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Current treatment beyond statins in hypercholesterolemia: the lower the better in prevention of atherosclerotic diseases

Tratamiento actual más allá de las estatinas en la hipercolesterolemia: cuanto más bajo mejor en la prevención de las enfermedades ateroscleróticas

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INTRODUCTION

Until 2020 and the appearance of COVID-19, atherosclerotic cardiovascular disease (ASCVD) still was one of the leading causes of death worldwide. One of its most important risk factors is dyslipidemia and the associated increase in low-density lipoprotein cholesterol (LDL-c) level. Statins via their mechanism of action inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase blocking the cholesterol synthesis in the liver, lowering the low-density lipoprotein cholesterol up to 50% depending on the statin therapy intensity (moderate or high). Over the last decades, the use of statins has lowered the risk of ASCVD by 37%,[1] consequently placing statins as the first-line drug of choice in the treatment of dyslipidemia. The use of statins has demonstrated both in large randomized controlled trials and epidemiologic studies reduction in major cardiovascular events.

The American College of Cardiology and the American Heart Association 2018 guidelines recognize that with higher reductions in density lipoprotein cholesterol with statin therapy, the benefit will have a major impact on patients clinical course.[1] However, there is a group of patients with special needs and residual risk, such as those with severe primary, genetic dyslipidemias like familial hypercholesterolemia or those with intolerance or adverse reactions to statins,[2] in whom the therapy goals with high-intensity statin therapy are not met and therefore are still at risk of recurrent ASCVD.

Breakthroughs in the development of new drugs have provided alternatives such as injectable biological products, and RNA-based therapies which offer the possibility of less frequent dosage prescriptions. Among the non-statin therapies, there are two alternatives which have shown additional LDL-c levels cardiovascular eve reduction and prevention of residual risk of nts, namely ezetimibe and in the case that the therapeutic goals are not met, the anti-PCSK9 monoclonal antibodies (mabs-PCSK9).[3] The following review addresses the mechanism of action, clinical indications, and current evidence supporting the use of these drugs.

EZETIMIBE

Mechanism of action

The first known mechanism of action was to inhibit the enzyme acyl-coenzyme cholesterol acyltransferase known as ACAT, however, during its development, it was demonstrated that ezetimibe inhibits the uptake of cholesterol in the small intestine where it binds to a transporter protein identified as Niemann-Pick C1-Like 1. This protein is the only intestinal entrance

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gate for all type of sterols; so cholesterol, oxysterols and phytosterols compete to enter the enterocyte, reducing thereby cholesterol absorption. NPC1L1 proteins are not only found in the intestine but are also greatly expressed in the liver where ezetimibe, and its metabolite ezetimibe-glucuronide, reduce the reabsorption of cholesterol from bile.[4]

How does this process unfold, step-by-step? After ingestion, 80% of ezetimibe undergoes a biochemical process of glucuronidation, being the enzymes responsible for this step the intestinal glucuronosyltransferases in the liver, forming a complex ezetimibe-glucuronide which has more affinity for the NPC1L1 transporter than the original compound. Both, trough the entero-hepatic cycle. Secondarily, some phytosterols and phytostanols activate other type of membrane proteins, the ATP-binding cassettes transporters (ABCC2, ABCC3, and ABCG2) which expel the already absorbed cholesterol to the intestine lumen.

The estimated half-life of ezetimibe and its metabolite is around 22 hours.[4]

In conclusion: ezetimibe is a specific inhibitor of the cholesterol transporter found in the brush border of the enterocyte (NPC1L1). By inhibiting this transporter ezetimibe causes a decrease in the absorption of cholesterol and precipitates a decrease of decrease of serum LDL-c cholesterol. In addition, ezetimibe blocks also de liver NPC1L1, impeding the excess of biliary cholesterol *(Figure 1)*.[3,4]

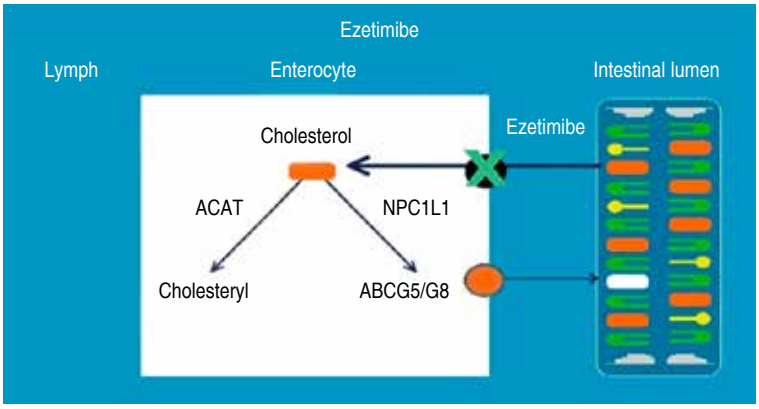

Figure 1: Mechanism of action of ezetimibe.
NCP1L1 = Niemann-Pick CIL1 protein; ABC G5 and G8, proteins of the ABC (ATP-bound cassettes) superfamily. Modified from: Lipids Online Slide Library.

