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Scientific rationale for the evolution of LDL-c goals

Racionalidad científica para la evolución de las metas de LDL-c

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INTRODUCTION

Dyslipidemia is a public health problem in Mexico. Its prevalence is very high, and most cases are not detected or treated. This favors the development of atherosclerosis and its organic complications such as myocardial infarction (IM) and ischemic stroke, two of the main causes of loss of years of productive life, disability, premature death, and high economic and social costs. The data from the 2012 National Health and Nutrition Survey are worrying; 87% of the patients were unaware of their cholesterol level and only 3% were diagnosed, treated and in control. This explains why the burden of cardiovascular disease in our population is very large and constantly increasing. Ischemic heart disease and cerebrovascular disease, closely linked to atherosclerosis, are among the leading causes of death in our country. An additional, continuous, and coordinated effort is required to adequately detect and treat patients, reduce the burden of atherosclerosis, and strengthen the health of our population.[1]

DYSLIPIDEMIA CAUSES ATHEROSCLEROSIS

Dyslipidemia is a heterogeneous group of diseases with a genetic background, which develop because of inadequate diet, sedentary lifestyle, and smoking, and which are frequently associated with abdominal obesity, arterial hypertension (HT) and diabetes mellitus (DM). They begin early in life, their evolution is subclinical, and they are characterized by elevated or inadequate levels of lipids and lipoproteins in plasma that cause atherosclerosis and organic complications. Their prevalence is very high *(Table 1)*, and they are considered the most common modifiable cardiovascular risk factors in Mexico. Given its «silent» nature, screening with a complete lipid profile in every health evaluation visit is a cost-effective strategy in cardiovascular prevention.[2]

ATHEROSCLEROSIS CAUSES CHRONIC ORGANIC DISEASE

Atherosclerosis is a disease of the arterial wall secondary to a chronic and progressive inflammatory process that begins in childhood and has a long subclinical course. Its main causal factor is the high or inadequate level of cholesterol, especially that transported in low-density lipoproteins (LDL-c), although smoking, abdominal obesity, HT, and DM accelerate it through various mechanisms. The damage begins with the entry, retention, accumulation, and oxidation of LDL in the intima of the arteries. This causes inflammation, endothelial dysfunction, changes in vascular reactivity, increased platelet aggregation, and activation of processes such as apoptosis, fibrosis, and angiogenesis. With the development of atheroma plaque, there is vascular remodeling, arterial lumen is gradually reduced, and blood flow is disturbed. The consequences are ischemia and organ damage and dysfunction *(Table 2)*. The clinical course of atherosclerosis is unpredictable and various types of intervention have shown that its natural history can be modified.[3,4]

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ATHEROSCLEROSIS CAUSES ACUTE COMPLICATIONS

Atherosclerosis is a process that develops gradually over decades, although its acute complications generally occur suddenly and without previous clinical manifestations. This transition from an apparently stable to an unstable process is due to the progressive incorporation of lipids, inflammatory activity, the weakness of the fibrous layer, its increased stress, and damage to the endothelium with erosion or rupture. When this occurs, substances that activate coagulation are exposed and form the thrombus that partially or totally occludes the vascular lumen. This situation is optimally treated with reperfusion procedures, anti-ischemic, anti-thrombotic, and lipid-lowering drugs (statins), which together improve organ perfusion, accelerate tissue repair, and prevent new atherothrombotic outcomes. The rapid, significant, and sustained reduction of LDL-c, qualitatively modifies the atheroma, decreases its lipid content and inflammation, modifies macrophage activity, increases collagen content, strengthens the fibrous layer, decreases the production of thrombogenic substances, stabilizes the plate and reduces the risk of rupture. Despite this, the patient with complicated atherosclerosis continues at a very high-risk level (residual risk), for which more intensive treatment strategies have been developed with increasingly lower LDL-c goals.[5-7]

