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

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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

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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

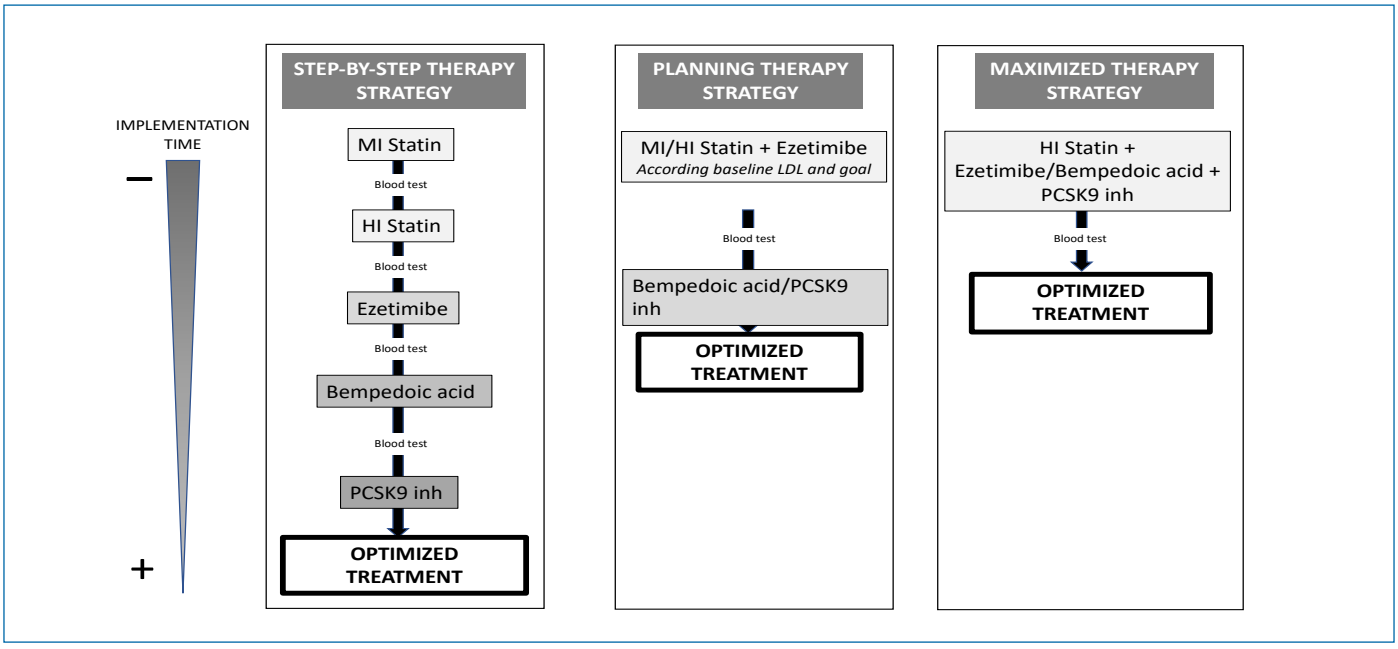

Figure 1 | Different strategies to optimize lipid-lowering therapy.

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

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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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