Review Article

From new biomarkers to emerging lipid-lowering therapies. What do the new 2026 American dyslipidemia guidelines tell us?

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ABSTRACT

Atherosclerotic cardiovascular disease is the leading cause of death. The new ACC/AHA dyslipidemia guidelines, endorsed by a total of eleven societies, provide the latest evidence and recommendations for evaluating and treating dyslipidemia. The guidelines highlight the importance of early promotion of cardiovascular health by a healthy lifestyle, early lipid screening, and precision-based primary and secondary prevention. Key takeaways include the early screening for dyslipidemia in childhood for identifying hereditary dyslipidemias, one-time screening for lipoprotein(a), and increased testing of apolipoprotein B in selected individuals. For improved decision making in individuals with borderline and intermediate risk, the guidelines recommend coronary artery calcium scoring and evaluating other high-risk conditions, such as family and reproductive history, cardiovascular-kidney-metabolic syndrome, and others. There is greater emphasis on treatment goals, not only for LDL but also for non-HDL cholesterol and apolipoprotein B. Statins remain the cornerstone of treatment, in addition to broader use of other evidence-based non-statin therapies in individualizing discussions between healthcare providers and patients.

Statement of conflict of interests

Mónica Acevedo has participated in Advisory Boards for AstraZeneca, Novo Nordisk, Boehringer Ingelheim, and Novartis. She has received fees for lecturing for: Adium Pharma, AstraZeneca, Boehringer, Novo Nordisk, Axon Pharma, Bayer, and Abbott.

Paola Varleta has participated in Advisory Boards for Axon Pharma, Novo Nordisk, Boehringer, and Novartis. She has received fees for lecturing for: Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Axon Pharma, Abbott, Bayer and Adium. Investigator in clinical studies: Horizon (Novartis) / Victorion Prevent (Novartis).

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INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the first cause of mortality in the world,[1] in spite of advancements in pharmacological treatments and percutaneous intervention.

Dyslipidemia is still the main risk factor (RF) for ASCVD. Currently, it is known that not just LDL cholesterol is a cause for the disease, but there are also other atherogenic particles, such as lipoproteins rich in TG (TRLP) and lipoprotein(a) [Lp(a)], which may go through the intima and contribute to the atherogenic process.[2] This wider view of atherosclerotic CV risk, and the assessment of using new biomarkers and new tools for measuring CV risk have been clearly defined in the new 2026 US guidelines for the management of dyslipidemia, which also include the ACC and AHA (American College of Cardiology and American Heart Association, respectively) leadership, and another 11 societies involved in health care and with ASCVD patients.[3]

In this article, we will review what, from the point of view of the authors, are the main messages in the guidelines. The essential points to discuss are:

1. LDL cumulative exposure hypothesis.
2. Significance of healthy lifestyle, both in primary (PP) and secondary prevention (SP).
3. PREVENT-ASCVD risk score.
4. Use of the advanced biomarkers for the evaluation of CV risk and/or to determine the aims of the treatment, Lp(a) and apolipoprotein B (ApoB).

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5. Aims for the treatment for LDL, non-HDL cholesterol and ApoB.
6. New therapies for the management of dyslipidemia.

We invited Doctor Samia More, a US cardiologist expert in Lipidology, future president of the International Atherosclerosis Society, and one of the authors of the recently published guidelines, to participate in order to communicate as best as possible, the importance of these new guidelines.