ATHEROGENIC LIPOPROTEINS

LDL is the main causal factor of atherosclerosis and LDL-c is the main goal of treatment.[8,9] However, LDL-c does not include other lipoproteins such as VLDL and its remnants that are triglyceride-rich particles (TG) with apolipoprotein B (ApoB), capable of diffusing to the sub endothelium and participating in the atherogenic process. Non-HDL cholesterol (mon-HDL-c), which includes LDL, VLDL and their remnants, and lipoprotein (a) or Lp(a), and ApoB levels, are the best markers of total atherogenic lipoproteins and are they can be used as a secondary goal of treatment in patients with elevated TG, DM, or abdominal obesity. Non-HDL-c is obtained by subtracting HDL-c from total cholesterol, correlates well with total lipoproteins with ApoB, is not affected by triglyceride level, it does not matter if the sample was not taken in fasting conditions, and its measurement does not add any cost. This parameter is important in our country where the combination of high TG levels and low HDL-c levels is present in 34.5% of adults.[1,3,9,10] Another atherogenic lipoprotein is Lp(a), which is a LDL particle with an apolipoprotein called apo (a) on its surface. In most patients (~90%) is genetically determined, can spread to the sub endothelium, and has pro-thrombotic and pro-inflammatory effects. Its elevated level is associated with a greater atherothrombotic risk, although this depends mainly on the increase it causes in the plasma level of LDL-c. Its measurement is recommended to identify

Table 1: Prevalence of dyslipidemia in Mexico.[1]

Phenotype	Diagnostic criteria (mg/dL)	Prevalence (%)
Hypercholesterolemia	≥ 200	30.6
Hypertriglyceridemia	≥ 150	47.4
Hypercholesterolemia + hypertriglyceridemia	≥ 200 + ≥ 150	22.1
Low HDL levels	< 40	55.2
Elevated LDL levels	≥ 100	56.1
Elevated Non-HDL levels	≥ 130	56.8

HDL-C = Cholesterol in high-density lipoproteins, LDL-C = Low-density lipoprotein cholesterol, Non-HDL-C = Total cholesterol minus HDL-C.

Table 2: Dyslipidemia causes atherosclerosis and organic complications.

Dyslipidemia	Vascular damage	Organic damage
Inadequate levels of: • LDL • VLDL • Remnants of VLDL • Lp(a) • Apo B • HDL • Non-HDL C	Atherosclerosis • Coronary • Carotid • Aortic • Peripheral	Complications • Ischemic heart disease; MI, UA, SD, arrhythmias, HF • Cerebrovascular disease; TIA, cerebral infarction, cognitive impairment • Aortic disease; Aneurysm, renovascular hypertension, CKD, mesenteric ischemia • Peripheral arterial disease

LDL = low-density lipoproteins, VLDL = very low-density lipoproteins, Lp(a) = Lipoprotein a. Apo B = Apolipoprotein B, HDL = high density lipoproteins, Non-HDL C = total cholesterol minus HDL. MI = myocardial infarction, UA = unstable angina, SD = sudden death, HF = heart failure.

patients with a high level of genetic origin (> 180 mg/dL), in those with a family history of premature atherosclerotic disease, and for reclassification in those with an intermediate risk level *(Figure 1)*.[1,9,10-14]

THE FIRST STEP IS TO ESTIMATE THE OVERALL CARDIOVASCULAR

The level of LDL-c is only one of the indicators used to estimate global cardiovascular risk. This is determined by the synergistic effect of all the risk factors present in the patient and exists from the beginning of the atherogenic process. Knowing the level of risk of suffering an atherosclerotic outcome is the critical step in the primary prevention strategy. To estimate it, algorithms designed based on the results of prospective cohort studies with medium and long-term follow-up are used that considering the rate of cardiovascular disease and death in each country. These algorithms are not exact, but they are a good approximation and an excellent educational resource to make the physician and the patient perceive the risk. In addition, they provide the opportunity to use additional risk indicators for reclassification or to complement the estimate with subclinical atherosclerosis detection studies. In secondary prevention, that is, in high or very high-risk patients, it is not necessary to make this estimate. Their main utility is that they help to identify the patient in whom the pharmacological intervention is more likely to be beneficial individually and socially. This strategy seeks the maximum net benefit of the intervention with the greatest safety and at the lowest cost for the patient.[9,15]