Drug tolerability

Given that its main effect is exerted in the enterohepatic system, its systemic exposition is limited, which leads to a low potential for adverse drug interactions.[5] Ezetimibe presents some pharmacological interactions. Its bioavailability increases when it is co-administered with gemfibrozil, fenofibrate or cyclosporine.[4] Notably, ezetimibe is a well-tolerated drug with lower intolerance and hepatic impairment rate than statins.[5]

Impact of ezetimibe in atherosclerosis: is there a difference to statins?

Ezetimibe may or may not act in different atherosclerotic pathways than statins, therefore impacting the risk of atherosclerotic cardiovascular events; the pathways involved are briefly summarized below *(Figure 2)*.

Effects in blood lipids: ezetimibe has been shown to reduce low-density lipoprotein levels up to 22.3% compared to placebo. This effect is added to the lowering action of statins, so in some studies a reduction from 35 to 60% has been shown. In addition, produce beneficial effects on high-density lipoprotein cholesterol (HDL-c), triglycerides (TG) and apolipoprotein B100.[5,6]

Effects on glucose metabolism: the beneficial effect of ezetimibe on glucose metabolism cannot be asserted, as there are no studies to prove it, emphasize that its benefit on the incidence of type 2 diabetes mellitus is not clear.[6]

Inflammation: inflammation is an important component of the process of atherogenesis. Several randomized controlled trials have investigated the effect of ezetimibe alone or in combination with statins in the reduction of high-sensitivity CRP (hs-CPR), but the available data from various meta-analyzes do not conclude a significant effect on hs-CRP levels when used as monotherapy.[5]

Platelet aggregation: even though statin therapy has been associated with reduced platelet aggregation due to their pleiotropic effects and a mechanism that is LDL independent, no such effect has been demonstrated with ezetimibe as monotherapy.[6]