1. CONCEPT OF LDL-CHOLESTEROL BUILDUP DURING LIFE

It is known nowadays that atherosclerosis occurs due to the accumulation of LDL cholesterol and lipoproteins containing ApoB on the arterial wall (VLDL, IDL, chylomicron remnants), including Lp(a), over life.[2] The greater the buildup of these particles on the arterial wall, the greater the risk of ischemic CV events. In other words, risk does not depend only on how elevated is LDL, but also on the extent of time of such exposition. This explanation has been called the theory of LDL cumulative exposure in terms of all ApoB-containing lipoproteins. However, it nearly always refers to LDL buildup, as 90% of these lipoproteins correspond to LDL. These lipoproteins that contain ApoB may go through the endothelium by transcytosis. The greater the accumulation in the intima, the more the atherosclerotic plaque will grow. If the plaque breaks, it produces a plaque rupture. Thus, accumulated LDL can be used to monitor plaque progression and the absolute risk of an acute atherogenic CV event. The risk of such event is not linear, but logarithmic, after an individual crosses the threshold of accumulated LDL from which plaque ruptures may occur. Therefore, if exposure to LDL is reduced from an early age, progression of atherosclerosis and event occurrence could be slowed and delayed.[4] Obviously, the predisposition of a person to an event depends on "their" accumulated load, hereditary predisposition, and the existence of other arterial wall damage factors, such as hypertension, diabetes and smoking. The LDL buildup threshold from which CV events start occurring can be estimated by the level of LDL cumulative exposure with the corresponding rate of events for each age: in men with average levels of LDL, the accumulated risk of acute CV events is ~1% after the accumulation of 130 years-plaque (in mmol/l) and 10% after 200 years-plaque (mmol/l). In women, it reaches 1% after 150 years-plaque (mmol/l) and 10% after 240 years-plaque (mmol/l). After menopause, years-plaque in women tend to be equal to men, as endogenous estrogens in the perimenopause period reduce LDL transcytosis in the intima. Therefore, currently the message about LDL cholesterol is: *"the lower the better, the earlier the better, and the longer the better"*.

2. SIGNIFICANCE OF HEART-HEALTHY LIFESTYLE

A heart-healthy lifestyle remains the cornerstone of both primary and secondary CV prevention. Guidelines emphasize again the need to promote and reinforce, since childhood to maturity, healthy habits that would contribute to reducing the risk of dyslipidemia and ASCVD. Among them, an appropriate diet, regular physical activity, healthy weight maintenance, proper sleep hygiene, stress management and abstinence from smoking and limited alcohol consumption stand out.

Evidence shows that reaching targets related to CVRF and healthy behaviors, including Life's Essential 8 from AHA, can reduce ~50% of relative risk of CV events, even in people with a genetic predisposition to ASCVD.[5,6]

Adopting a healthy diet since childhood is associated to a lower chance of developing dyslipidemia in adulthood. In general terms, a diet rich in fruits, vegetables, nuts, seeds, high-fiber foods, and monounsaturated and polyunsaturated fats are recommended. Between the different alternatives, the Mediterranean diet is the most recommended one due to its impact on reduction of CV mortality.[7] However, although healthy food patterns generate multiple CV benefits, such as weight loss, less inflammation, and blood pressure and glycemia control, its direct effect on LDL is usually modest.[3]

In regard to the impact of specific interventions on LDL, a vegan diet may reduce LDL in average 14.8 mg/dL, while the Mediterranean diet does not usually produce reduction of this magnitude. Daily consumption in three daily portions of fiber (28 g each) can reduce LDL ~5 mg/dL. The Portfolio diet, which combines nuts, soy protein, fiber and margarine enriched with plant sterols, can achieve reductions of ~26 mg/dL.[8]

Diet can also play a significant role in the treatment of hypertriglyceridemia (HTG). TRLP contribute to the development and progression of the atherosclerotic plaque, and therefore, to an increase in the risk of ASCVD.[2] For any degree of HTG, reducing consumption of sugar, total fat, and alcohol is a fundamental measure. Furthermore, it is advised to improve the quality of carbohydrates, favoring those with higher fiber content and lower glycemic index.[9] The risk of acute pancreatitis increases considerably when TG levels are ≥1000 mg/dL. In patients with genetic syndromes, such as the familial chylomicronemia syndrome, restricting carbohydrates is essential. In them, supplementing with liposoluble vitamins, minerals and medium-chain TG is usually required. Any person with TRLP elevation should supplement their diet with moderate to intense aerobic activity, plus resistance exercises for the upper and lower limbs, favoring a higher sensitivity to insulin, and contributing to weight maintenance and TG reduction.[9]