LDL-C, THE LOWER THE BETTER

In 27 clinical studies, that compared statin versus placebo and intensive versus less intensive statin regimen, it was shown that lowering the LDL-c level intensively, reduces major adverse cardiovascular events (MACE), coronary death, myocardial infarction, need for revascularization and ischemic stroke, in all risk groups. This benefit was directly proportional to the degree of LDL-Cc decrease and more evident at the highest risk level. In general, statins were able to reduce the atherothrombotic risk by 22% for every 38.6 mg/dL decrease in LDL-c during 5 years of treatment. The effect maintained throughout the studies was independent of baseline LDL-C and remarkably constant in all subgroups of patients. In the studies that compared the most intensive with the least intensive strategies, an additional decrease of 20 mg/dL of LDL-c was associated to an added reduction of 15% in higher outcomes, 13% in coronary outcomes, 19% in coronary revascularization, and 16% in Ischemic stroke. Total mortality was reduced by 10%, mainly because due to reduction

of coronary death and s from other cardiac causes. This benefit far outweighed any risk from the use of these drugs and allowed to conclude that greater decreases in LDL-c are safe and achieve a further reduction in the incidence of major vascular outcomes. These results permit to assume that the benefit is directly proportional to the absolute decrease in LDL-c, that is, the greater the 13% in coronary outcomes, 19% in coronary revascularization, and 16% in Ischemic stroke. Total mortality was reduced by 10%, mainly because on coronary death and on death from other cardiac causes. This benefit far outweighed any risk from the use of these drugs and allowed to conclude that greater decreases in LDL-c are safe and achieve a further reduction in the incidence of major vascular outcomes. These results permit the assumption that the benefit is directly proportional to the absolute decrease in LDL-c, that is, the greater the greater the decrease in LDL-c attained with statins, the greater the prevention of atherothrombotic outcomes *(Figure 2)*.[16-18]

REDUCING LDL-C INDUCES REGRESSION OF ATHEROSCLEROSIS

The atherosclerosis evaluation studies by intracoronary ultrasound demonstrated an inverse relationship between the degree of LDL-C decrease and the rate of progression of the atherosclerotic process. An early study compared a strategy of lower intensity, pravastatin 40 mg/day, with another of greater intensity, atorvastatin 80 mg/day, and showed that the higher intensity approach reduced LDL-c by almost 50% (20% more than the lower intensity treatment), greater decrease in other lipoproteins and inflammation markers, and lower rate of progression of coronary atheroma. These results confirmed that it is possible to change the natural history of the disease, slow its progression and achieve regression in some cases. A paradigm shift was generated towards more intensive lipid-lowering strategies to stop and reverse the atherogenic process.[19] This and other studies consistently demonstrated that the progression of coronary atherosclerosis could be halted if LDL-C levels were reached less than 70 mg/dL. However, intensive strategies with lower LDL-c goals finally achieved results compatible with regression of the atherogenic process. A study with rosuvastatin 40 mg/day, which attained an average LDL-c of 60.8 mg/dL, showed a reduction of both, the area and the volume of coronary atheroma plaques, and established that at this level of LDL-c, atheroma regression is reached in patients with coronary artery disease.[20] Another study compared rosuvastatin 40 mg/day versus atorvastatin 80 mg/day, and showed similar results in regression of coronary atheroma despite the fact that rosuvastatin achieved a lower LDL-C level than atorvastatin (62.6 vs 70.2 mg/dL).[21] Although it is inferred that there is clinical benefit from the regression of atherosclerosis, in these studies no correlation was made with clinical outcomes since this requires a greater number of patients, a higher rate of main outcomes, and longer time of follow-up. The above mentioned is a solid foundation for the concept that the regression of atheroma plaques is accomplished by reaching LDL-C levels below 70 mg/dL or by reducing it by at least 50% from the baseline level.