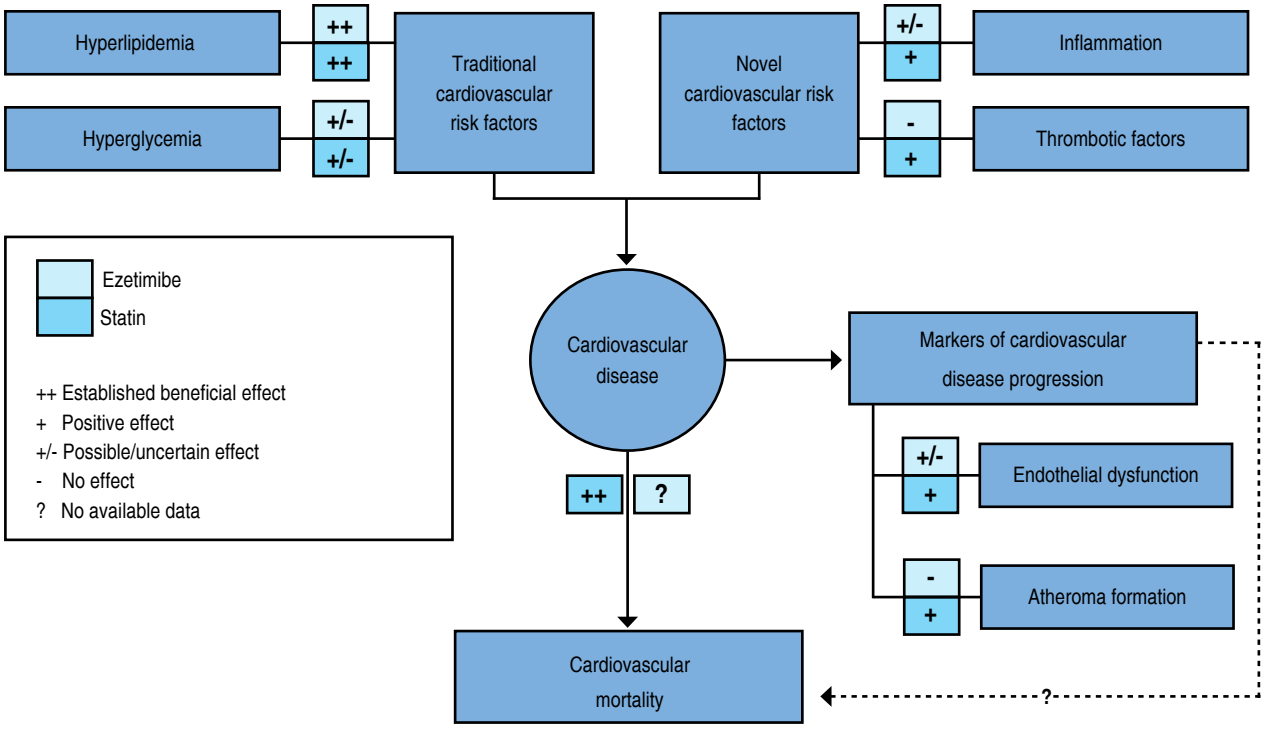

Figure 2: Established or possible cooperative actions of statins and ezetimibe to reduce CV risk. Modified from: Al Badarin FJ et al.[6]

Indications and clinical evidence

The American College of Cardiology and the American Heart Association 2018 guidelines recognize the importance of the adequate management according to individualized risk of major cardiovascular events (MACE) in patients with a history of ischemic heart disease, ischemic cerebrovascular disease or peripheral arterial disease. In these patients, low-density lipoproteins should be reduced vigorously to optimal levels. The more it is reduced the better. As an example, in a high-risk patient, the recommended therapeutic goal of proposed low-density lipoprotein levels is less than 70 mg/dL or a reduction of 50% compared to baseline.[7]

The importance of using ezetimibe or mabs-PCSK9 if therapeutic goals of LDL-C have not been reached was previously mentioned. Ezetimibe, has specific indications for the reduction of total cholesterol (TC), low-density lipoproteins, and apolipoprotein B, in the following scenarios: primary hyperlipidemia, either alone or in combination with statins, mixed hyperlipidemia when co-administered with fenofibrate, and homozygous familial hypercholesterolemia co-administered with statins, in order to reduce total cholesterol and low-density lipoproteins.[5] The suggested dose, which is 10 mg/day, should be prescribed, with the advantage that it can be administered at any time since it has no direct effect on statin potency or metabolism. The patient should be followed every three to six months *(Table 1)*.[8]

PROPROTEIN CONVERTASE SUBTILISIN/ KEXIN TYPE 9 INHIBITORS

Mechanism of action. The role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in the metabolism of LDL-C was discovered after identifying a gain of function in mutations in PCSK9 in some French families with familial hypercholesterolemia, while mutations in other genes had previously been ruled out.[9,10] Posteriorly, other investigators showed that subjects carrying PCSK9 loss-of-function (LOF)

mutations, after discarding the inhibition in the synthesis and/or the absorption of cholesterol as the determinant factors, reduced LDL-C levels, with a lower rate of cardiovascular events.[11] All of these evidences were the basis for investigations on a potential pathway for efficient therapies to further reduce the LDL-C levels, beyond the currently used therapies.[9]

Step-by-step mechanism of action. LDL-C receptors (LDL-R) are synthesized mainly in the liver. The synthesis is regulated by the transcription factor SREBP2 dependent on the intracellular levels of cholesterol (less intracellular cholesterol yields to more SREBP2 transcription, more LDL-R units, more, and less blood cholesterol levels. After its synthesis, the LDL-R is inserted in the hepatocyte cell surface where it captures LDL-C particles and internalizes them forming an endosome. Lastly, the endosome will fuse with lysosomes, whose enzymes degrade LDL-c particles. The LDL-R withstands the enzymatic action of degradation and is recycled to the cellular surface. This recycling process can occur up to 150 times in 24 hours.

What is the role of the PCSK9? The PCSK9 protein is released into the circulation after being synthetized in the liver and the intestine, it is also regulated by the SREBP2 factor transcription. PCSK9 account as a counter-regulatory protein

Table 1: Summary the main clinical studies that evaluated combined therapy with ezetimibe and statin vs statin alone.