Obesity constitutes a great epidemiological problem in South America. Besides increasing CVRF, it may be considered a CV disease per se. It is frequently associated to atherogenic dyslipidemia. For this reason, a Mediterranean, a vegetarian or a vegan diet is recommended, always accompanied by aerobic and resistance exercises. In all people with dyslipidemia and overweight/obesity, a weight loss of at least 5% is recommended. This loss is mainly associated to a reduction in TG; the impact on LDL is limited. The glucagon-like peptide-1 (GLP-1) receptor agonists and dual GLP-1/GIP receptor agonists have shown significant effects on weight loss, TG and LDL reduction, glycosylated hemoglobin decrease, and improvement in atherosclerotic CV events.[10] Likewise, metabolic bariatric surgery has shown consistent benefits on TG and LDL, besides a reduction in CV risk.

Finally, in regard to exercise in people with dyslipidemia, moderate to intense aerobic exercise ≥150 minutes per week is advised, associated with resistance exercises twice a week. This favors the metabolism of lipids and increases the use of fatty acids

as an energy source. Exercise reduces TG and may increase HDL, besides contributing to controlling weight, improving sensitivity to insulin and improving RF[11]

3. ADDITION OF A NEW RISK STRATIFICATION TOOL, THE PREVENT-ASCVD, WITH BETTER CALIBRATION AND MORE ACCURATE THAN THE PREVIOUS POOLED-COHORT EQUATION, CLASSIFYING PEOPLE SINCE AGE 30

Atherosclerotic CV risk estimation is essential for decision-making to treat dyslipidemia, both for the indication of pharmacological therapy and to define the desired therapeutic target. International recommendations for the management of dyslipidemia always add some CV risk score that would meet validation criteria and applicability to their population. In the United States, the score used was the Pooled-Cohort Equation (PCE), recommended in 2013 by the AHA/ACC, and promoted because it adds multiple US cohorts in its validation. Another great strength of the PCE was having included atherosclerotic stroke in the risk estimation. Nevertheless, over the years it became evident that the PCE tended to overestimate the risk of ASCVD. Thus, in 2024, a group of AHA experts led by Sadiya Khan reviewed the prediction models and generated a new sex-specific CV risk equation, not differentiated by race, with better discrimination and calibration than the PCE, representing all the US population.

This new tool called PREVENT (Predicting Risk of CVD Events) seems to be an attractive and contemporary proposal, with modifications in regards to its predecessor.[12] PREVENT grants the chance to estimate CV risk within 10 and 30 years. In turn, it allows to estimate atherosclerotic CV risk, and the risk of heart failure and/or total CVD (ASCVD + heart failure). It also stands out due to the age range width, from 30 to 79 years. This is favorably compared with the SCORE (Systematic Coronary Risk Evaluation) of the European Society of Cardiology with two age ranges: the SCORE2, in apparently healthy individuals from 40 to 69 years and the SCORE2 OP in ≥70 years.[13,14] The PREVENT equation also integrates the concept of cardiovascular-kidney-metabolic syndrome (CKM), adding glomerular filtration rate and body mass index. As options, it adds the urine albumin/creatinine ratio and hemoglobin A1c. Finally, it introduces the social variable through the social deprivation index, providing a more equitable approach for the implementation of CV prevention. Due to the strength of the PREVENT, the AHA and the ACC decided to add it in this new guideline.

Along with the risk estimation by the PREVENT-ASCVD, the guideline recommends personalizing and possibly reclassifying the risk of individuals if necessary. Personalization is based on including particular conditions of the CV risk of some people, which should be taken into account, such as: family history of atherosclerotic CVD, being a carrier of some inflammatory disease, or having a gynecologic history of risk. Within these risk enhancing factors, elevated serum biomarkers are added, such as Lp(a) and high-sensitivity C-reactive protein *(Figure 1)*.

