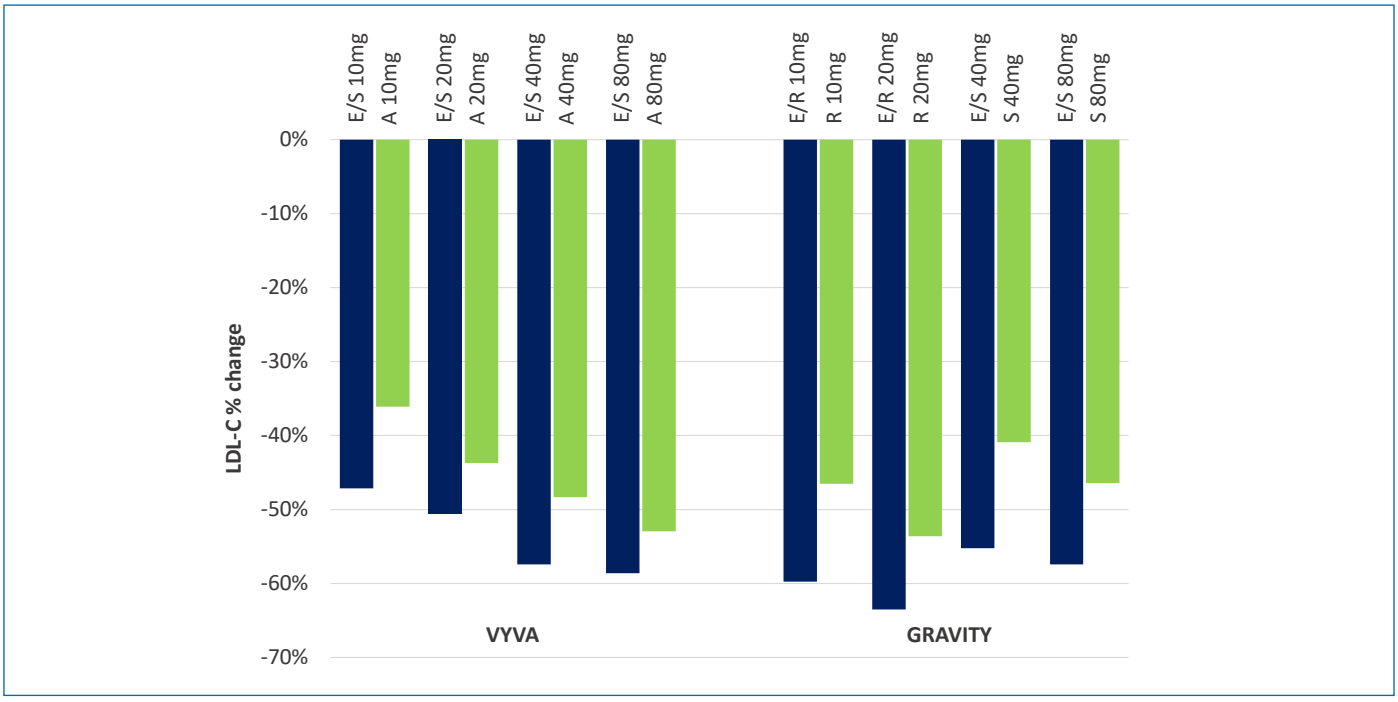

Figure 6 | Comparing the LDL-C-lowering efficacy of different regimens. The VYVA trial compared the effect of atorvastatin in monotherapy with the combination ezetimibe+simvastatin. The GRAVITY study compared the efficacy of the combinations ezetimibe/rosuvastatin and ezetimibe/simvastatin.
LDL-C, low-density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

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

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

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

Ezetimibe+PCSK9 inhibitors

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

Ezetimibe+bempedoic acid

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

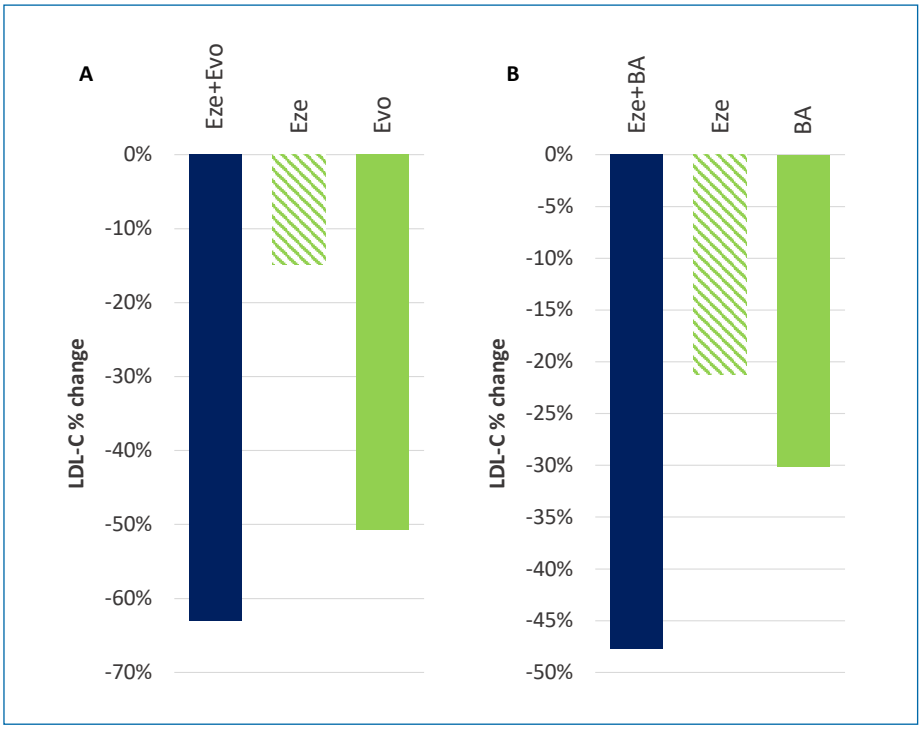

Figure 7 | Efficacy of ezetimibe addition on a PCSK9 inhibitor (A) or bempedoic acid (B). (A) LDL-C percent change in patients intolerant to statins receiving ezetimibe, evolocumab, or the combination ezetimibe+evolocumab (GAUSS trial). (B) Effect of ezetimibe and bempedoic acid alone or in combination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

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

Use of ezetimibe in special populations

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

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

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

Conclusions

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

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None

Conflicts of interest

Neither Dr. Harold Bays, nor his affiliated Research Center Institution & Weight Management Center, own pharmaceutical stocks or patents. In the past 12 months, Dr. Harold Bays' research site institution has received research grants from 89Bio, Akcea, AstraZeneca, Esperion, Matinas, Merck, Novartis, Pfizer, Regeneron, Sanofi, and TIMI. In the past 12 months, Dr. Harold Bays has served as a consultant/advisor for 89Bio and Esperion, and speaker for Esperion.