Study	ENHANCE (2008) Phase III	SHARP (2011) Phase III	IMPROVE-IT (2015) Phase III
Intervention	Simvastatin 80 mg daily or a combination of simvastatin 80 mg + ezetimibe 10 mg daily	Simvastatin 20 mg vs ezetimibe/ simvastatin 10 mg/20 mg	Simvastatin 40 mg vs ezetimibe/ simvastatin 10 mg/40 mg
Patient population	720 patients with familial hypercholesterolemia and LDL-C ≥ 210 mg/dL	9,270 patients with chronic kidney disease with no known history of myocardial infarction or coronary revascularisation	18,144 patients hospitalized in the last 10 days for an ACS, who were 50 years or older, low-density lipoprotein levels between 50 and 100 mg/dL if they received lipid-lowering therapy or 50 to 125 mg/dL if they did not receive lipid-lowering therapy
Duration	24 months	4.9 years	6 years
Primary endpoint	Increase in carotid intima-media thickness (cIMT)	Major vascular events (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure) and progression to ESRD (in nondialysis patients)	Composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥ 30 days after randomization), or nonfatal stroke
Results	Change in the cIMT was 0.0058 ± 0.0037 mm in the simvastatin-only group and 0.0111 ± 0.0038 mm in the combined-therapy group	Combined therapy produced a 17% proportional reduction in major atherosclerotic events (11.3% simvastatin plus ezetimibe vs 13·4% placebo; rate ratio [RR] 0·83, 95% CI 0·74-0·94; log-rank p = 0.0021)	Rate for the primary end point at 7 years was 32.7% in the simvastatin-ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; p = 0.016)

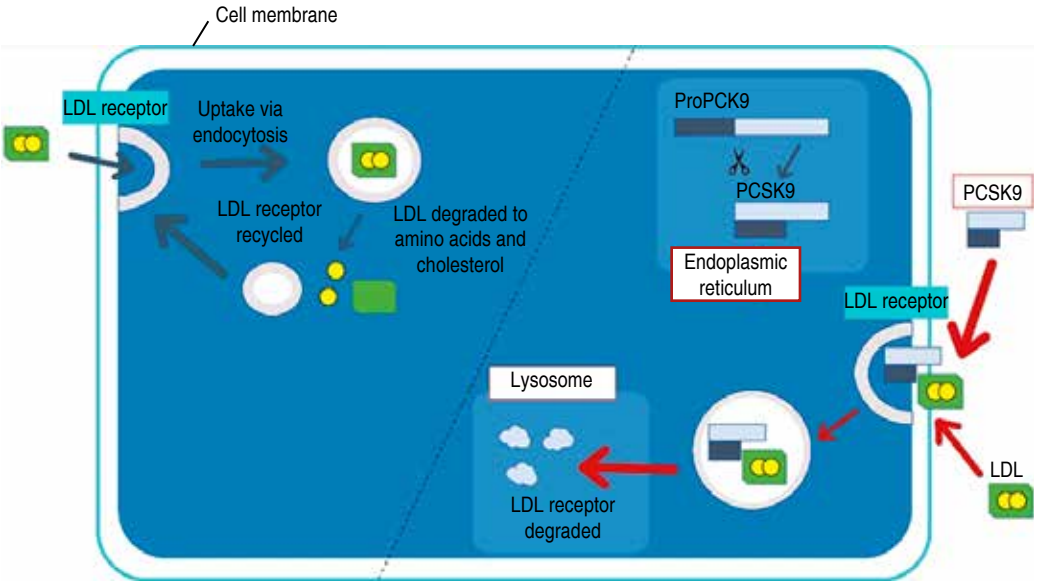

Figure 3:

Mechanisms of action of PCSK9 inhibitors. Modified from: Ogura M.[11]

(Ying-Yang), by preventing the excess of intracellular cholesterol and its potential cytotoxic effects, due to the increased LDL-R synthesis and expression, by means of maintaining the LDL-R levels controlled and constant. After being released, PCSK9 binds to LDL-R and prevents the receptor from adopting its spatial configuration necessary to avoid degradation *(Figure 3)*.

The result is that the number of LDL-R diminishes, and by doing so, the capacity of the liver of clearing circulating LDL particles. PCSK9 inhibitors are produced with the replacement of genomic sequences between mice and humans. First, the genomic sequences that encode the synthesis of immunoglobulins are eliminated in the mouse and these are replaced by human genomic sequences; in this way, MABs-PCSK9i (complete human monoclonal antibodies) are produced, «the mouse produce full human immunoglobulins» with the advantage that an immune response is not generated from the human host to neutralize its effects. The MABs-PCSK9i while in the plasma avoid the PCSK9 union to the LDL-R, blocking its effects on the receptor and its recycling. Therefore the receptor can extend its biological cycle resulting in increased concentration of LDL-R in the cell surface, producing a better internalization capacity of LDL particles, and more degradation of LDL particles, finally decreasing the LDL-c blood levels.[12]