Reclassification is recommended in individuals in intermediate risk, with PREVENT score between 5% to <10%. Reclassification is made by the evaluation of subclinical atherosclerosis by coronary artery calcium test (CAC). This recommendation is based on the high percentage of reclassification yielded by CAC. It has been observed that in some studies, up to ~40% of patients in intermediate risk would present CAC = 0, and 25% CAC ≥100, which would lead to a reclassification into low and high risk, respectively. CAC is a test with a low dose of radiation and very cost-effective.[15]

4. A GREATER USE OF ADVANCED BIOMARKERS FOR THE EVALUATION OF RISK AND/OR TO DETERMINE THE GOALS OF THE TREATMENT, INCLUDING A SINGLE TEST OF LIPOPROTEIN(A) [LP(A)] FOR ALL INDIVIDUALS, AND A MORE WIDESPREAD USE OF APOB MEASUREMENT

The traditional lipid profile, both in a fasting state or not, is still the most useful tool to assess CV risk, guide the treatment, monitor the therapeutic response and verify targets are met. It is recommended to measure since age 9 to research familial dyslipidemias. This profile includes the direct determination of total cholesterol, HDL and TG; while LDL is estimated by mathematical formulas. Currently, it is advised to carry out the lipid profile in a fasting state in patients with TG ≥400 mg/dL and/or familial history of premature ASCVD or genetic dyslipidemias.

FIGURE 1.
Cardiovascular risk enhancers

New suggestions to determine LDL cholesterol

One of the main changes in the 2026 guidelines is the recommendation to use the Martin/Hopkins or Sampson/NIH equations instead of the Friedewald formula, for the estimation of LDL.[16,17] This is due to its greater accuracy in a wider range of LDL and TG concentrations. This suggestion is particularly relevant in patients with TG ≥150 mg/dL, LDL <70 mg/dL or non-HDL cholesterol <100 mg/dL. Both equations use LDL measurement as reference by β-quantification, and offer a more accurate estimation than the Friedewald formula, especially in patients with elevated TG and low LDL.

Apolipoprotein B

Another novel aspect is the recommendation of measuring ApoB in selected patients. Although LDL cholesterol is still the main parameter for CV risk evaluation and to define therapeutic targets, it only shows the amount of cholesterol transported by LDL particles. ApoB instead quantifies the total number of circulating atherogenic particles, as each LDL, VDLD and Lp(a) particle contains a single ApoB molecule.[18] The determination of ApoB becomes particularly relevant when there is a mismatch between LDL cholesterol and ApoB. This happens when LDL is within the control targets, but ApoB remains elevated, indicating a residual load of atherogenic particles, and the possible need to intensify the treatment. This mismatch is more frequent in patients with diabetes (DM), CKM syndrome, ASCVD or elevated TG. In this groups, LDL could be "controlled" while there remains a significant residual CV risk. ApoB in these cases would allow to research this residual risk as it is a direct measurement of the total number of atherogenic particles, including LDL, VLDL and Lp(a). The guideline, however, does not support a widespread use of ApoB in primary prevention of events, because there is no prospective evidence that measuring it would improve the prediction of CV events. In other words, ApoB should be considered as a supplementary tool, that improves but does not replace the treatment based on LDL cholesterol.

Lipoprotein(a)

A relevant incorporation to this guideline, also included in the last European guidelines of dyslipidemia, is the recommendation of measuring Lp(a), which is a particle similar to LDL, containing an apolipoprotein(a) bound to ApoB. Its concentration is mainly determined by the LPA gene, and it varies according to ascendancy.