COMBINED LIPID-LOWERING THERAPY ACHIEVES BETTER RESULTS

Ezetimibe, a selective inhibitor of the Niemann-Pick C1-Like 1 (NPC1L1) protein that transports cholesterol from the intestinal lumen to the interior of the enterocyte, reduces cholesterol absorption, decreases LDL-c by 15-20%, and up-regulates of the LDL receptor in several tissues. In a comparative study between simvastatin and ezetimibe 40/10 mg/day versus simvastatin 40 mg/day, the combination achieved a lower LDL-c level (54 mg/dL) than monotherapy (70 mg/dL), a difference of 16 mg/dL (17%) which meant an additional 2% reduction in the absolute risk of the primary endpoint of analysis that included cardiovascular (CV) death, MI, unstable angina (UA), revascularization procedures and ischemic stroke. MI was reduced 13% and ischemic stroke 21%. There was no difference between groups in CVD or death from any cause. This result allowed ezetimibe to be included in the intensive treatment strategy, especially after an acute coronary outcome if

the LDL-c goal has not been achieved with a high-intensity statin at the maximum tolerated dose.[22] In a study of atherosclerosis regression the combination of atorvastatin (20-80 mg/day) and ezetimibe (10 mg/day) decreased LDL-c an additional 10% to monotherapy and achieved higher indicators of regression of coronary atheroma. Ezetimibe also suppressed the compensatory increase in intestinal cholesterol absorption that occurs with statins, which could explain part of the benefit.[23] Current guidelines recommend adding ezetimibe to patients who have not achieved the goal despite maximum tolerated doses of statins, in patients with primary hypercholesterolemia and in those who do not tolerate high doses of statins.

PCSK9 (Proprotein Convertase Subtilisin Kexin 9) is a soluble protein enzyme that participates in the regulation of cholesterol content in the liver. Its function is to bind together with LDL to the specific receptor, intern with the complex formed through endocytosis and promote the degradation of the receptor to reduce its expression on the surface of the hepatocyte. Evolocumab and alirocumab are PCSK9 inhibitor monoclonal antibodies that prevent the degradation of the LDL receptor, favoring its re-expression on the

