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Lipid lowering combination therapy: From prevention to atherosclerosis plaque treatment

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ABSTRACT

Statins have contributed to the prevention of numerous atherosclerotic cardiovascular (CV) events and cardiovascular deaths in the past three decades. The benefit of statins is mainly mediated by the lowering of LDLc. According to scientific evidence, the current international guidelines recommend very low LDLc goals in patients at high/very high cardiovascular risk because they are associated with fewer CV events and improvements in atherosclerotic plaques. However, these goals often cannot be obtained with statins alone. Recent RCTs have demonstrated that these CV benefits can also be obtained with nonstatin LDLc-lowering drugs such as PCSK9 inhibitors (alirocumab and evolocumab), ezetimibe and bempedoic acid, while evidence with inclisiran is upcoming. Icosapent ethyl, a lipid metabolism modifier, has also shown an effect on event reduction. Physicians should take advantage of the currently available lipid-lowering therapies, choosing the drug or combination of drugs that is most appropriate for each patient according to his or her CV risk and baseline LDLc concentration. Strategies implementing combination therapies from early stages or even from the outset may increase the number of patients attaining LDLc goals, thereby preventing new CV episodes and improving existing atherosclerotic lesions.

1. Introduction

Statins have contributed to the prevention of numerous atherosclerotic cardiovascular (CV) events and cardiovascular deaths in the past three decades. Despite its critical role in cardiovascular event prevention, heart disease remains one of the world's leading causes of death. Data from the European Society of Cardiology show that one in three women and one in four men die of ischaemic heart disease or stroke, more than all types of cancer combined [1]. A significant number of randomized controlled trials (RCTs) have shown that lowering circulating LDL cholesterol (LDLc) is associated with reductions in the relative (RR) and absolute risk of cardiovascular diseases (CVDs). Each mmol/L reduction in LDLc is associated with a RR reduction of approximately 22 % [2]. Recent studies have shown that this association is maintained up to very low levels of LDLc. In fact, a floor profit level has not yet been identified [3]. Based on this scientific evidence, current international guidelines recommend very demanding low LDLc concentrations that generally cannot be obtained with statin monotherapy. On the other hand, a benefit similar to that obtained with statins has been achieved by nonstatin therapies. Data from the Improve-it trial with ezetimibe and the Fourier and Odyssey Outcomes trials with evolocumab and alirocumab added-on the highest tolerated statin dose, and the Clear Outcomes with bempedoic acid in statin-intolerant patients, demonstrate a similar incremental benefit of lowering LDL with these nonstatin therapies [4–7]. These data have raised the following questions: What is the incremental benefit of LDLc-lowering combination therapies? What is the rationale for their use? When and how should they be prescribed? To what values should we lower LDLc?

2. Why should lipid-lowering combination therapy be used?

As mentioned above, evidence from a large number of RCTs strongly

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supports a dose-dependent association between LDLc lowering and CV event risk reduction [2]. The progressive achievement of lower LDLc values in the intervention groups led to current LDLc goals recommendations included in the international clinical guidelines [8]. Data from the Prove-it [9] and TNT [10] were the basis for a reduction in the LDLc goal recommendation from 100 mg/dl to 70 mg/dl in secondary prevention patients. In the last years, the Improve-it, Fourier and Odyssey Outcomes trials have demonstrated that achieving an LDLc below 55 mg/dl is associated with an incremental benefit. Consequently, more recent guidelines recommend this value as the optimal goal of lipid-lowering therapy [11,12]. Recent data from a long-term extension of the Fourier study have confirmed that attaining extremely low LDLc levels is associated with even better results [13].

Interestingly, the achievement of these very low LDLc levels is safe and not associated with any increase in side effects, including neurocognitive alterations, cancer, new-onset diabetes or haemorrhagic stroke, to mention those of major concern. The reasons for the apparent safety of low LDLc concentrations are complex. Among them, it should be noted that statins, ezetimibe, PCSK9 inhibitors and bempedoic acid reduce LDLc by increasing the catabolic rate of the particle through its physiological LDL receptor pathway, so they do not alter the supply of intracellular cholesterol; furthermore, all tissues can synthesize cholesterol in the event of a shortage of supply.

The pathophysiological explanation for the lack of adverse events with extremely low LDLc concentrations has been extensively reviewed [14].