The evidence from prospective and genetic tests shows a causal association between elevated concentrations of Lp(a) and a greater risk of ASCVD, calcified aortic valve stenosis, CV events and mortality. The risk of high Lp(a) is independent from LDL and other CVRF. It is considered high when an Lp(a) concentration is ≥125 nmol/L (50 mg/dL), which would be associated to an increase in the risk of ASCVD of 40%. The pathophysiological mechanisms of damage by Lp(a) include proatherogenic, proinflammatory and oxidative effects.[19]

Lp(a) levels are genetically determined and remain stable through life, so one measurement is usually enough to assess CV risk. Inheritance is autosomal codominant, and cascade genetic testing is recommended in first-degree relatives when elevated. The main limitation for measurement is the variability of Apo(a) isoforms. Currently, it is advised to use methods independent from isoform, and expressing results preferably in nmol/L.[20] *Figure 2* shows the steps to follow if Lp(a) is high.

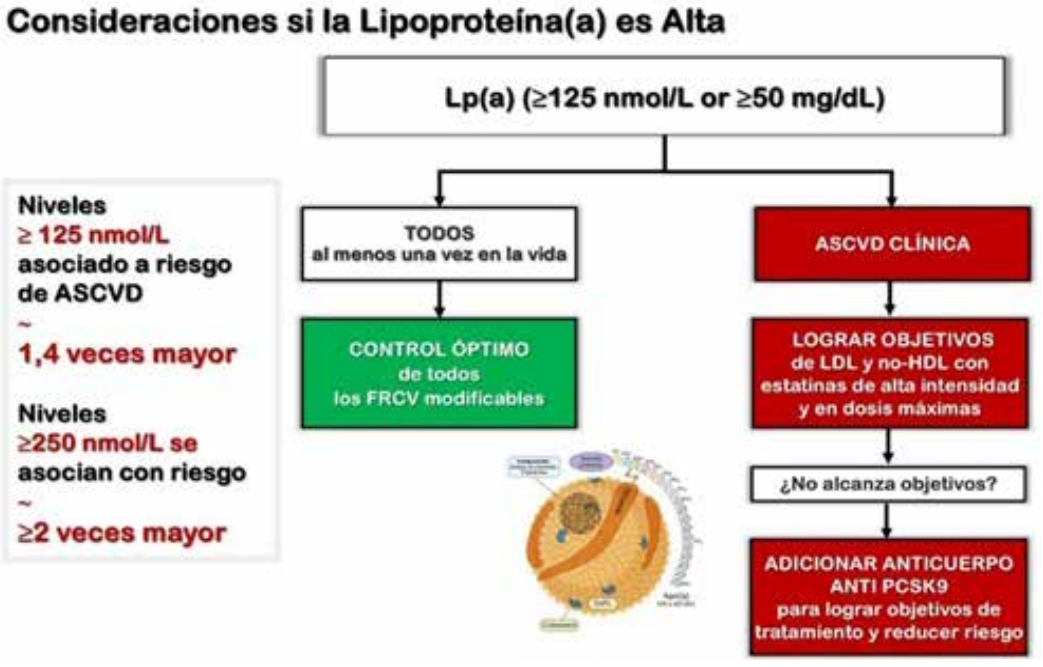

FIGURE 2. Considerations if Lp(a) is elevated

5. REINCORPORATION OF TREATMENT TARGETS, NOT JUST FOR LDL, BUT ALSO FOR NON-HDL CHOLESTEROL AND APOLIPOPROTEIN B (APOB) *(Table 1)*

The 2026 guideline reintroduces numerical and specific percentage treatment targets for LDL and non-HDL cholesterol in all risk categories, and for ApoB individuals in whom it was measured.

Table 1 summarizes control targets for the different risk categories. The recommendations in primary prevention in adults with ages from 30 to 79 years with LDL levels from 70 to 189 mg/dL are summarized in *Table 2.*

After estimating the PREVENT-ASCVD risk within 10 years, the risk-benefit balance should be evaluated to decide to start a lipid-lowering therapy, considering co-morbidities, life expectancy and preferences of the patient.