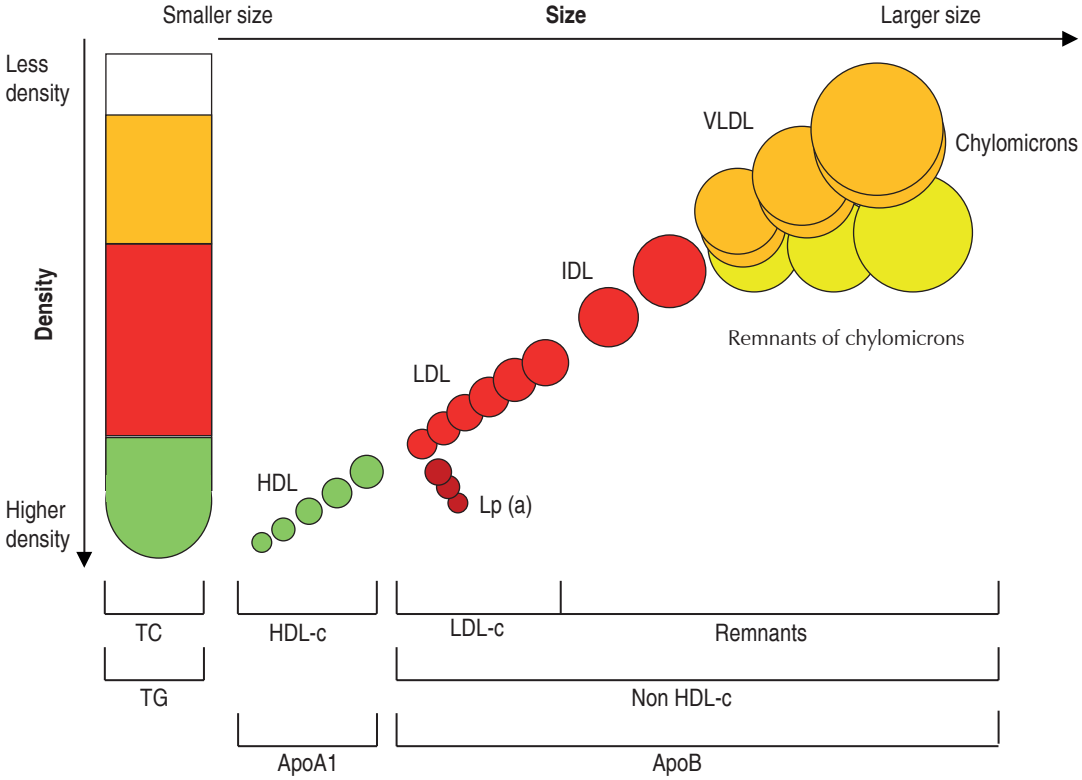
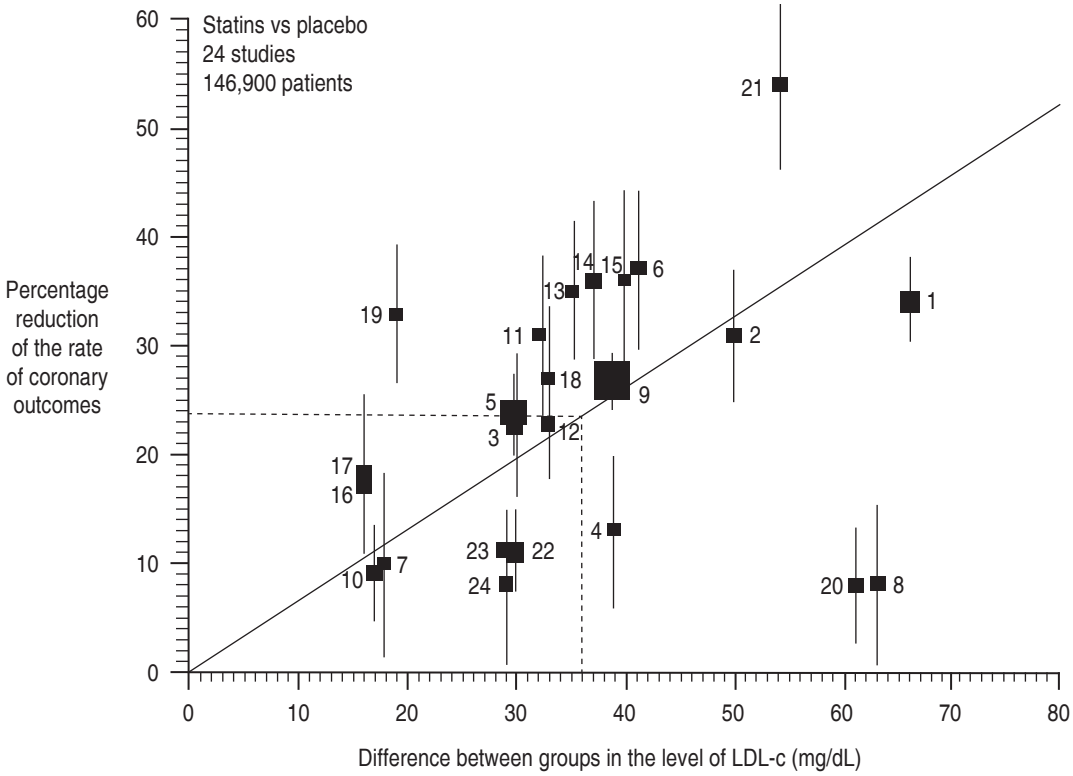


Figure 1: Plasma lipoproteins according to their density, size, and representativeness in the fractions measured in the laboratory.

Lipoproteins according with their density, size, and representativeness in the fractions measured in the laboratory. The typical lipid profile consists in the measurement of total cholesterol (TC), triglycerides (TG), cholesterol linked to high-density lipoproteins (HDL-c), cholesterol linked to very low-density Plasmatic lipoproteins (VLDL-c), and cholesterol linked to low-density lipoproteins (LDL-c). However, sometimes also are estimated the remnants of VLDL (Remnant-c), and the cholesterol no liked to HDL (Non-HDL-c). Remnant-c is calculated as follows: TC - HDL-c-LDL-c, i.e., the amount of cholesterol do not linked to LDL and HDL, representing only the TG-rich lipoproteins (VLDL, their remnants, and in the postprandial state, also the chylomicron remnant. Non-HDL is estimated as follows: TC-HDL-c, representing a total measurement of atherogenic lipoproteins. The measurement of Apo-I and Apo B100 is an alternative of estimating HDL and LDL lipoproteins. Cholesterol content o Lp(a), representing one third of the mass of this lipoprotein, is included in the estimation of TC, LDL and non-HDL-c. The measurement of Apo B, includes the content of this apolipoprotein in the Lp(a.)
Langlois MR et al.[10]