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Combination therapy in the guidelines: from high-intensity statins to high-intensity lipid-lowering therapies

Luis Masana[1], Daiana Ibarretxe[1], Natalia Andreychuk[1], Meritxell Royuela[1,2], Celia Rodríguez-Borjabad[1], Nuria Plana[1]

[1]Unitat de Medicina Vascular i Metabolisme, Hospital Universitari Sant Joan, Universitat Rovira i Virgili, IISPV, CIBERDEM, Reus, Spain;
[2]Unitat de Lípids i Risc Vascular. ALTHAIA. Xarxa assistencial universitària de Manresa, Manresa (Barcelona), Spain

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ABSTRACT

The causal role of cholesterol in atherosclerosis was established more than 100 years ago. Along with the fact that the higher the cholesterol, the greater the risk of atherosclerotic cardiovascular diseases (ASCVD), many randomized controlled trials (RCT) have shown that lowering LDL cholesterol (LDL-C) is associated with a lower incidence of ASCVD. This impact of lipid-lowering therapies on cardiovascular risk is independent of the drug used, as shown by several meta-analyses and Mendelian randomization studies. Therefore, the concept of using "high-intensity statins" should be changed to "high-intensity lipid-lowering therapies" that go beyond the use of statins.

Recent RCTs using non-statin lipid-lowering therapies has provided scientific evidence that the lower the LDL-C, the better in terms of cardiovascular events. Based on these observations, current guidelines recommend achieving very low LDL-C levels in patients with high and very-high cardiovascular risk.

To achieve these demanding goals, the physician must use the full spectrum of lipid-lowering therapies, beyond high-intensity, high-dose statins. Oral combination therapies and, when necessary, subcutaneous treatments become the new standard of care for hypercholesterolemia.

However, the number of patients achieving LDL-C goals is unacceptably low. This is due in part to insufficient prescription and insufficient treatment. To improve the efficacy of therapy, several strategies have been proposed, step by step, planning therapy and maximizing treatment, based on the needs of the patient.

A wider use of lipid-lowering therapies focused on the circumstances of the patient is a step towards personalized and precision medicine.

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Introduction

More than 100 years ago, Nikolai Anitschkow established the causal role of cholesterol in the development of arteriosclerosis (1). Rabbits fed egg yolk, very high in cholesterol, developed atherosclerotic plaques, while those fed egg white did not. The last century has provided a series of epidemiological and clinical data that support the importance of plasma cholesterol concentrations in cardiovascular (CV) risk. Fundamental research has also defined the mechanisms that explain the role of cholesterol in the pathogenesis of atherosclerosis. More clinically important is that cholesterol-lowering drugs reduce the burden of atherosclerotic cardiovascular disease (ASCVD).

Over the past 40 years, many randomized controlled trials (RCT) using lipid-lowering therapies (LLT) have stubbornly shown that lowering plasma cholesterol saves not only ASCVD events, but also lives. The first data using cholestyramine and first-generation fibrates already indicated the beneficial effect of lowering cholesterol. The discovery of statins in the 1980s provided physicians with a powerful cholesterol-lowering tool. Seminal studies with pravastatin (Woscops) (2) and simvastatin (4S) (3) changed the paradigm of ASCVD prevention forever. The 4S showed a significant

Corresponding Author
Luis Masana: luis.masana@urv.cat

impact of simvastatin therapy in patients with very high baseline LDL-cholesterol (LDL-C) levels. The intervention group achieved an LDL-C of ~120 mg/dL, which was associated with significant reductions in cardiovascular and total mortality and events compared to placebo.

The Heart Protection Study (4) reinforced the 4S data, and since then statins are a mandatory component of any therapy plan aimed at preventing cardiovascular disease, and RCTs with a placebo arm were no longer allowed. Additional RCTs comparing high- versus low-intensity or high- versus low-dose statins showed an incremental benefit of high- and high-intensity doses. The PROVE-IT (5) and TNT (6) studies demonstrated that lowering LDL-C below 70 mg/dL was associated with fewer ASCVD events. Consequently, the guidelines issued at that time recommended reaching this LDL-C concentration in patients with ASCVD.

A series of RCT failures to reach the primary endpoint using non-statin LLTs (fibrates, niacin, and some CETP inhibitors) add on statins suggested that the protective effect seen in statin RCTs might have been associated with the use of statins rather than cholesterol reduction per se. Consequently, in 2013, the ACC/AHA issued guidance on cholesterol management recommending the use of statins regardless of LDL-C levels (7). The main goal of secondary prevention therapy was to administer high-intensity statins to patients. The advent of PCSK9 inhibitors and ezetimibe data changed the concept.

Three new trials using non-statin LLT, IMPROVE-IT (8) with ezetimibe, FOURIER (9) with evolocumab, and ODYSSEY OUTCOMES with alirocumab (10) have shown that the lower the LDL-C, the better regardless of the treatment used. The LDL-C concentration achieved by the active therapy groups in these trials was less than 55 mg/dL, providing scientific evidence for current guidelines.

LDL-C is an etiological factor of atherosclerosis

As mentioned above, the implication of cholesterol in the etiology of atherosclerosis was established more than 100 years ago. Cholesterol is a unique molecule, vital to all animal cells. All animal tissues have the ability to synthesize cholesterol. It is a component of all cell membranes and a precursor of steroid hormones and bile acids. Animal life is not possible without cholesterol. On the other hand, there is no enzymatic mechanism capable of degrading or eliminating cholesterol. Cholesterol is eliminated from the body mainly unchanged or slightly modified as bile acids, by excretion through the bile and the digestive system. Excess LDL and other apoB-containing lipoproteins infiltrate the arterial wall. LDL particles can become trapped by extracellular matrix components in the subendothelial layer of arteries and engulfed by macrophages. When this deposit cannot be counteracted by the extracting function of HDL, cholesterol accumulates inducing a kind of foreign body reaction, mediated by inflammation and cell proliferation that leads to the formation of atherosclerosis plaque.

The role of LDL-C as an etiological factor of atherosclerosis has been extensively reviewed recently (11). Data from cell and animal models to epidemiological and clinical data establish the causal role of LDL-C in ASCVD. Among them, randomized controlled trials using lipid-lowering drugs have provided strong evidence. The decrease in LDL-C slows the progression of atheroma plaque or even induces regression as determined by intravascular ultrasound studies. These therapies have been widely associated with fewer cardiovascular events.

LDL-C-lowering therapies are the only ones targeting the etiology of ASCVD.

The reduction in cardiovascular risk induced by lipid-lowering drugs is mediated by the reduction of LDL-C

The Cholesterol Treatment Trialist Collaboration (12) has provided several meta-analyses showing that the reduction in relative cardiovascular risk induced by statin therapy correlates with the absolute amount of decrease in LDL-C. For every 1 mmol/L (~39 mg/dL) reduction in plasma LDL-C concentration, there is a relative risk reduction of approximately 22%, regardless of age, gender, or baseline absolute CV risk.

Recent meta-analyzes that include non-statin LLTs have extended this observation to other lipid-lowering drugs such as ezetimibe or PCSK9 inhibitors (13). These data have been reinforced by Mendelian randomization studies (14) showing that people who carry genetic variants associated with lower concentrations of LDL-C have fewer cardiovascular events. Interestingly, the effect is similar for variants in genes encoding the LDL receptor, HMG-CoA reductase, PCSK9, NPC1L1, or ATP citrate lyase. These genes encode proteins inhibited by the main LLT (statins, PCSK9 inhibitors, ezetimibe, bempedoic acid), suggesting that the main determinant of CV risk reduction is the decrease in LDL-C, regardless of the metabolic pathway affected.

Interestingly, the magnitude of the genetic effect on LDL-C levels is several times greater than that of LLT, suggesting that low LDL-C levels from birth have a greater impact than lowering LDL-C from adulthood. Therefore, the term "the lower, the better" is now completed with the sentence "the sooner, the better".