Primary prevention is based on a healthy lifestyle. When a pharmacological treatment is required, statins are the therapy of choice, with LDL reduction targets of ≥30% and ≥50% in people with greater CV risk. If the response is not enough, adherence should be optimized and the treatment should be intensified, with ezetimibe being the first drug to associate.

Cardiovascular risk estimation within 30 years supplements the 10-year evaluation, and it allows identifying individuals with PREVENT-ASCVD risk <3% within 10 years that may benefit from the treatment, particularly when LDL ≥160 mg/dL. Lipid-lowering therapy should be installed after optimizing lifestyle, in people

TABLE 1
Lipoprotein control targets for the different risk categories

Category of risk	LDL target (mg/dL)	Non–HDL target l (mg/dL)	ApoB target (mg/dL)
Borderline to intermediate risk	< 100	<1 30	< 90
High risk	< 70	< 100	< 70
Very high risk	<55	<85	<55

TABLE 2

Patients	LDL <100 mg/dL non-HDL<130 mg/dL	LDL<70 mg/dL non-HDL<100 mg/dL	LDL<55 mg/dL non-HDL<85 mg/dL
Primary prevention	PREVENT-ASCVD < 10% if TG ≥ 150 to 499 mg/dL - target apoB <90mg/dL	PREVENT-ASCVD ≥ 10% If TG ≥ 150 to 499 mg/dL - target apoB <70mg/dL	No data
Severe hypercholesterolemia	WITHOUT clinical ASCVD WITHOUT FH, WITHOUT CVRF WITHOUT subclinical atherosclerosis	WITHOUT clinical ASCVD WITH FH, WITH additional CVRF, or WITH subclinical atherosclerosis	FH WITH clinical ASCVD
Diabetes	WITHOUT CVRF for ASCVD or WITHOUT specific RF modifiers-of-DM - target apoB: <90 mg/dL	WITH CVRF for ASCVD WITH specific RF-modifiers of-DM- - target apoB: <70 mg/dL	No data
Subclinical atherosclerosis	CAC ≥1 to 99 and < p75 for age, sex and race	CAC ≥100 to 299 or ≥Pc75th for age, sex and race CAC ≥ 300 to 999 AU Optional targets: - LDL< 55 mg/dL - non-HDL < 85 mg/dL. - apoB <55 mg/dL.	CAC ≥ 1000 AU
Hypertriglyceridemia	<50 years WITHOUT additional risk enhancers	WITH clinical ASCVD and NO very high risk - ApoB: < 70 mg/dL 40 -75 years WITH ≥1 RF for ASCVD - ApoB: <70 mg/dL	WITH clinical ASCVD of very high risk -ApoB: <55 mg/dL
Clinical ASCVD	No data	WITHOUT very high risk Optional targets: - LDL< 55 mg/dL - non-HDL < 85 mg/dL. - ApoB <55 mg/dL	WITH very high risk -ApoB: <55 mg/dL WITH CKD

CVRF: cardiovascular risk factors; **ASCVD:** atherosclerotic cardiovascular disease; **DM:** diabetes mellitus; **p:** percentiles; **FH:** familial hypercholesterolemia; **CKD:** chronic kidney disease; **CAC:** coronary artery calcium score.

with PREVENT-ASCVD within 30 years of ≥10%, and in those with high levels of atherogenic lipids, multiple CVRF or moderate CAC. Given the relative reduction of risk with statins is relatively constant, the absolute benefit increases according to the baseline risk. For this reason, if the risk within 10 years is ≥3%, therapy with a statin of moderate intensity can be started. In those with PREVENT-ASCVD between 3% and <10%, the target is an LDL reduction of ≥30%. In this group, the targets are: LDL <100 mg/dL and non-HDL cholesterol <130 mg/dL.