Security and tolerability

Currently, there are two MABs-PCSK9i, alirocumab and evolocumab both of which are human monoclonal antibodies. Both drugs are safe and minimal adverse reactions have been reported, including some very common such as injection site pain and nasopharyngitis. Interestingly, the risk of myalgias or muscular toxicity is low, thus making them an excellent option when there is a history of statin-associated myopathy. Also, no statistical significance has been found regarding neurocognitive disorders (delirium, dementia, amnesic conditions, or cognitive alterations), even with very low LDL cholesterol levels.[13]

Clinical evidence

Several large randomized, controlled trials have studied the use of MABs-PCSK9, among which the most important is the FOURIER trial, in which more than 27,000 patients with atherosclerotic cardiovascular disease and low-density lipoprotein levels outside of adequate or optimal ranges despite high-intensity statin treatment, were randomly assigned to a PCSK9 inhibitor (evolocumab) or placebo. The other important trial is ODYSSEY study. Outcomes which confirmed

the benefit of alirocumab in reducing the risk of atherosclerotic cardiovascular disease *(Table 2)*.

Indications and therapeutic algorithm

The European Society of Cardiology 2019's update guidelines, suggest that patients with high cardiovascular risk should achieve blood LDL cholesterol levels in the blood of 70 mg/dl, but there is in a group of patients with a higher risk known as very high risk, even further reductions are recommended (55 mg/dL or less). Therefore, to achieve these very challenging goals, the great majority of patients will require the addition of potent pharmacological agents.

According to the European Society of Cardiology (ECS), patients can be classified according to their risk of major cardiovascular events, emphasizing two determining groups: high risk and very high risk. Each group different characteristics, thus, high-risk patients are those with a SCORE qualification between 5% and 10%, TC ≥ 310 mg/dL, LDL-c ≥ 190 mg/dL, blood pressure ≥ 180 mg/dL, chronic kidney disease with glomerular filtration rate between 30 and 59 mL/min and diabetic patients without damage to target organs, or more than 10 years after diagnosis. Finally, there are included patients with familial hypercholesterolemia without other major risk.

The other group of patients are those at very high risk, who present a risk SCORE greater ≥ 10%, familial hypercholesterolemia but with significant risk factors, chronic kidney disease with a glomerular filtration rate less than 30 mL/min, diabetics with damage to target organs or type 1 diabetics lasting more than 20 years. Obviously, all of these are characteristics that suggest a very high risk of cardiovascular events, so control must be optimal.[9]

In general, the indications by the ESC suggested that the use of PCSK9i can be divided into primary and secondary prevention: all patients with a very high risk, in the context of primary prevention, without a history of familial hypercholesterolemia, whom do not reach the goal of LDL cholesterol with statins at the maximum tolerated dose plus ezetimibe, adding a PCSK9 inhibitor may be considered.

Table 2: Main clinical studies that evaluated therapy with PCSK9i.

Study	FOURIER (2017)	ODYSSEY outcomes (2018)
Intervention and design	Evolocumab (either 140 mg every 2 weeks or 420 mg monthly) vs placebo 1:1 randomization with 69% px in high-intensity therapy, 31% moderate or low-intensity, and 5% ezetimibe	Alirocumab subcutaneously 75 mg every 2 weeks vs placebo 1:1 randomization with 89% px in high-intensity therapy, 8% moderate or low-intensity, and 3% ezetimibe
Patient population	27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg/dL or higher who were receiving statin therapy	18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, who were previously under optimal tolerated treatment with high-intensity statins, but with serum levels of non-HDL cholesterol of at least 100 mg/dL, apolipoprotein B of at least 80 mg/dL, or LDL cholesterol of at least 70 mg/dL
Duration	2.2 years	2.8 years
Median cholesterol baseline value	92 mg/dL	92 ± 31 mg per deciliter
Primary endpoint	Composite of cardiovascular death, myocardial infarction, stroke, unstable angina that requires hospitalization, or coronary revascularization	Composite of cardiovascular death, non-fatal myocardial infarction, fatal or nonfatal ischemic stroke, angina that requires hospitalization
Results	Evolocumab treatment significantly reduced the risk of the primary end point from 11.3% to 9.8% (hazard ratio 0.85; 95% CI; $p < 0.001$)	Alirocumab treatment reduced the risk of composite primary end-point event from 11.1% to 9.5% (HR 0.85; 95% CI, 0.78 to 0.93; $p < 0.001$)