As mentioned above, RCTs with LLT without statins, meta-analyses, and Mendelian randomization data have shown that the relative reduction in CV is led by the reduction in LDL-C regardless of the therapy used, which is in line with the evidence of causality of LDL-C for atherosclerosis.

Taking these data into account, we recommend changing the term "high-intensity statin therapy" to "high-intensity lipid-lowering therapy", which goes beyond the use of statins.

Lipid lowering tools to achieve the very low LDL-C therapy goals

The most recent guidelines from several scientific societies involved in cardiovascular prevention recommend achieving even lower LDL-C levels (15). For high- and very-high risk individual, in addition to achieving a 50% reduction from baseline values, LDL-C concentrations below 70 mg/dL and 55 mg/dL, respectively, are defined. The IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES trials provide scientific evidence on the benefit of treating patients with atheromatous cardiovascular disease (heart, brain, or peripheral), with LDL-C above 70 mg/dL despite intensive lowering therapy. Patients in the active arm who used complementary therapies with ezetimibe, evolocumab, or alirocumab reduced their LDL-C concentrations to below 55 mg/dL (30 mg/dL in the FOURIER), which was associated with a significant incremental reduction in relative CV risk of the same magnitude of statin reduction per unit LDL-C. The reduction of LDL-C with statins, ezetimibe, or PCSK9 inhibitors has been shown to be of the same quality in terms of prevention of CV events. The evidence has been translated into new guidelines and its implementation in clinical sites is our current task.

Considering that in monotherapy high-intensity statins will only lower LDL-C by approximately 50%, achieving the recommended goals requires the use of combination therapies.

A mathematical equation makes possible to calculate the theoretical lipid-lowering efficacy of a combination of drugs accord-

Table 1 | Lipid-lowering therapies classified according to their efficacy. Suitable patients for each category of therapy.

Suitable patients	High-risk patients with baseline LDL-C up to 140 mg/dl Very High-risk patients with baseline LDL-C up to 110 mg/dl	High-risk patients with baseline LDL-C up to 175 mg/dl Very High-risk patients with baseline LDL-C up to 140 mg/dl	High-risk patients with baseline LDL-C up to 230 mg/dl Very High-risk patients with baseline LDL-C up to 185 mg/dl	High-risk patients with baseline LDL-C up to 350 mg/dl Very High-risk patients with baseline LDL-C up to 275 mg/dl
Minimum LDL % reduction to achieve goals	**≥ 50%**	**≥ 60%**	**≥ 70%**	**≥ 80%**
Oral Monotherapy	High Intensity Statins			
Oral combination therapy	Moderate Intensity Statin + Ezetimibe or Bempedoic acid	High Intensity statin + Ezetimibe or Bempedoic acid High or Moderate Intensity Statin + Ezetimibe + Bempedoic acid		
Oral and subcutaneous combination therapy		Inclisiran + Ezetimibe or Bempedoic àcid Alirocumab or Evolocumab +Ezetimibe or Bempedoic Acid	Inclisiran or Alirocumab or Evolocumab + Moderate Intensity Statin Inclisiran + High Intensity Statin Inclisiran or Alirocumab or Evolocumab + Ezetimibe + Bempedoic acid	Alirocumab or Evolocumab + High Intensity Statin Inclisiran + High Intensity Statin+ Ezetimibe Inclisiran or Alirocumab or Evolocumab + High or Moderate Intensity Statin + Ezetimibe + Bempedoic acid

- The efficacy of the combined therapy has been calculated according to the lipid-lowering efficacy in monotherapy applying the formula in reference 16. The lipid-lowering efficacy values in monotherapy used for the calculations have been Ezetimibe 20%; Bempedoic acid 18% (without statins 23%); Statin of moderate intensity 40%; Statin of High intensity 50%; Inclisiran 50%; Alirocumab (highest dose) 60%; Evolocumab 60%.
- High intensity statins: Rosuvastatin 20 - 40 mg / day; Atorvastatin 80 mg / day.
- Statins of moderate intensity (LDL reduction 40-50%): Rosuvastatin 10-5 mg / day; Atorvastatin 40-20 mg / day; Pitavastatin 4-2 mg / day; Pravastatin 40 mg / day; Simvastatin 40-20 mg / day; Fluvastatin 80 mg / day.
- Bempedoic acid increases plasma concentrations of simvastatin or pravastatin increasing the risk of side effects. Avoid these combinations.
- Alirocumab is considered at the highest dose of 150 mg / 14 days. Administration of 75 mg / 14 days or 300 mg / month should be considered with a similar efficacy to Inclisiran.

ing to their effect in monotherapy (16) (**Table 1**). According to their lipid-lowering efficacy, drug therapies can be classified as low (30% reduction), moderate (40%), high (50%), very high (60%), and extremely high (80%) reducing intensity. These reductions can be obtained by using three different approaches: oral monotherapy, oral combination therapy, and oral and subcutaneous combination therapy. Oral monotherapy, primarily high-dose, high-efficacy statins, can achieve a 50% reduction in LDL-C, similar to oral combination therapy using a moderate-efficacy statin plus ezetimibe or bempedoic acid. Interestingly, the fixed combination of ezetimibe and bempedoic acid would reduce LDL-C by about 40%, which is a useful alternative in statin-intolerant patients. The combination of a high-intensity statin plus ezetimibe or bempedoic acid provides a high-intensity lipid-lowering effect of approximately 60% reduction. Triple oral therapy with statin, ezetimibe, and bempedoic acid will reduce LDL-C by 60-70%, depending on the intensity (moderate or high) of the statin used in the combination. The combination of high-intensity statins and PCSK9 targeting therapies (PCSK9 tt) increases the lipid-lowering efficacy from 75% to more than 80%, depending on the PCSK9 tt and the dose used. This efficacy can be increased by up to 87% by triple or quadruple therapy (PCSK9 tt+statin+ezetimibe+bempedoic acid) (**Table 1**).

It is important to consider all of these therapies as opportunities to tailor the best lipid-lowering regimen for patients, with the aims of achieving LDL-C goals in accordance with the overall CV risk and decreasing side effects to increase tolerance, and thus hence, to greater adherence.

Strategies to optimize lipid-lowering therapy, the only therapy aimed at ASCVD etiology

Lipid-lowering therapy is the only therapy that addresses the etiology of ASCVD, so optimizing this therapy is crucial. ASCVDs continue to be the leading cause of morbidity and mortality in the world. Lowering LDL-C from 100 mg/dL to the recommended target of 55 mg/dL will prevent a quarter of CV events. However, the current percentage of high- and very-high-risk patients at target is unacceptably low.