Individuals with PREVENT-ASCVD ≥10% within 10 years should receive high-intensity statins for an LDL reduction of ≥50%, with LDL targets <70 mg/dL and non-HDL <100 mg/dL. If the target is not reached, ezetimibe could be added. Bempedoic acid has also proven to reduce CV events in patients in high risk who are intolerant to statins. PCSK9 inhibitors and inclisiran, although strong LDL reducers, still lack definitive evidence of CV event reduction in primary prevention. There is no neat benefit proven to start statins when LDL is <70 mg/dL and non-HDL <100 mg/dL.

The recommendations for adults with diabetes and no established atherosclerotic cardiovascular disease are shown in *Table 2.*

Individuals with DM present an elevated risk of ASCVD; in them, an intensive control of LDL is a priority in primary prevention. In most adults from 40 to 75 years of age, it is recommended to start with statins of moderate intensity to reduce LDL of 30.49%.

In patients with additional CVRF or with PREVENT-ASCVD ≥10% within 10 years, it is recommended to reduce LDL ≥50%, with high-intensity statins. If the target is not met or there is intolerance to statins, ezetimibe can be added, or even PCSK9 inhibitors or inclisiran, powerful drugs to reduce LDL. In patients with DM and additional RF and persistent elevation of TG (150-499 mg/dL), in spite of treatment with statins, eicosapentaenoic acid (EPA) can be considered to reduce residual risk.

In adults >75 years, use of statins of moderate or high intensity should be individualized according to life expectancy, comorbidities and risk of adverse effects in patients.

In young people with DM with ages from 20 to 39, evidence of treatment and reduction of ASCVD is limited. Statins of moderate intensity can be considered in people with T2D ≥10 years or T1D ≥20 years coursing, particularly if it coexists with hypertension, smoking or microvascular complications. The goal is a reduction in LDL ≥30%, intensifying the treatment if the risk is higher. In all cases with DM >30 years, PREVENT-ASCVD within 10 and 30 years is recommended to guide the intensity of the lipid-lowering treatment and the control targets.

The recommendations for the secondary prevention of ASCVD are shown in *Table 2*.

In individuals with ASCVD that do not present a very high CV risk, treatment should be started with high-intensity statins for a reduction ≥50% in LDL cholesterol, to reach a target of <70 mg/dL and non-HDL cholesterol <100 mg/dL to reduce the risk of recurrent CV events. Patients with ASCVD with very high risk also require high-intensity statins to reduce LDL ≥50%. The LDL target is <55 mg/dL and non-HDL cholesterol <85 mg/dL, with an optional ApoB <55 mg/dL. Patients with ≥2 major ASCVD (acute coronary syndrome <12 months, myocardial infarction different from the previous one, ischemic stroke, and symptomatic peripheral vascular disease) or a major CV event associated to 2 or more high risk conditions, are considered to be in very high risk *(Figure 3)*.

In patients with ASCVD with very high risk, who do not reach the established targets, it is possible to add ezetimibe, PCSK9 inhibitors, inclisiran or bempedoic acid (reduction of ~20%, ~60%, ~50% and ~20%, respectively). Evidence has shown safety, even with LDL ~30 mg/dL in the follow-up of patients up to 8 years. In patients with ASCVD without very high risk, the target is LDL <70 mg/dL and non-HDL cholesterol <100 mg/dL; but, in some cases, LDL <55 mg/dL and non-HDL <85 mg/dL can be requested.

The recommendations for the management of adults with subclinical coronary atherosclerosis (men ≥40 or women ≥45 years) are shown in *Table 2.*

FIGURE 3.
Criteria to define very high cardiovascular risk

Subclinical atherosclerosis has acquired great relevance in the prevention of ASCVD. It has been proven that CAC provides sound prognostic information, with an almost linear relationship between CAC load and the risk of events. In men ≥40 and women ≥45 years and people with PREVENT-ASCVD borderline or intermediate, CAC can help to define the onset of lipid lowering drugs.

