

Position Statement

Intersocietal document on apolipoprotein B

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ARTICLE INFORMATION

Received on September 16, 2025.

Accepted after review on December 1, 2025.

www.revistafac.org.ar

Keywords:

Apolipoprotein B,
atherogenic lipoproteins,
low density lipoproteins,
cardiovascular risk.

ABSTRACT

Apolipoprotein B (ApoB) is the main protein component of atherogenic lipoprotein particles, such as very low density (VLDL), intermediate density (IDL), and low density (LDL) particles. Therefore, the plasma concentration of ApoB allows the total number of atherogenic particles to be estimated. In recent years, various epidemiological and intervention studies have shown that ApoB measurement independently predicts cardiovascular risk, even surpassing conventional lipid parameters such as LDL-bound cholesterol (LDL-C), which remains the main therapeutic target in lipid treatment, with clearly established goals.

The objective of this collaborative effort between prestigious scientific societies is to develop a position paper that addresses, in a clear and practical manner, various aspects related to ApoB measurement by answering ten key questions. The main messages are summarized in the central figure.

Statement of conflicts of interest: ALBERTO LORENZATTI: Consultancy: Amgen, PTC and Novartis, Lectures: Amgen, PTC, Novartis, NovoNordisk, Adium and Elea, Research Agreements: Amgen, NovoNordisk, Novartis, MSD and Arrowhead, IONIS; SANTIAGO LYNCH: Lectures: Adium, Gador and Elea; WALTER MASSON: Lectures: Novartis, Novo Nordisk, Casasco, Gador, Adium, Ultragenix, Eurofarma; JUAN PATRICIO NOGUEIRA: No conflicts of interest; VIVIANA ARIAS: No conflicts of interest; FÁTIMA CARREÑO: No conflicts of interest; PABLO CORRAL: Lectures: Amgen, Silanes, Bagó, Gador, Servier, Novartis, PTC, Teva, AstraZeneca, Baliarda, Amryt, Boehringer Ingelheim, Pfizer, Sanofi, Ultragenix, MSD, Casasco, Nolter; SILVINA CUARTAS: No conflicts of interest; SERGIO GIMÉNEZ: Lectures: Novartis, Ultragenix, Adium; GUSTAVO GIUNTA: Lectures: Adium, Casasco, Novartis, Elea, Montpellier, Baliarda; MELINA HUERIN: No conflicts of interest; AUGUSTO LAVALLO-COBO: Lectures: Adium, Bagó, Casasco, Servier, Baliarda, Novo Nordisk, Novartis, Gador, Consultancy: Gador, Elea, Research agreements: Novartis, Elli-Lilly, Astra Zeneca; STELLA MARIS MACIN: No conflicts of interest; GABRIELA PORTUNATO: No conflicts of interest; LAURA SCHREIER: No conflicts of interest; MELANY VILLAREAL-GALVEZ: No conflicts of interest; GABRIELA BERG: Lectures: Novartis Argentina; Mindray, Consultancy: PTC Therapeutics; Mindray Argentina, Research agreements: PTC Therapeutics; CARLOS CÚNEO: No conflicts of interest; GERARDO DAMIAN ELIKIR: Lectures: Adium, Consultancy: Eurofarma.

INTRODUCTION

Apolipoprotein B (ApoB) is the main protein component of atherogenic lipoprotein particles, such as those of very low density (VLDL), intermediate density (IDL) and low density (LDL). Therefore, ApoB plasma concentration allows to estimate the total number of atherogenic particles. In recent years, different epidemiological and intervention studies have proven that ApoB measurement predicts cardiovascular risk independently, even exceeding conventional lipid parameters, such as LDL cholesterol (LDL-C), which is still the main therapeutic target in lipid treatment, with clearly established goals.¹

The aim of this collaborative study, carried out by prestigious scientific societies, is developing a position statement

that would approach, in a clear and practical manner, different aspects related to ApoB measurement, by answering ten key questions. The main messages are summarized in the *central figure*.

WHAT SHOULD WE KNOW ABOUT APOB PHYSIOLOGY?