To achieve these very demanding low LDLc levels combination therapies are mandatory because these goals can rarely be achieved with statins alone. However, there is doubt about the efficacy of nonstatin drugs in reducing vascular events.

In the statin era, several nonstatin pharmacological approaches to improve CV event prevention by modulating lipoprotein metabolism failed to show additional benefit. This is the case for cholesterol ester transfer protein (CETP) inhibitors [15–17], niacin [18,19] and even fibrates [20,21]. The recent data from the Prominent study using pemafibrate in diabetic patients have confirmed the futility of these therapies [22].

The data from Improve-it, Fourier, Odyssey Outcomes and Clear Outcomes trials have shown the CV benefit of LDLc lowering by nonstatin therapies, supporting the causal role of LDLc in atherosclerosis development.

The causality of LDL in the process of atherosclerotic lesion development is beyond any doubt. There are excellent and comprehensive reviews on the scientific evidence of LDL atherosclerosis causality [23,24]. LDL-lowering therapies stop the artery wall damage and progression of atherosclerotic plaques, allowing the action of healing mechanisms, stopping the inflammatory response, cleaning molecular and cell debris and reducing the atheroma volume, resulting in plaque regression [25,26]. Thus, the combination of statin and non-statin therapies work synergistically to lower LDL in other words, tackling the aetiology of atherosclerosis.

2.1. *What about icosapent ethyl?*

The Reduce-it trial showed that 2 g/bid icosapent ethyl (IPE) added to optimized statin therapy in patients with atherosclerotic (or high-risk) CVD and high triglycerides reduced the number of cardiovascular events by 25 % [27]. These results contrast with those of the Strength study which show no CV effects of a mixture of IPE and docosahexaenoic acid (DHA) [28]. Despite the controversy over the biological properties of IPE and DHA and the confounding effect of the mineral oil used as a placebo in the Reduce-it trial, the overall evidence is strong enough to support a beneficial effect of IPE in the prevention of CVD. Importantly, the results were independent of changes in the concentration of triglycerides and lipoproteins; therefore, IPE cannot be considered a lipid-lowering drug but rather a lipid modulator. Although the mechanisms of action have not been fully demonstrated, metabolic changes in lipid pathways and the lipid composition of cell membranes leading to improved endothelial function and anti-inflammatory, antiplatelet, and antioxidant effects should be considered [29]. Therefore, the combination of lipid-lowering drugs with high doses of IPE should be considered in therapeutic strategies aimed at CVD prevention.

3. Intense LDLc lowering: from cardiovascular prevention to the treatment of atherosclerotic lesions

The reduction of circulating LDLc prevents the development of new atherosclerotic lesions and the progression of existing plaques and leading to their regression. The impact of lipid-lowering therapies on atherosclerosis progression is directly related to the LDLc lowering [30]. For more than 3 decades, different research approaches based on lesion imaging techniques have investigated the possibility of atherosclerosis lesion regression in humans. The first imaging approach was the study of coronary angiograms before and after a lipid-lowering intervention. Several studies demonstrated that coronary stenosis due to arteriosclerotic plaques was reduced, albeit to a limited extend, by LDLc-lowering therapies [31]. However, coronary lumen stenosis is not a good marker of plaque size. Seymour Glagov demonstrated that plaques of remarkable size can be present in the artery with minimum lumen disturbance due to eccentric remodelling of the arterial walls [32]. The implementation of intravascular ultrasound (IVUS) techniques changed the paradigm of in vivo arteriosclerotic lesion evaluation. Many studies have shown that LDLc lowering can stop plaque progression and reduce plaque volume [30,33,34]; in other words, it leads to plaque regression. Findings from IVUS virtual histology studies suggest that the modifications in the artery wall are mediated by composition changes lead by an increase in the thickness of the fibrous cap and reduction in the size of the necrotic core of the lesion [35].

As mentioned above, the effect of statins on plaques is dose dependent. Data from different IVUS studies testing the vascular effect of statins defined a threshold of 70 mg/dl LDLc as the starting point for the regression [30]. More recently, nonstatin lipid-lowering therapies and new imaging techniques have confirmed the effect of LDLc reduction on plaque lesions. The Glagov study showed the incremental effect of evolocumab on arteriosclerotic plaque regression assessed by IVUS [30]. The plaque regression rate was directly associated with the achieved LDLc value, and the association linearity was maintained until extremely low LDLc values.