A CAC ≥1000 AU identifies patients in very high CV risk, comparable to that observed in secondary prevention. In them, it is recommended to reduce LDL ≥50%, with LDL goals >55 mg/dL and non-HDL <85 mg/dL. A combination of high-intensity statins, ezetimibe, PCSK9 inhibitors, inclisiran and/or bempedoic acid may be required to reach the targets. People with CAC between 300 and 999 AU also present a risk that is similar to that of patients with ASCVD. In them, LDL-C <70 mg/dL and non-HDL <100 mg/dL is proposed, and LDL-C <55 mg/dL, non-HDL <85 mg/dL and ApoB <55 mg/dL can be considered. Patients with CAC ≥100 AU show rates of events similar to those observed in secondary prevention, and clearly benefit from statins, with a reduction in major events and less progression to the atherosclerotic plaque. For this reason, the same therapeutic goals are suggested than with CAC ≥300 AU. Finally, in adults with CAC between 1 and 99 AU, it is considered reasonable to start statins, seeking to reduce LDL-C ≥30% and a target of LDL-C <100 mg/dL.

6. NEW THERAPIES FOR THE MANAGEMENT OF DYSLIPIDEMIA

Emerging lipid-lowering therapies are oriented toward three great goals: a more intensive reduction of LDL, a decrease of Lp(a) and control of severe HTG.

Inclisiran: it is a small RNAi, producing the catalytic destruction of mRNA of PCSK9, decreasing LDL receptor degradation and reducing LDL ~50%. Its advantage is the six-month administration after the load dose. It is considered in patients with ASCVD or severe hypercholesterolemia that do not reach their targets.

Bempedoic acid inhibits ATP citrate lyase, an enzyme previous to HMG-CoA reductase, reducing LDL-C ~18-25%. It has shown efficacy, safety and reduction of CV events in patients intolerant to statins. Guidelines add it as additional therapy in primary prevention of high risk and secondary prevention.

Olezarsen is a new antisense oligonucleotide, that binds to the mRNA of the ApoC-III and degrades it, thus reducing ApoC-III. Therefore, it increases TG and VLDL removal. Its use has been only approved for the treatment of familial chylomicronemia. It is administered monthly subcutaneously, reaching an average reduction of TG of 50% in 6 months. Other agents being developed: plozasiran, zodasiran and solbinsiran. They all act on ApoC-III or ANGPTL3 and may reduce triglycerides in more than 70%.

Evinacumab corresponds to a 100% human monoclonal antibody that binds to the ANGPTL3 enzyme and inhibits it. ANGPTL3 is a protein that is secreted and expressed only in the liver, inhibiting lipoprotein lipase. It produces reduction of TG, ApoB and LDL. LDL reduction is independent from the LDL receptor and it would occur by reduction in liver secretion of VLDL and increase in LDL removal, reducing LDL ~49%. Evinacumab is administered intravenously every 4 weeks in doses of 15 mg/kg. Currently, its use is restricted to patients with homozygous familial hypercholesterolemia.

Therapies for Lp(a): currently there is no treatment approved specifically to reduce CV events associated to Lp(a), but studies are very promising:

Pelacarsen (antisense oligonucleotide inhibiting Apo(a)), olpasiran (RNAi for Apo(a)), lepodisiran (siRNA of prolonged action) and muvalaplin (oral inhibitor of Apo(a)-Apo(b) binding). These therapies achieve Lp(a) reductions of 80-95% in phase 2 studies. The results of cardiovascular outcomes are expected between 2026 and 2028.

Lomptapida selectively inhibits the microsomal TG transfer protein (MTP), which is essential for the assembly of lipoproteins containing ApoB in the liver. Thus, it inhibits the synthesis of chylomicrons and VLDL, reducing LDL cholesterol by 40% to 50%. Its use is also limited to patients with homozygous familial hypercholesterolemia. It is associated with significant secondary gastrointestinal effects, with hepatotoxicity and hepatic steatosis. It is an oral drug, requiring liposoluble vitamin supplements and other fats to alleviate the malabsorption produced by these liposoluble vitamins and other fatty acids.

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