	Study	Reduction: C-LDL	Reduction: Outcomes
1	4S	66	34
2	WOSCOPS	50	31
3	CARE	30	23
4	Post-CABG	39	13
5	LIPID	30	24
6	AFCAPS/TexCAPS	41	37
7	GISSI-P	18	10
8	MIRACLE	63	8
9	HPS	39	27
10	ALLHAT-LLT	17	9
11	LIPS	32	31
12	PROSPER	33	23
13	ALERT	35	35
14	ASCOT-LLA	37	36
15	CARDS	40	36
16	ALLIANCE	16	17
17	4D	16	18
18	ASPEN	33	27
19	MEGA	19	33
20	CORONA	61	8
21	JUPITER	54	54
22	GISSI-HF	30	11
23	AURORA	29	11
24	SHARP	29	8
	Mean	36	24

The results of 24 clinical studies comparing the effects of statins versus placebo, that included 146,900 patients with diverse clinical conditions, showed that lessening LDL-c concentration, mainly in intensive form, is associated to a reduction of major outcomes (coronary death, myocardial infarction, need of revascularization, and ischemic stroke), in all risk categories.

Figure 2: Linear association between the decrease in the plasma level of LDL-C with statins and the reduction in the rate of coronary outcomes.

hepatocyte surface and lowering the LDL-c level an additional 40 to 60%. In a study that included 27,564 patients with atherosclerotic cardiovascular disease on statin treatment and a LDL-c level out of the recommended goal (70 mg/dL or non-HDL-c <100 mg/dL), evolocumab was able to decrease the LDL-c from 92 to 30 mg/dL while in the placebo group there was no significant change from baseline. This decrease bring-off an additional 1.5% reduction in the absolute risk of the primary endpoint of analysis that included CVD, MI, stroke, UA and coronary revascularization, during a median of 2.2 years of follow-up. The benefit was sustained during treatment, it was consistent in all the studied subgroups but greater in those that attained lower levels in LDL-c, as well than in those with the highest baseline absolute risk. There were no differences in CV death and death from any cause. Evolocumab also decreased the Lp (a) level by 27%, possibly contributing to the benefit.[24] Another study included 18,924 patients with history of a recent acute coronary outcome, on statin treatment at the maximum tolerated dose and with a level of LDL-c < 70 mg/dL, non-HDL-C < 100 mg/dL, or ApoB < 80 mg/dL. Alirocumab decreased LDL-c from 92 to 37 mg/dL what was associated to an additional 1.6% reduction of absolute risk of the primary endpoint of analysis, including MI, CVD, stroke, and hospitalization for UA, during a median of 2.8 years of follow-up. The risk reduction was greater in patients with baseline LDL-C ≥ 100 mg/dL than in those with a level below it. Although there was a 0.4-0.6% reduction in the absolute risk of CV death and death from all causes, the difference was not significant.[25] Both studies demonstrated that these drugs are safe and well tolerated, strengthening the concept that patients with atherosclerosis benefit from lowering LDL-C to a level less than 50 mg/dL and that at least in the medium term, there is no secondary harm from this. PCKS9 inhibitors are indicated in high and very high-risk patients (secondary prevention or severe primary hypercholesterolemia) who have not achieved the LDL-C goal despite ezetimibe and high-intensity statins at the maximum tolerated dose, or well in those who have had statin toxicity.

Another drug studied in combination with statins with the aim of reducing ischemic cardiovascular outcomes is ethyl-eicosapentaenoic acid (EPA), a highly purified and stable ethyl ester of EPA that decreases TG levels by reducing liver production of VLDL and increasing its depuration. The study included 8,179 patients with very high cardiovascular risk treated with statins, and with fasting TG between 135 and 499 mg/dL and LDL-c between 41 and 100 mg/dL, and compared a group treated with statins and ethyl-eicosapentaenoic acid 4 g/day versus another with statins and placebo. The primary endpoint of analysis was a composite of CV death, MI, stroke, UA, and coronary revascularization, with a median follow-up

Table 3: Evolution of the LDL-C goals* in cardiovascular prevention.