Recently, two important imaging studies, Pacman-AMI using alirocumab and Huygens using evolocumab, have provided new insights into arteriosclerotic lesion regression [36,37]. In the Pacman-AMI study, patients with a previous AMI were randomized to receive either alirocumab 150 mg subcutaneously twice a month or placebo. The participants underwent a comprehensive intravascular imaging assessment of nonculprit coronary lesions, including IVUS, near-infrared spectroscopy (NIRS) and optical coherence tomography (OCT), before and after therapy. The mean LDLc level obtained in the active therapy arm of the study was 24 mg/dl, whereas that obtained in the placebo arm was 75 mg/dl. This difference was associated with a decrease in the total plaque volume, an important reduction in the lipid core, and an increase in the thickness of the fibrotic cap of the lesion leading to a smaller and more stable plaque [36]. The Huygens study using evolocumab showed similar results. The patients in the active arm achieved a mean LDLc of 37 mg/dl (93 in the placebo group), which was associated with an increase in the fibrotic cap of the lesions assessed by OCT, leading to plaque stabilization. Interestingly, plaque improvement was directly associated with LDLc reduction [37].

There is robust evidence showing a causal association between intensive LDLc lowering and both CV event reduction and artery wall injury improvement.

The mechanisms involved in plaque regression have not yet been fully elucidated, but changes in the macrophage inflammatory to anti-

inflammatory phenotype and the activation of inflammation-resolving mechanisms have been proposed [25,26,29]. Interestingly, these mechanisms are elicited by lipid-lowering therapies such as statins and PCSK9 inhibitors [25].

The Evaporate study explored the effect of IPE 2 g/twice daily on coronary plaques assessed by multidetector computed tomography. In patients with acute myocardial infarction, IPE produced a significant reduction in low-attenuation coronary plaques compared with placebo [38]. Again, this effect was independent of circulating lipid concentrations. Although some concern has been raised about the possible effects of mineral oil on lesion enhancement in the placebo group, mineral oil has shown a similar effect on plaque progression as non-mineral oil placebo [39]. Consistent with the Reduce-it results, these data support the use of high-dose IPE in combination with lipid-lowering therapies in selected patients.

In conclusion, with these therapies, we are not just preventing the disease but also treating it by modifying its progression. We should change our approach and think that LDLc intensive reduction is not only a prevention strategy but also a chronic therapy for atherosclerosis.

In patients who have already had an event, therapy should also be directed at treating the arterial lesion, and lipid-lowering combination therapy is mandatory to achieve the lowest possible LDLc. (Fig. 1).

4. Scientific evidence reinforcing the use of oral and subcutaneous combination therapy

The use of cholesterol-lowering combination therapy, both oral (statins, ezetimibe and bempedoic acid) and subcutaneous (adding PCSK9 inhibitors), is widely supported by scientific evidence [4–7]). Moreover, the combination of IPE and statins in high-risk patients with elevated triglycerides is also supported by scientific evidence provided by the Reduce-it study [27] (Fig. 2).

The Improve-it study showed that simvastatin and ezetimibe reduced the number of cardiovascular events compared to simvastatin monotherapy. The RR reduction of about 7 % was in line with the incremental LDLc lowering of 16 mg/dl (0.4 mmol/L) obtained according to the Cholesterol Treatment Trialists Collaboration meta-analyses. In the Fourier and Odyssey OT trials, the combination of high-intensity statins and evolocumab or alirocumab reduced the number of major CV events by 15 % in approximately 2 years, in intensively previously treated patients with a mean baseline LDLc of 90 mg/dL after achieving mean

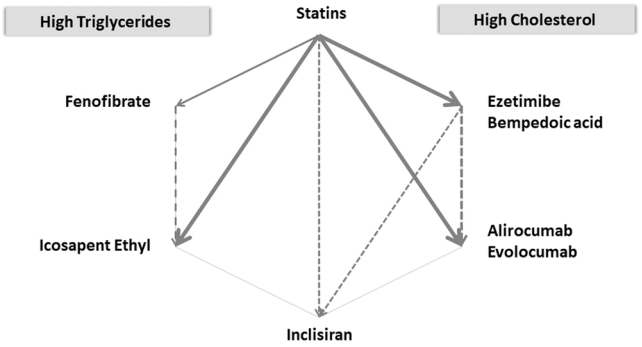

Fig. 2. (two columns), Lipid-lowering combination therapies. Thick arrows indicate that scientific evidence supports its effect on CV event reduction. Bempedoic acid evidence obtained in statin intolerant patients. Thin arrows indicate that scientific evidence is based on post hoc analyses. Discontinuous arrows indicate that evidence is limited to LDLc reduction.