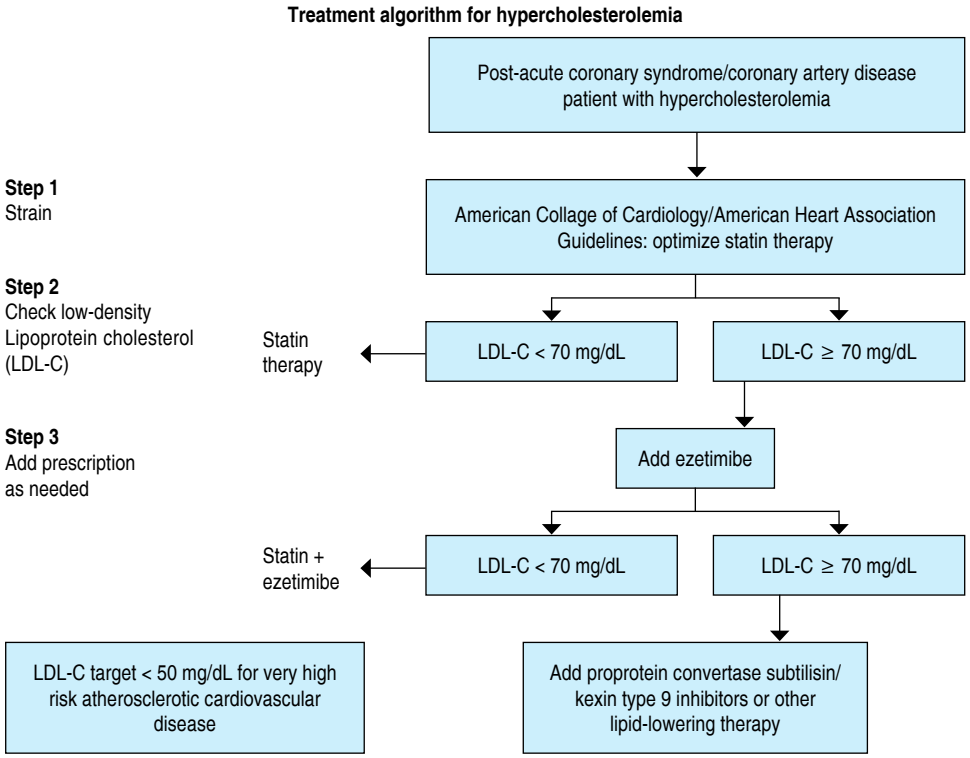

Figure 4:

An algorithm for the treatment of hypercholesterolemia. Modified from Rosenson et al.[9]

However, the indication is even stronger in the context of secondary prevention, since it is highly recommended to add a combination with PCSK9 inhibitor in high risk patients who do not achieve objectives despite the use of statins at the maximum tolerated dose plus ezetimibe. In the setting of patients with documented familial hypercholesterolemia, the combination of a PCSK9 inhibitor is also recommended in case the goals with statins plus ezetimibe at the maximum tolerated dose are not achieved. In case the patient does not tolerate a statin regimen at any dose, should be considered the use of a PCSK9 inhibitor.[9]

Finally, we have the following scenario: high-risk patients with acute coronary syndrome, the ESC recommends with a high level of evidence to add a PCSK9 inhibitor if the therapeutic goals of LDL cholesterol are not reached at four or six weeks with statins at the maximum tolerated dose plus ezetimibe. The level of evidence is lower in patients with acute coronary syndrome, who were already taking a maximum tolerated dose of statin plus ezetimibe, but who did not have optimal LDL cholesterol levels at the time of the event, in this scenario we should considered adding a PCSK9 inhibitor early during hospitalization.[9]

Figure 4 describes the level of evidence and therapeutic algorithm suggested by current 2018 guidelines by the American College of Cardiology and American Heart Association and the European Society of Cardiology 2019's update.[14,15]

CONCLUSIONS

In conclusion, despite the use of statins and their benefits, reducing the rate of ASCVD, the concept of residual atherosclerotic risk is very important in a specific group of patients who cannot achieve therapeutic goals of LDL-c, even with the maximum dosage of statins, or who are intolerant to them. In those patients, both; ezetimibe and MABs-PCSK9 have sufficient evidence that justifies their use and ultimately demonstrates their importance in reducing significantly atherosclerotic cardiac events, making these drug classes an excellent therapeutic option in addition to their tolerability and security.

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