Risk level	ATP I 1988	ATP II-III 1994-2001	ATP III 2004	ESC/EAS 2011-2016	ACC/AHA 2013-2018	ESC/EAS 2019
Very high	< 130	< 100	< 70	< 70	< 70	< 55
High	< 160	< 130	< 100	< 100	< 100	< 70
Moderate	–	< 130	< 130	< 115	–	< 100
Low	–	< 160	–	< 115	–	< 116
* Values in mg/dL				≥ 50% reduction from basal level		

ATP = adult treatment panel, NCEP = National Cholesterol Education Program, ESC = European Society of Cardiology, EAS = European Atherosclerosis Society, ACC = American College of Cardiology, AHA = American Heart Association.

of 4.9 years. The combination decreased the TG level by 18.3% (39 mg/dL) while in the placebo group it increased 2.2% (44.5 mg/dL). LDL-c increased 3.1% (2 mg/dL) with the combination and 10.2% (7 mg/dL) in the placebo group, that is, about 6.6% (5 mg/dL) increased less with the combination than with placebo ($p < 0.001$). The primary endpoint of analysis was 25% lower with the combination, which meant a reduction of 4.8% in the absolute risk and a necessary number to treat (NNT) of 21 patients to treat for 5 years to avoid a primary outcome. In general, the incidence of ischemic outcomes was lower with the combination, and this included a 20% lower risk of CVD. It is important to note that these results were obtained in patients treated with statins and a baseline median LDL-c of 75 mg/dL. A safety aspect to consider is the higher rate of hospitalizations for atrial fibrillation or flutter (3.1 vs 2.1%, $p=0.004$) and the higher incidence of bleeding (2.7 vs 2.1%, $p = 0.06$) in the group that received ethyl acid-eicosapentaenoic. The magnitude of the result obtained is not sufficiently explained by the decrease in the TG level. Other effects, antithrombotic, anti-inflammatory, at the level of the atheroma plaque or on the stability of the membrane could be involved, Up to date, the mechanism or mechanisms responsible for the benefit are unknown. The divergence of the outcome incidence curves suggests a late onset of benefit from reducing the TG level or the start of other mechanisms.[26]

The combination of high-intensity statins with other lipid-lowering drugs with different mechanisms of action is a recommended therapeutic option in specific cases to achieve an additional decrease in LDL-c and a greater reduction in cardiovascular outcomes.[27]

EVOLUTION OF LDL-C TREATMENT GOALS

Clinical studies indicate that the greater the absolute decrease in LDL-C, the greater the reduction in atherosclerotic outcomes, and that the strategies of greater intensity are the ones that obtain the best results. It has also been shown that the higher the level of risk, the greater the benefit for achieving the recommended goals and that there is no threshold level of LDL-c below which the benefit is lost or there is some type of harm. The timely initiation of treatment and the achievement and maintenance of the goal are very important in the prevention of atherothrombotic outcomes. Clinical practice guidelines emphasize this, and the recommendations evolution is the product of advances in knowledge and better understanding of the biology of atherosclerosis. The goals have increasingly gone beyond what was previously established *(Table 3)*, especially, because, while the goals are more stringent, the preventive results are better.[9,28-35]

CONCLUSIONS

Reducing LDL-C and other atherogenic lipoproteins is the primary goal of prevention of atherosclerotic cardiovascular outcomes. The intensity of the therapeutic intervention should be proportional to the level of cardiovascular risk estimated in all patients. Therapeutic modifications in lifestyle are essential to improve the lipid profile and that of the other present risk factors. In most high-risk patients, the goal should be to lower LDL-c to below 70 mg/dL or to achieve a reduction of at least 50% from baseline LDL-c. In very high-risk patients, it is appropriate to reduce LDL-c below 55 mg/dL. If the goal is not achieved with a high intensity statin at the maximum tolerated dose, the addition of ezetimibe and if required, a PCSK9 Inhibitor is indicated. It is the significant and permanent reduction in LDL-c that has achieved the best results in clinical studies. LDL-c reduction, the sooner, faster, lower, and longer the better, is a concept that has solid scientific support. However, the residual risk continues to be high in most patients in secondary prevention and this has motivated the search for different intervention strategies. New lipid-lowering drugs are in development that have shown efficacy and safety in initial clinical studies. Changes in cardiovascular prevention strategies are likely to occur in the coming years.

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