LDLc concentrations of 30 and 54 mg/dl (0.8 and 1.4 mmol/L) respectively. Inclisiran, a small interfering RNA designed to block PCSK9 synthesis, has also shown an impact on LDLc concentrations and the effect on CV events is ongoing [40]. The Clear outcomes study showed that bempedoic acid, an ATP citrate lyase inhibitor, that blocks cholesterol synthesis upstream of the same pathway than statins, reduced LDLc by 21 % and CV events by 13 % in statin-intolerant patients [7].

The Treat to Target project has provided a unique piece of evidence for the use of combination therapy [41]. In this study, approximately 3000 patients with a history of ischaemic stroke or ischaemic transitory accident (ITA) were randomized to be treated to obtain an LDLc below 70 mg/dl or between 90 and 110 mg/dl regardless of the therapy used to achieve these objectives. The group with the lower LDLc goal had a 30 % reduction in the primary endpoint (five components' MACEs). Interesting, to achieve these LDLc goals, the physicians used statins in monotherapy in 93 % of the patients in the higher cholesterol arm, but 40 % of the patients in the lower LDLc arm received oral combination therapy (statin plus ezetimibe). Regarding the statin plus ezetimibe combination, recent data demonstrate that both lipid objectives and cardiovascular prevention are more frequently obtained by combination

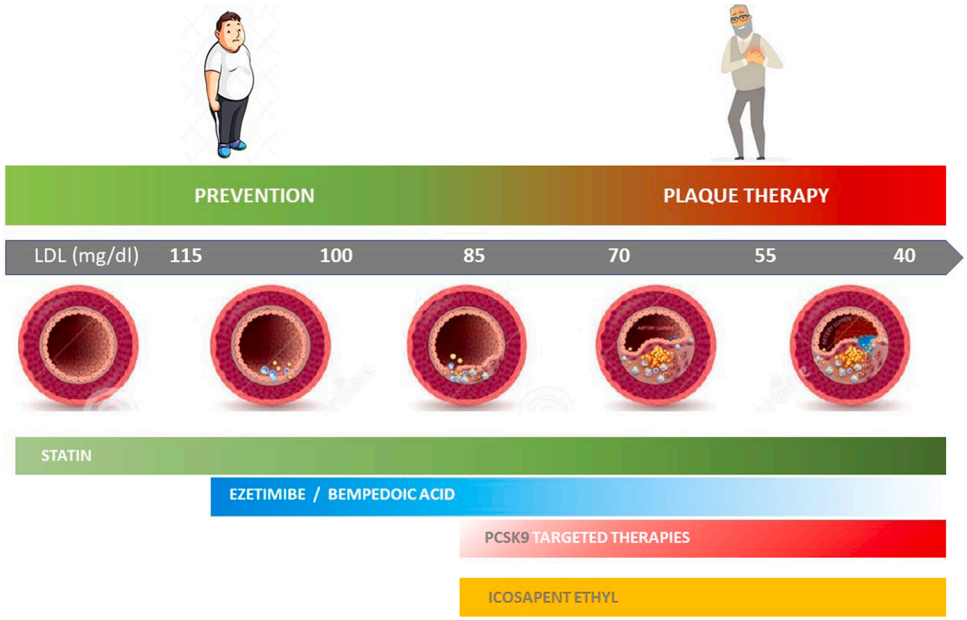

Fig. 1. (Color, two columns), Combination therapy indications. Lipid-lowering combination therapy from the prevention to the treatment of atherosclerotic plaques.

therapy and particularly by fixed-dose combination therapy [42,43]. Even a moderate statin dose combined with ezetimibe has a more efficient effect on LDLc levels and is noninferior in CV event prevention than high-intensity statin monotherapy [44].

As previously mentioned, the combination of statins plus IPE has also shown a significant reduction in the number of CV events. The Reduce-it trial demonstrated that 2 g bid of IPE reduces the number of new cardiovascular events by approximately 25 % in patients with optimized lipid-lowering therapy with triglycerides higher than 150 mg/dl and a history of a major CV event or diabetes plus one additional risk factor. The robustness of the Reduce-it results has led to guideline recommendations for the use of IPE in high-/very high-risk patients with triglyceride levels greater than 150 mg/dl.