The reasons for this poor performance of therapy are various, but an important one is insufficient prescription and treatment. According to recent data from the DA VINCI study (17), although only 30% of very-high-risk patients achieved goals, only 40% were on

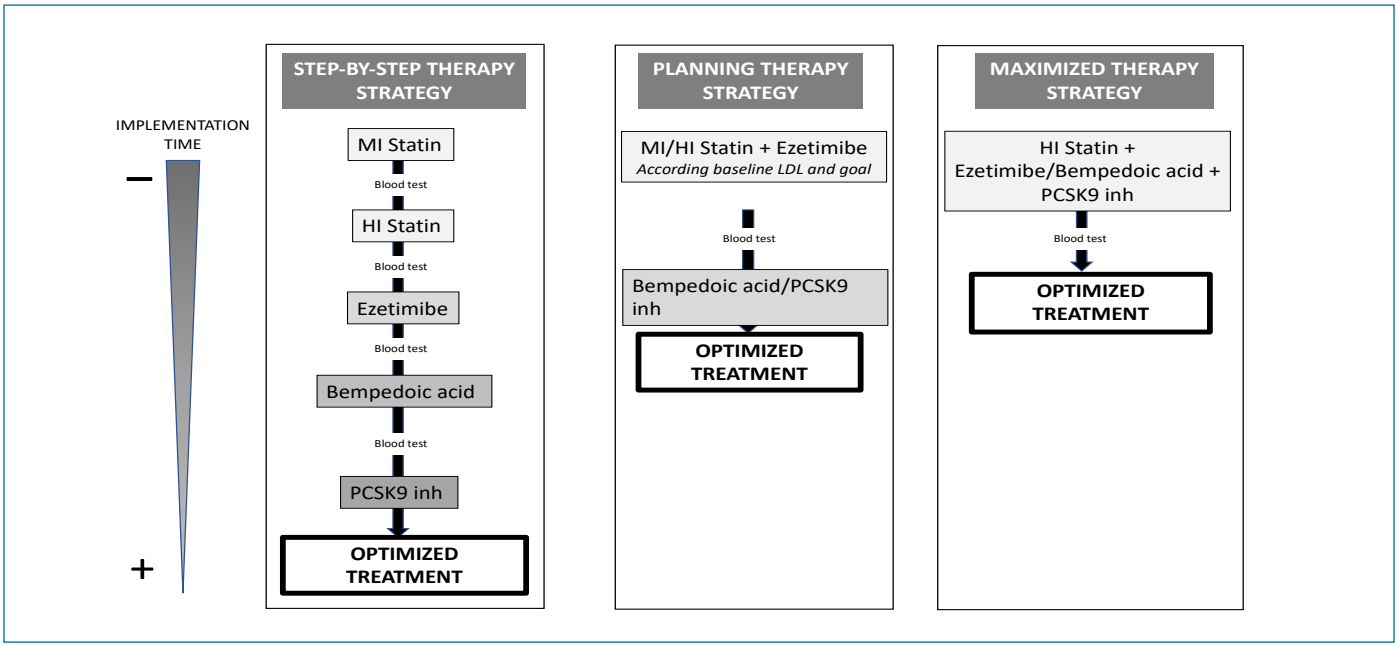

Figure 1 | Different strategies to optimize lipid-lowering therapy.

high-intensity statin therapy, 9% were on oral combination therapy, and 1% on PCSK9 inhibitors. Data from the Swedish CV registry have also shown that the earlier LDL-C is lowered, the better the prognosis (18).

It is mandatory to develop strategies to implement the appropriate therapies. According to the ESC/EAS guidelines, there are two possible strategies to consider: a step-by-step strategy and a planned strategy. In the view of a recently published expert group opinion, a third strategy, the maximized strategy, should be considered (19-21).

The stepwise strategy is the procedure supported by scientific evidence. In the first step, patients should be treated with high-intensity statins from the beginning or increasing the dose from moderate to the highest dose. After clinical and analytical evaluation, combination therapy with ezetimibe may be recommended and, in a third or fourth step, PCSK9 inhibitors should be considered if indicated. The advantages of this strategy are several. It is the direct application of scientific evidence according to RCT. During follow-up, side effects can be evaluated by tailoring therapy to the patient's needs. However, there are several disadvantages. The most important is that it takes too long to optimize therapy. A three- to four-step strategy will take almost a year. During this period, many patients are lost to follow-up, going to doctors from other health care system levels with different points of view, and the inertia of the therapy increases.

In the planned strategy, the initial LLT should be directed at the LDL-C goal. Depending on the risk category of the patient, the LDL-C goal is defined. The distance between the current or baseline LDL-C and the target is calculated, and the appropriate drug or drug combination should be prescribed according to their theoretical efficacy from the outset. The advantage of this strategy is that the minimum 50% reduction recommended by the guidelines will always be achieved and optimization of therapy can be achieved more quickly, even in a single step. As negative aspects, the monitoring of side effects is less. This strategy has been proven by the "treat stroke to target" trial (22), an RCT conducted in stroke patients showing that regardless of the LLT used, therapy directed at lower LDL-C goals increases CV benefits.

According to the maximized therapy strategy (19), high- and very-high-risk patients should receive a very high- or extremely high-intensity lipid-lowering therapy, including double or triple therapy from the beginning. It derives from two concepts well based on scientific evidence: "the lower the better" and "the sooner the better". Based on these aspects, LDL-C goals should be viewed as a minimum. Patients who achieve even lower values would have greater clinical benefit without increasing side effects due to low LDL-C concentrations. The advantage is to get the lowest LDL-C as soon as possible. Again, this strategy is based on expert opinion based on RCTs, meta-analyses, and focused clinical studies, but this strategy has not been directly tested (**Figure 1**).

These three strategies are not exclusive, and it is advisable to use the last two in patients with very-high and extremely-high cardiovascular risk.

The standard step-by-step strategy is clearly not efficient enough, obtaining unacceptable low performance; therefore, treatments based on planned or maximized strategies should become the standard of care for lipid-lowering therapies for cardiovascular prevention.

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Conflicts of interest

LM has received personal fees for lectures and advisory work from Sanofi, Amgen, Amarin, Amryt, Servier, Daiichi-Sankyo, Novartis, Rubió. NP has received personal fees for lectures from Sanofi, Amgen, Mylan. DI has received personal fees for lectures from Sanofi, Rubió. MR has received personal fees from Amgen, Sanofi, Daiichi-Sankyo, Viatris. NA and CR-B have nothing to declare regarding this work.

Author Contributions

LM, DI, NP: conception, writing, and final approval of the manuscript. NA, MR, CR-B: literature review, manuscript review, and final approval.

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Lipid-lowering for the prevention of cardiovascular disease in the new era: A practical approach to combination therapy

Erin D. Michos[1], Keith C. Ferdinand[2]

[1]*Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA;*
[2]*Tulane University Heart and Vascular Institute, Tulane University School of Medicine, New Orleans, LA, USA*

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Lipid-lowering; Combination therapy; Atherosclerotic cardiovascular disease; LDL-cholesterol; Therapy adherence

ABSTRACT

Low density lipoprotein-cholesterol (LDL-C) is the main etiologic factor for the development and progression of atherosclerotic cardiovascular disease (ASCVD) and LDL-C reduction is a central tenet of ASCVD treatment and prevention. Moreover, ASCVD risk reduction is proportional to the magnitude of LDL-C lowering. Recent European guidelines have recommended a goal of <55 mg/dL (<1.4 mmol/L) for patients at very-high cardiovascular risk, while the U.S. guideline considers an LDL-C ≥70 mg/dL (≥1.8 mmol/L) as a threshold to intensify therapy with the addition of a non-statin therapy to statins. To reach these lower LDL-C goals of <55 mg/dL or <70 mg/dL, combination therapy is necessary in the majority of these patients. Drug combinations, and in particular single-pill combinations, may substantially increase adherence to therapy. Adherence is essential for achieving a clinical benefit and, as many patients discontinue medications, the long-term adherence to lipid-lowering therapy represents a major issue in ASCVD prevention. Secondary prevention or high-risk primary prevention patients, such as those with familial hypercholesterolemia in whom maximally-tolerated statin doses alone would not be anticipated to sufficiently lower LDL-C, would benefit from combination therapy. In current clinical practice, statins with ezetimibe, statins plus PCSK9 inhibitors (with or without ezetimibe), and, most recently statins or ezetimibe with bempedoic acid are the most commonly used combination therapies for LDL-C-lowering. This review outlines the importance of using combination therapy for the achievement of LDL-C treatment goals and discusses some practical approaches for the initiation of combined therapy in patients at the highest risk.