5. Lipid-lowering combination therapy in special clinical settings

There are clinical situations associated with dyslipidaemia and increased cardiovascular risk needing specific therapy approaches. Patients with chronic inflammatory/autoimmune disease, chronic viral infection, organ transplant or cancer, among others, can develop severe dyslipidaemia, increasing their cardiovascular risk [11]. Moreover, the complex therapies of these clinical situations can lead to drug-to-drug interactions.

Choosing a low dose of a statin with a low interaction profile (pravastatin, rosuvastatin) [45] combined with ezetimibe is generally a good option.

Hyperlipoprotein (a) (Lp(a)) syndrome is associated with increased CV event risk. Statins are recommended in these patients even in primary prevention [46]. However, statins can increase Lp(a) with an effect that is dose- and intensity-dependent [47]. In these cases, combination therapy with an intermediate dose of statin and ezetimibe, addressed to maintain LDLc efficiency with a lower statin dose, could be considered.

Homozygous familial hypercholesterolemia (HoFH) is an extremely severe rare disease. The treatment of HoFH is out of the scope of this review. All these patients must be on special combined lipid-lowering therapies. HoFH patients have a severe disruption of the LDL-LDL receptor (LDLR) pathway; therefore, drugs that increase LDLR function, such as statins, ezetimibe, bempedoic acid and PCSK9-targeted therapies, are inefficient. LDLR-independent lipid-lowering treatments such as LDL apheresis should be applied. Recently, lomitapide and evinacumab have shown efficacy in HoFH patients. Lomitapide blocks the microsomal triglyceride transfer protein (MTP) that binds triglycerides and Apo B:100 to form VLDL in the liver or Apo B:48 in enterocytes to produce chylomicrons. Lomitapide decreases the amount of lipoprotein released into the bloodstream, halving the LDLc in HoFH patients [48,49]. Because fat secretion from the liver is reduced, close monitoring of liver fat is mandatory. Evinacumab blocks the action of angiopoietin-like 3 (ANGPTL-3), which is an inhibitor of lipoprotein and endothelial lipases. Individuals with lack-of-function mutations of the ANGPTL-3 gene have lower levels of all lipoproteins. Given intravenously once a month, evinacumab (anti ANGPTL-3 monoclonal antibody) decreases LDLc by more than 50 % [50,51] in HoFH patients. All HoFH patients must be on combination therapy, including lomitapide and/or evinacumab, along with LDL apheresis if necessary.

6. Efficacy and safety of LDLc-lowering combination therapy

The LDLc-lowering efficacy of lipid-lowering therapies, both monotherapy and combination therapy, is conditioned by important individual variations; however, an average effect can be predicted according to the available clinical data and mathematical models. An approach to the efficacy of available lipid lowering drugs and their combinations was reported in the EAS 2019 guidelines [11]. Toth et al. recently communicated the results of a meta-analysis showing the mean LDLc changes of nonstatin lipid-lowering drugs [52]. Knowledge of the efficacy of statin plus nonstatin therapies allows the planning of therapy according to CV event risk and baseline LDLc values to attain the goals [11,52]. Both combination therapies and living with very low LDLc concentrations are safe. Data from randomized controlled trials show that these therapies are associated with a safety profile identical to that of placebo. No differences in neurocognitive state or the incidence of new-onset diabetes, cancer or haemorrhagic stroke, among others, were observed. This safety profile also applies to those patients achieving extremely low LDLc levels. Data from the open-level extension (OLE) of the Fourier study reinforce the safety and benefit of these lipid-lowering strategies at the long time [53–55]. In the table, we provide the average LDLc reduction that can be obtained by different lipid-lowering drugs in monotherapy and combination therapy (Table 1).

7. Strategies to implement combination therapy

Scientific evidence on LDLc-lowering therapy has been obtained in a sequential manner. Each drug was tested independently and randomly compared to placebo. Since 1994, when the Scandinavian Simvastatin Survival Study (4S) was published [56], the inclusion of a placebo arm without statins in an RCT of patients at high cardiovascular risk has been considered unethical. In the statin era, new drugs have been tested in a background of optimized statin therapy. In this context, several drug families showed no additional benefits to baseline lipid-lowering therapy, including cholesterol ester transfer protein (CETP) inhibitors, fibrates or niacin [15–22].