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Introduction

There is overwhelming evidence from genetic, population, and interventional data that low density lipoprotein cholesterol (LDL-C) is causally related to the development of atherosclerotic cardiovascular disease (ASCVD) (1, 2). As such, LDL-C remains a crucial target of both primary and secondary ASCVD prevention strategies, with the recommended intensity of therapy generally matched to the absolute risk of the patient (3). All patients across the risk spectrum benefit from the implementation of favorable lifestyle changes throughout the lifespan, including regular physical activity and healthy diet patterns. However, patients at elevated ASCVD risk are additionally recommended for statin therapy as first line pharmacotherapy for ASCVD prevention (4, 5).

For patients at high or very-high cardiovascular (CV) risk, recent guidelines from the American Heart Association (AHA)/American College of Cardiology (ACC)/Multi-societies and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) recommend the initiation of a high-intensity statin to achieve an LDL-C reduction of ≥50% (4-6). Additionally, the ESC/EAS guidelines (5) have established risk-based LDL-C goals, with a goal of <55 mg/dL (<1.4 mmol/L) for patients at very-high-risk, while the AHA/ACC guideline (4) considers an LDL-C level of ≥70 mg/dL as a threshold to intensify therapy with the addition of non-statin agents to statins. The general theme across both guidelines is that lower LDL-C is better for longer periods of time. Notably, both sets of guidelines indicate that if patients are unable to reach treatment goals for LDL-C with maximally tolerated statins, add-on therapy with non-statins is recommended (4, 5).

Corresponding Author
Erin D. Michos: edonnell@jhmi.edu

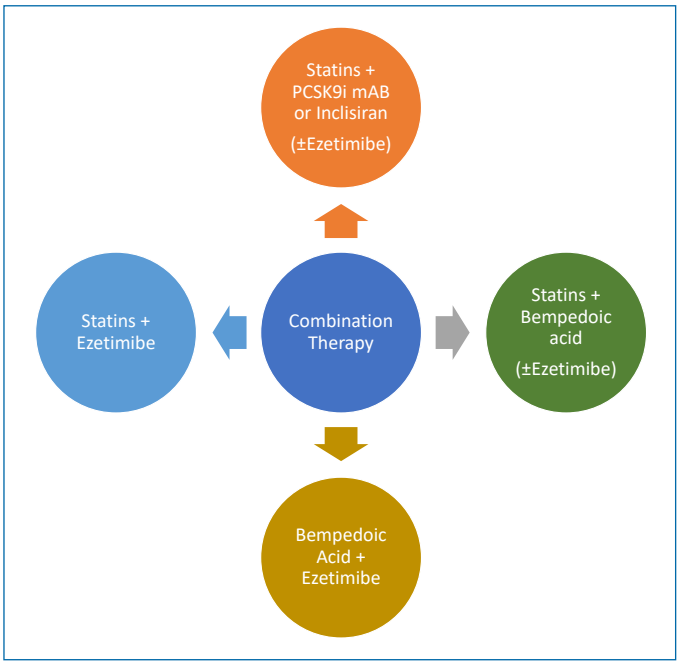

Figure 1 | Options for Combination Therapy.

In this review, we highlight the importance of using combination therapy for the achievement of LDL-C treatment goals and outline some practical approaches. The currently available non-statin therapies for LDL-C lowering that have demonstrated benefits for the reduction in major adverse cardiovascular events (MACE) when added to statins include ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i). Additional effective therapies for LDL-C lowering, but with on-going cardiovascular outcome trials, include bempedoic acid and inclisiran.

Other LDL-C-lowering agents reserved for homozygous familial hypercholesterolemia (HoFH) include evinacumab, mipomersen, and lomitapide, which are beyond the scope of this review, but have been described elsewhere (7). Additionally, icosapent ethyl, a highly purified form of eicosapentaenoic acid (EPA), at a dose of 4 g/day, has also shown incremental benefit for reduction in MACE among patients at high ASCVD risk already treated with statin therapy (8). Icosapent ethyl therapy lowers triglycerides, but not LDL-C, but it is an important therapeutic strategy for patients with high residual risk associated with elevated triglycerides. However, for the purposes of this review, we will be discussing combination therapy for LDL-C lowering.

In current clinical practice, statins with ezetimibe, statins with PCSK9i (with or without ezetimibe), statins with bempedoic acid (with or without ezetimibe), and bempedoic acid with ezetimibe are the most commonly used combination therapies for LDL-C lowering (**Figure 1**).

The current landscape: Suboptimal achievement of LDL-C targets

Unfortunately, many high-risk patients do not achieve guideline-recommended LDL-C levels. The EUROASPIRE IV study (published in 2016) enrolled patients with coronary artery disease (CAD) who had a recent acute coronary syndrome (ACS) or coronary revascularization (9). Despite statin use in 86% of these patients, less than 20% achieved LDL-C of <70 mg/dL (<1.8 mmol/L). There was also a high prevalence of suboptimal control of other risk factors such as persistent smoking, unhealthy diet, inadequate physical activity levels, obesity, and diabetes, and cardiac rehabilitation was substantially underutilized, with an only 50% referral rate (9).

The EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care (the DA VINCI study) enrolled 5,888 patients (3000 primary and 2888 secondary prevention) from 18 countries between 2017-2018 and examined achievement of guideline-recommended LDL-C goals in a real world setting (10). Only about half of patients achieved their LDL-C goal based on the 2016 guideline, and even fewer (33%) would be at target if the newer 2019 ESC/EAS guideline recommendations had been applied. Disappointingly, only 20% and 38% of very-high-risk primary and secondary prevention patients were treated with high-intensity statins. At that time, only 9% of patients were using a combination therapy of moderate-to-high-intensity statins plus ezetimibe and only 1% on PCSK9i combination. However, those using PCSK9i were more likely to have achieved LDL-C goals. These data highlight the implementation gap between guidelines and clinical practice, and emphasize that a greater use of combination therapy is needed so that more high-risk patients are able to achieve LDL-C goals (10, 11).

The Treatment of High- and Very-High-Risk Dyslipidemic Patients for the Prevention of Cardiovascular Events (SANTORINI) registry, which started after the release of 2019 ESC/EAS cholesterol guidelines, recruited 9,606 patients at high- or very-high CV risk requiring lipid lowering therapy (LLT), from 14 European countries, with the objective to determine the effectiveness of current treatment modalities in achieving LDL-C control in a real world setting (12). Despite high-risk status, the mean LDL-C was 95 mg/dL (2.45 mmol/L), 18.6% of patients were not receiving any LLT, and 54% of patients were receiving monotherapy, predominantly statins (13). Only 27% of patients were using combination therapy, including statin plus ezetimibe in 17%, PCSK9i plus an oral medication in 4.1%, and 6% with other oral combinations. As similarly noted in DA VINCI (10), these data continue to show that LDL-C remains above goal in high-risk patients and combination is sorely underutilized (13).

The Getting to an Improved Understanding of Low-Density Lipoprotein-Cholesterol and Dyslipidemia Management (GOULD) registry examined whether LLT was intensified among high-risk patients with ASCVD who were treated with LLT at baseline (14). Among those ASCVD patients with suboptimal control with LDL-C >100 mg/dL, only 22% had their LLT intensified over the next 2 years, with 6.4% having statin therapy intensified, 6.8% having ezetimibe added, and 6.3% with PCSK9i added. The corresponding numbers for those with LDL-C 70-99 mg/dL who underwent LLT intensification was even lower, with only 14% being intensified, including 6.3% placed on higher statin dose, 4.5% with ezetimibe added, and 2.2% with PCSK9i added. Notably, approximately two-thirds of these ASCVD patients remained at suboptimal LDL-C level of >70 mg/dL at 2 years.

There are many, multifactorial, complex reasons why guideline recommended LDL-C levels are not achieved in clinical practice, including: clinician inertia, insufficient patient education, costs, tedious pre-authorization and reimbursement barriers, perceived side effects, fear and mistrust, pill burden, and polypharmacy. Implementation of team-based care approaches (such as pharmacist-led interventions and allied health professionals providing further clinician and patient education), systems protocols (electronic reminders and electronic health record flags) (15), and the use of combination therapy (16) can help overcome some of these barriers.

Adherence: A challenge in clinical practice

Adherence to therapy is essential for achieving a clinical benefit and, as many patients stop taking their medications, the long-term adherence to LLT represents a major issue in ASCVD prevention. This may be particularly true for familial hypercholesterolemia (FH) patients, who need lifelong LLT. Preventive pharmacotherapy does not benefit patients who do not take it and non-adherence translates to poorer outcomes. In a large healthcare utilization registry in Italy, the risk of cardiovascular outcomes was 55% lower among patients who had a high adherence to LLT (proportion of days covered with LLT >75%) compared to those with low adherence (<25% days covered), reinforcing that adherence is a central driver of success (16).

Low statin adherence was also associated with increased risk of mortality among U.S. Veterans Affairs patients (17). In yet another real-world example from a U.K. primary care cohort of patients at high CV risk, patients receiving low-intensity LLT and reduced adherence had the greatest risk for subsequent MACE, whereas the lowest CV risk was observed among adherent patients who were receiving high-intensity therapy (18). This underscores the importance of strategies that can improve both adherence and greater intensity of LDL-C lowering to substantially impact CV risk.

Several studies have shown that combination therapies, and in particular fixed-dose combination therapies, may substantially increase the adherence to treatment (16, 19).

Incremental ASCVD reduction conferred by lower LDL-C

As previously noted, LDL-C levels are the main etiologic factor of atherosclerosis, and LDL-C reduction is the major goal of ASCVD treatment and prevention. Every 39 mg/dL (1 mmol/L) reduction in LDL-C confers an approximate 21% [RR 0.79 (0.77-0.81)] reduction in major vascular events, and more intensive LLT has consistently shown further CV benefits (20). For example, a meta-analysis by the Cholesterol Treatment Trialists Collaboration of 5 randomized clinical trials (RCTs) including over 39,000 participants demonstrated that a more intensive statin regimen, compared to less intensive statin therapy, conferred a 15% (95% CI 11-18%) greater reduction in MACE (21). The main determinant of risk reduction in statin RCTs was the absolute LDL-C reduction, and there was no threshold effect, meaning that further LDL-C lowering conferred further reduction in MACE.

A more recent meta-analysis examining 11 trials and over 130,000 participants compared a more intensive vs a less intensive LLT strategy (22). The more intensive LLT group was defined as treatment regimens to achieve LDL-C <70 mg/dL (using high-intensity statins, ezetimibe plus statins, or PCSK9i) vs a less intensive LLT strategy defined as treatment with less potent active control or placebo that conferred higher achieved LDL-C levels ≥70 mg/dL. This analysis similarly confirmed further benefits in the reduction of all-cause mortality [RR 0.94 (95% CI, 0.89-1.00)], CV mortality [RR 0.90 (0.81-1.00)] and MACE [RR 0.89 (0.84–0.93] with the more intensive LLT regimen (22). Notably, these benefits were achieved without increasing the risk for incident cancer, diabetes mellitus, or hemorrhagic stroke (22). The risk reduction in ischemic endpoints and safety were independent of baseline LDL-C or the specific drug therapy.

Notably, the degree of LDL-C lowering itself matters rather than drug class per se, as all therapies that work by up-regulating the LDL receptor reduce ASCVD risk proportionally to their magnitude of LDL-C (and apoB) lowering (23).

Even with the use of a high-intensity statin, patients may not achieve the anticipated 50% reduction in LDL-C. For example, in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) primary prevention trial examining 20 mg/day dose of rosuvastatin, only 46% of patients achieved a ≥50% reduction in LDL-C. In addition, 43% achieved a reduction of only >0 but <50%, and 11% of patients experienced no reduction or an increase in LDL-C (24). Many factors may contribute to a suboptimal response, including genetic factors, but also issues related to adherence and persistence to therapy.

Therefore, high-intensity statin monotherapy may not be sufficient in many patients. For these individuals at high- or very-high CV risk, there are multiple benefits for use of combination LLT. For one, combination therapy takes advantage of the synergistic effect of drugs acting on different aspects of LDL metabolism, which is beneficial in patients who cannot achieve adequate LDL-C lowering on high-intensity therapy. Furthermore, although high-intensity statin is the guideline recommended intervention and is tolerated by the majority of patients, there are some patients that report limiting side effects. Combination therapy may help facilitate obtaining similar LDL-C-lowering efficacy using lower statin doses if needed to reduce adverse events that are more prevalent with higher statin doses, such as muscle symptoms, increase of liver enzymes, or diabetes. Higher tolerability may lead to higher adherence, which can be further reinforced by the use of the fixed-dose combinations. Fortunately, multiple LLT combinations are currently available.

Which patients might be good candidates for combination?

Heterozygous FH (HeFH) patients, statin intolerant patients, and patients at high CV risk who are unable to achieve recommended LDL-C goals on maximally tolerated statin doses all represent excellent opportunities to use combination therapy.

HeFH is a genetic disorder, typically with a mutation in one allele of either the *LDLR*, *APOB*, or *PCSK9* genes (7). HeFH patients have life-long elevated LDL-C levels (about two times higher than the general population) and a substantially increased ASCVD risk that occurs at an earlier onset in life than age-matched peers (7, 25). Although statins are the main-stay of treatment in these patients, many HeFH patients are unable to successfully reach optimal LDL-C levels even with maximally tolerated statins, and require add-on therapy.