The Improve-it, Fourier, Odyssey OT, Clear outcomes [4–7] and more recently the Reduce-it trials [27] have demonstrated an incremental benefit of ezetimibe, evolocumab, alirocumab, bempedoic acid or IPE addition on a statin background. The international guidelines strictly follow this sequence and recommend starting always with statins and following a stepwise strategy, adding nonstatin lipid-lowering drugs sequentially if necessary [11].

However, some aspects must be considered. Repeatedly, studies such as Eurospire, Da Vinci and Santorini [57–59] show that only one-third of high-risk and very high-risk patients attain the LDLc recommended objectives. Moreover, incomprehensibly, these patients at high risk for CV events are undertreated. According to the Da Vinci study, 45 % of very high-risk patients are on low-/moderate-intensity statin monotherapy, and only 10 % are on combination therapy [60]. According to current guidelines patients at high and very high CV risk, besides achieving the LDL targets, should reduce their LDLc by 50 % that can be obtained only by the highest dose of the higher intensity statins in monotherapy, that is prescribed in less than 40 % of these patients. Moreover, the first prescribed lipid-lowering therapy is rarely uptitrated. The ACS follow-up study showed that an intensification of therapy is recommended in less than 50 % of post-ACS patients who are not on goal in the first follow-up visit [61]. A non-negligible cause of undertreatment is statin intolerance, mainly muscle pains, occurring in about 7 % of patients [62]. The Clear outcomes trial has opened a new therapy frame for statin-intolerant patients [7].

Additionally, several studies have shown that the earlier the objective is achieved, the better.

The Swedeheart study demonstrated that reducing the LDLc level by more than 1 mmol/L in the first three months after ACS results in a better prognosis than lowering it by less than 0.5 mmol/L [63]. Therefore, in high-/very high-risk patients, it seems reasonable to start sooner, probably from the beginning, with intensive combined lipid-lowering therapy. Several expert committees have recommended prescribing oral combination therapy, including statins and ezetimibe (or bempedoic acid if available) and even PCSK9 targeted therapies in high-/very-high CV event risk patients, from the outset [8,64,65]. Accordingly, in addition to the step-by-step strategy, other possibilities must be considered [11,66]. The planned therapy strategy suggests prescribing the drug or drug combination treatment based on the efficacy of the lipid-lowering drug and distance to goal. The maximized efficiency

Table 1
Theoretical efficacy of lipid-lowering treatment with monotherapy and combination therapy. Average LDLc reduction by lipid lowering monotherapy and combination therapies and baseline LDLc suitable to be reduced to the LDLc goal of 55 mg/dl (1.4 mmol/L) by different therapies.

	% Change of LDLc[a]: Mono therapy	Maximum Baseline LDL to attain 55 mg/dl[c] (1.4 mmol/L)	% Change of LDLc: Combined with MI Statin[d]	Maximum Baseline LDL to attain 55 mg/dl[c] (1.4 mmol/L)	% Change of LDLc: Combined with HI Statin[d]	Maximum Baseline LDL to attain 55 mg/dl[c] (1.4 mmol/L)	% Change of LDLc: Combined with HI Statin+ Ezetimibe[d]	Maximum Baseline LDL to attain 55 mg/dl[c] (1.4 mmol/L)	% Change of LDLc: Combined with HI Statin +Ezetimibe[d] +Bempedoic	Maximum Baseline LDL to attain 55 mg/dl[c] (1.4 mmol/L)
Moderate intensity (MI) Statin	**40**	92 (2.4)								
High intensity (HI) Statin	**50**	110 (2.8)								
Ezetimibe	**25**	73 (1.9)	**55**	122 (3.1)	**63**	149 (3.8)				
Bempedoic Ac	**23 (18)[b]**	71 (1.8)	**51**	112 (2.9)	**59**	134 (3.5)	**69**	183 (4.7)		
Bempedoic Ac +Ezetimibe	**42 (38)[b]**	89 (2.3)	**63**	149 (3.8)	**69**	177 (4.6)				
Evolocumab 140 (twice monthly)	**65**	157 (4.1)	**79**	262 (6.8	**83**	324 (8.4)	**87**	423 (10.9)	**89**	500(13)
Alirocumab 150 (twice monthly)	**62**	145 (3.7)	**77**	239 (6.2)	**81**	289 (7.5)	**85**	367 (9.5)	**88**	458(12)
Alirocumab 75 (twice monthly)	**53**	117 (3.0)	**72**	196 (5.1)	**77**	239 (6.2)	**82**	305 (7.8)	**85**	367(9.5)
Alirocumab 300 (once monthly)	**52**	115 (2.9)	**71**	190 (4.9	**76**	229 (5.9)	**82**	305 (7.8)	**85**	367(9.5)
Inclisiran (twice yearly)	**50**	110 (2.8)	**70**	183 (4.7	**75**	220 (5.7)	**81**	289 (7.5)	**85**	367(9.5)