Despite the above considerations, it should be emphasized that the vast majority of patients are able to tolerate statins, a very safe class of medications. The risk of statin-induced serious muscle injury such as rhabdomyolysis is <0.1%, the risk of serious hepatotoxicity is 1 in 100,000, and the risk of new-onset diabetes mellitus induced by statins is ~0.2% per year depending on underlying diabetes risk of the population (26). Nevertheless, some patients are unable to tolerate sufficient or any statin therapy and need alternative pharmacotherapy for adequate LDL-C lowering. In real-word data, among 5,696 patients with a clinical indication for statin therapy, there were 1511 individuals (26%) not on statin treatment, of which 31% had discontinued their therapy and 55% of those who had stopped statin therapy did so due to perceived effects (27). In an n-of-1 trial (a crossover design where patients served as their own controls) enrolling statin intolerant patients, 90% of the statin-associated muscle symptoms were also elicited by the placebo – a phenomenon called the "nocebo effect" (28). Many patients can tolerate statin therapy when offered a re-challenge and this should be tried first. Nevertheless, the nocebo effect notwithstanding, the perceived side effects from statins are still very real to many patients who may down-titrate or discontinue their statin treatment, leaving them vulnerable to the ASCVD risk related to poorly controlled atherogenic dyslipidemia. In

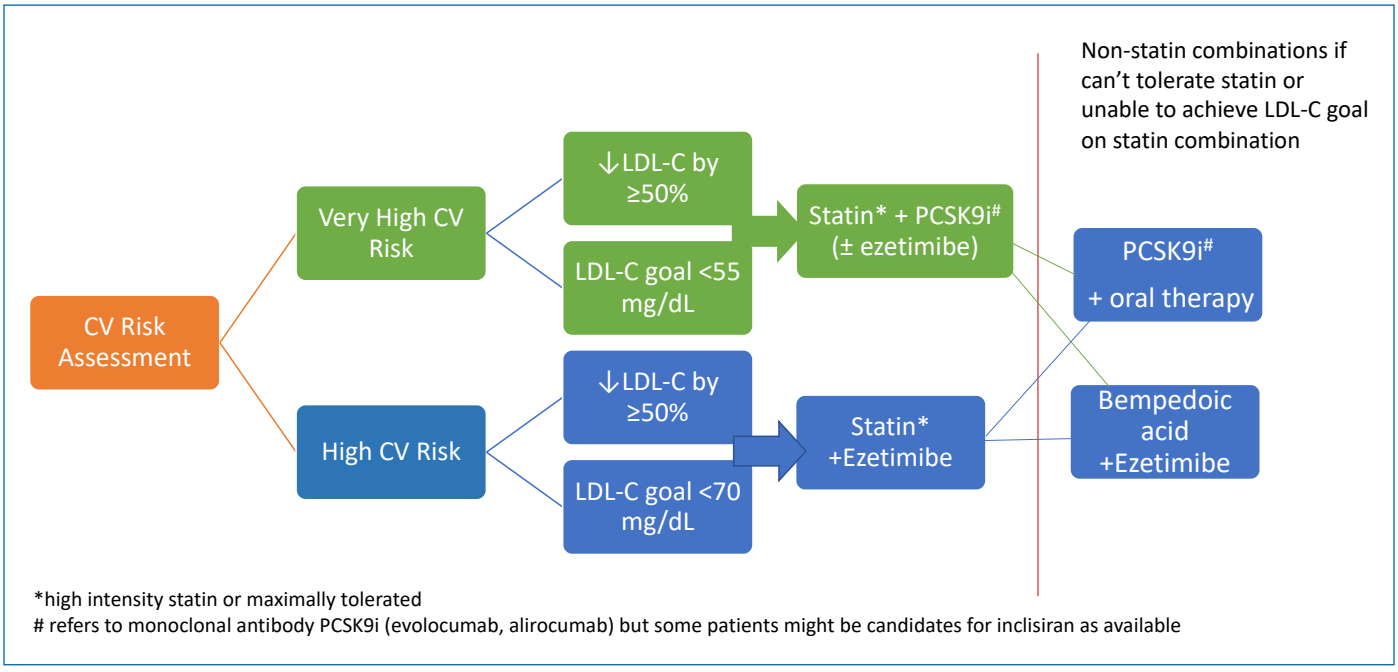

Figure 2 | Candidates for combination therapy.

consideration of the above factors, a combination of various agents may be needed to achieve desired LDL-C levels.

Additionally, even in patients who are optimally treated with statin therapy, there is significant residual risk with recurrent CV events, which can be further reduced by further LDL-C lowering (29-31). Secondary prevention patients or high-risk primary prevention patients in whom maximally tolerated statin doses alone do not sufficiently lower LDL-C, or patients who cannot take statins would benefit from combination therapy. Very-high-risk secondary prevention patients per the AHA/ACC guideline include those with recent ACS, history of myocardial infarction (MI), ischemic stroke, or symptomatic peripheral artery disease (PAD) with at least one other major risk factor, whose therapy should be intensified if the LDL-C remains above 70 mg/dL (4).

The ESC/EAS guidelines set goals of <55 mg/dL and <70 mg/dL for individuals at very-high-risk and high-risk, respectively (**Figure 2**) (5). "Very-high-risk" category includes individuals with documented ASCVD (prior ACS, stable angina, prior revascularization, stroke/TIA, PAD), but also those with ASCVD unequivocally demonstrated by imaging such as multivessel CAD with >50% stenosis seen on invasive coronary angiogram or coronary computed tomography angiography (CCTA) or significant plaque on carotid ultrasound (5). Additional very-high-risk patients include those with diabetes who have evidence of target organ damage or patients with diabetes and multiple major risk factors, early onset type 1 diabetes of long duration (>20 years), severe chronic kidney disease (CKD), a SCORE ≥10% for 10-year risk of fatal CVD, and FH with ASCVD or a major risk factor. "High-risk" category per the European guidelines includes patients with a single markedly elevated risk factor, FH without other risk factors, patients with diabetes without target organ damage but with at least one other risk factor or long duration of diabetes, moderate CKD, or a SCORE 5-10% 10-year risk of fatal CVD (5). In order to reach these more intensive LDL-C goals of <55 mg/dL or <70 mg/dL, combination therapy will likely be necessary in the majority of these patients.

Which types of combination therapy?

The most commonly used combination therapy is statin plus ezetimibe. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), studying high-risk patients after a recent ACS event, demonstrated that patients randomized to ezetimibe added to a statin achieved lower LDL-C (mean 54 mg/dL) compared to statin monotherapy (mean LDL-C 70 mg/dL) and experienced a 2% lower absolute risk and 6% lower relative risk of subsequent MACE. Moreover, the number needed to treat was only 50 to prevent one event (29). Indeed the subsequent 2018 AHA/ACC guideline for lipid management then endorsed the addition of ezetimibe to statin for patients at high- or very-high-risk if the LDL-C remained above a threshold of 70 mg/dL, and if PCSK9i was to be considered, it was recommended to start ezetimibe first (4). This latter recommendation of starting ezetimibe before PCSK9i likely was driven by cost concerns. It should be noted that there is now a combination pill of rosuvastatin 10-40 mg + ezetimibe 10 mg that is commercially available, which can reduce pill burden. The combination of rosuvastatin with ezetimibe can confer up to 60-75% reductions in LDL-C with a good safety profile (32).

In a large registry from Italy, patients who were prescribed a single pill combination (statin+ezetimibe) were 87% more likely to have high adherence to LLT compared to patients who were prescribed both pills separately (16). This advantage of a single-pill combination was seen across all age, sex, and clinical risk groups.

Statin plus PCSK9i

PCSK9i therapy using monoclonal antibodies reduces LDL-C by 50% to 60% when administered as monotherapy or when added to a baseline statin therapy (30, 31, 33). The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) (30) and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment

With Alirocumab (ODYSSEY OUTCOMES) (31) trials of PCSK9i evaluated evolocumab and alirocumab, respectively, among patients with ASCVD with baseline LDL-C ≥70 mg/dL. In these two trials, the background use of statins was high, and yet the benefit of PCSK9i was incremental to that of statins with a significant 15% reduction in MACE in both trials. In FOURIER, at baseline, nearly all patients were on background statin (69% high-intensity, 30% moderate-intensity), 5% also on ezetimibe, with mean baseline LDL-C of 92 mg/dL (30). In ODYSSEY OUTCOMES, at time of randomization 89% of patients were taking high-intensity statins and had a mean LDL-C of 92 mg/dL (31).

PCSK9i requires administration by injection once or twice a month. Access to PCSK9i had historically been challenging because of the requirement of prior authorization, high costs of the medication, and patients having LDL-C levels below the payer-specific threshold for monoclonal antibodies. However, with cost reduction, access and authorization approvals have become easier over time.

Inclisiran is a small interfering RNA that inhibits PCSK9 through a different mechanism than the aforementioned monoclonal antibodies. Based on ORION-10 and -11 trials, inclisiran was shown to confer a 45-55% reduction in LDL-C (34). Inclisiran is delivered by subcutaneous injection just twice a year, which may translate into improved adherence conferring more sustainable lower LDL-C levels, thus being particularly beneficial for young adults such as those with FH. However, the CV outcome trial (ORION-4, NCT03705234) is still ongoing. Inclisiran was recently approved by the U.S. Food and Drug Administration (FDA) in December 2021 as a treatment to be used along with diet and maximally tolerated statin therapy for adults with heterozygous FH or clinical ASCVD who require additional LDL-C lowering.

Statin plus bempedoic acid

Bempedoic acid is an oral inhibitor of the cholesterol synthesis pathway targeting adenosine triphosphate citrate lyase (ACL), an enzyme upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the target of statin therapy (35). Bempedoic acid has been approved by the FDA for patients with ASCVD or HeFH who require additional LDL-C lowering. Bempedoic acid is a pro-drug, and the enzyme required for its activation is only expressed in the liver and not in skeletal muscle tissue, so bempedoic acid has not been associated with muscle-related adverse side effects that have been described with statins (36). This makes it a potentially attractive oral option for patients with statin intolerance, but has been demonstrated to further reduce LDL-C even on top of statin therapy. Bempedoic acid should not be used with simvastatin doses greater than 20 mg or pravastatin doses greater than 40 mg.

The CLEAR Wisdom trial enrolled adults at high ASCVD risk with LDL-C level ≥70 mg/dL on maximally tolerated lipid-lowering therapy and showed that bempedoic acid conferred an additional 15% reduction in LDL-C (37). Furthermore, the CLEAR Serenity trial examined bempedoic acid in patients with statin-intolerance and showed a greater reduction in LDL-C of 21% compared to placebo (38). Reductions in LDL-C are even greater in combination with ezetimibe. In a trial evaluated a fixed-dose combination (bempedoic acid 180 mg/ezetimibe 10 mg once daily) or placebo added to stable background statin therapy, the fixed-dose combination reduced LDL-C by 36% (39). These data suggest that bempedoic acid and ezetimibe are more effective when used together, and this fixed-dose combination may be an attractive option to reduce overall pill burden for patients (40). Additionally, across all these trials, bempedoic acid has been consistently shown to reduce high sensitivity C-reactive protein (hsCRP) as well (35, 39). The CV outcome trial for bempedoic acid is on-going (CLEAR OUTCOMES, NCT02993406); this trial enrolled patients who are at high risk for ASCVD but who are statin-intolerant, with approximately 50% of participants being women.

Other oral combinations

Bile acid sequestrants are oral agents that can lower LDL-C by about 15-20% (41). However, bile acid sequestrants can raise triglyceride levels, cause gastrointestinal side effects such as constipation, and block absorption of other medications, thereby limiting their contemporary widespread use. Similarly, niacin has also fallen out of favor due to adverse side effects, and the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial did not demonstrate any benefits of the addition of niacin to a background of statin therapy for further MACE lowering (42).

Conclusions

LDL-C plays a central role in ASCVD development and its progression. It is the magnitude of LDL-C lowering (and not the drug class per se) that is associated with reduced risk of ASCVD outcomes. Since the anticipated degree of LDL-C lowering is established for each specific drug class, and based on an individual's baseline LDL-C and clinical risk profile, it can be predicted from the onset which high-risk patients would likely require combination therapy to achieve the newly recommended more intensive LDL-C levels of <55 mg/dL and <70 mg/dL. Commonly, statin monotherapy is initiated first. However, given substantial clinical inertia, LLT titration and intensification have been demonstrated to be poor in real world practice and LDL-C targets are not met in a substantial number of high-risk patients. One can get to LDL-C goals quicker and more efficiently with early implementation of combined therapies. Fixed dose combination single-pill therapies where available (i.e., the rosuvastatin+ezetimibe and the bempedoic acid+ezetimibe preparations) maybe attractive options for patients who desire to reduce overall pill count. With PCSK9i administered just once or twice a month and inclisiran administered just twice a year, this further can help achieve intensive LDL-C lowering with reduced burden of a daily medication. For patients at high- or very-high CV risk, combination LLT is better together and anticipated to further reduce ASCVD morbidity and mortality in high-risk populations.

Disclosures/Conflicts of Interest

EM reports Advisory Boards for NovoNordisk, Novartis, Astra Zeneca, Amarin, Bayer, Boehringer Ingelheim and Esperion.

KCF reports being consultant for Amgen, Novartis, Medtronic

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Ethical review

As this article was a literature review of published papers and did not involve enrollment of study participants, no ethical review board approval was required.

Authorship Roles

The concept and design for paper was by EDM and KCF. EDM drafted the first draft and KCF provided critical input to the manuscript draft for intellectual content and approved final document.

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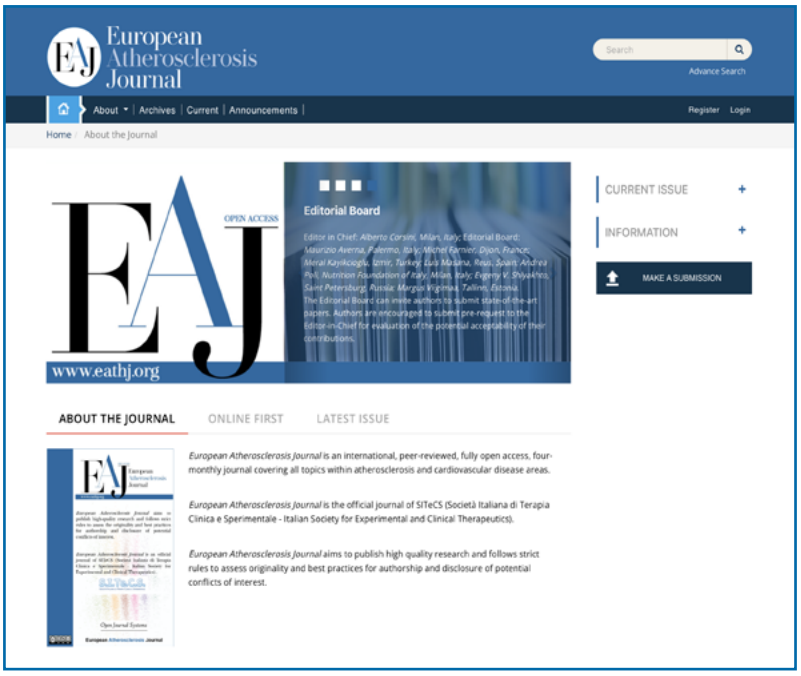

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