a: % Reduction of LDLc by MI and HI statins for definition. % Reduction of LDLc by other drugs were taken from Toth P et al. (reference 52)
b: % Reduction of LDLc by Bempedoic Ac without and in combination with statins.
c: Maximum LDLc concentration at which therapy can achieve 55 mg/dl (1.4 mmol/L)
d: Efficacy of combination therapies were calculated according to the following formula: %A + %B (1−%A) + %C [1 − (%A + %B (1−%A))] where %A is the theoretical LDL-C reduction induced by drug A, %B by drug B, and %C by drug C (reference 51)

strategy consists of prescribing combination therapy with maximal lipid-lowering potency, including PCSK9 inhibitors from the beginning, in patients at extremely high risk based on the evidence that the lower the LDL, the better (Fig. 3).

In conclusion, LDLc reduction is a cornerstone of cardiovascular event prevention and plaque lesion treatment. Achieving lower LDLc levels is associated with greater cardiovascular benefit. The sooner low LDLc concentrations are obtained, the better for patients. Physicians should consider all available lipid-lowering therapies to personalize the therapy. Combination therapies should allow LDLc objectives to be

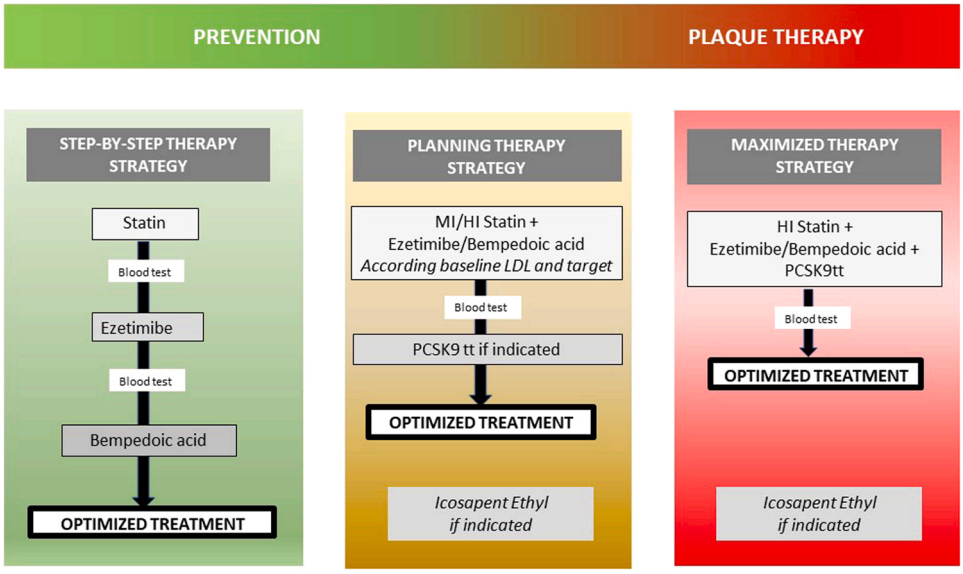

Fig. 3. Proposal of strategies for the implementation of lipid-lowering therapies according to cardiovascular event risk. (Color figure, 2 columns).

achieved in almost all patients. Lipid-lowering combination therapies should be considered the standard treatment for patients at high risk for CV events.

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CRediT authorship contribution statement

Conceptualization, L.M., D.I. Literature data collection L.M., D.I., N. P., N.A. Supervision, L.M. D.I. Writing, L.M, D.I. Review & editing, L.M., D.I., N.P., N.A. All authors approved the final version of the manuscript for submission.

Declaration of Competing Interest

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Data Availability

No data was used for the research described in the article.

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