All lipoproteins with atherogenic potential contain one ApoB as a main structural component, which is not exchangeable. In contrast, high-density lipoproteins (HDL), acknowledged for their anti-atherogenic properties, integrate Apolipoprotein A (ApoA) into its membrane.

ApoB-100 is intrinsically associated to VLDL, their remnants (IDL), LDL, as well as ApoB-48 to chylomicrons and

its remnants. As each of these particles contains a single ApoB molecule, the total plasma concentration of ApoB reflects precisely the total number of circulating atherogenic lipoprotein particles in blood.²

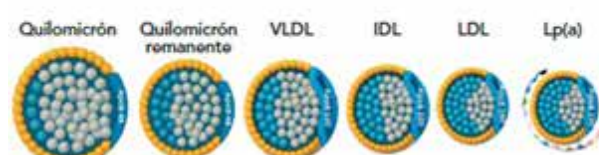
The gene that encodes ApoB is located in the short arm of chromosome 2 and has 29 exons. This gene originates two isoforms: ApoB-100, containing 4536 amino acids (550 kDa), and ApoB-48 (265 kDa), which is a truncated version of the former, with approximately half its length. ApoB-48 formation occurs in the small intestine by a single messenger RNA (mRNA) editing process: a highly specific post-transcriptional deamination of cytidine, mediated by an editing enzyme of mRNA called APOBEC-1.³ ApoB-100 is mainly synthesized in the liver and it is the main protein determinant of LDL, being identified by the ApoB/E receptor (LDL receptor). This acknowledgement activates LDL catabolism, mediated by the mentioned receptor.⁴ Finally, although less frequent than LDL receptor mutations, ApoB gene mutations may lead to familial hypercholesterolemia.³

Insulin plays a central role in the coordination of lipoprotein metabolism. The high levels of insulin act on adipocytes to promote triglyceride uptake, activating lipoprotein lipase (LPL) and inhibiting free fatty acid release by means of inhibition of hormone-sensitive lipase. This promotes triglyceride storage for subsequent use. In a fasting state, this process is reversed: insulin levels decrease and free fatty acids are released from adipocytes, and are delivered to the liver, which re-esterifies fatty acids into triglycerides and secretes them as VLDL. Moreover, the capacity of adipose tissue to uptake triglycerides is affected in absence of insulin, and therefore, triglycerides are used preferentially by other tissues, such as skeletal muscle and the liver.⁵

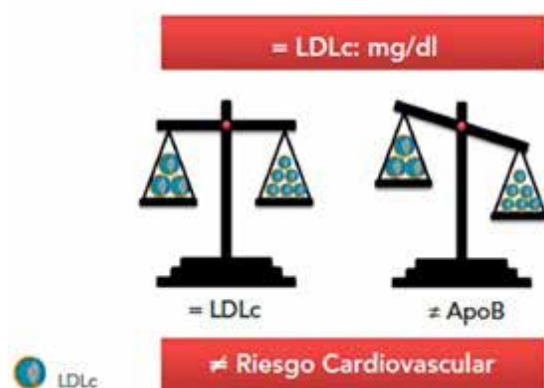
The synthesis and secretion of ApoB is a highly complex process. Surprisingly, most synthesized ApoB is degraded before being secreted, so the final amount of ApoB released into the extracellular milieu depends to a large extent on the proportion of recently synthesized polypeptides that manage to escape intracellular degradation mechanisms. Insulin regulates ApoB secretion through multiple mechanisms, acting in three main levels: 1) it decreases the synthesis of the microsomal triglyceride transfer protein (MTTP), essential to assemble very low-density

lipoproteins. 2) it increases the degradation of ApoB in the liver. 3) it increases the degradation of ApoB in the peripheral tissues. The synthesis and secretion of ApoB is a highly complex process. Surprisingly, most synthesized ApoB is degraded before being secreted, so the final amount of ApoB released into the extracellular milieu depends to a large extent on the proportion of recently synthesized polypeptides that manage to escape intracellular degradation mechanisms. Insulin regulates ApoB secretion through multiple mechanisms, acting in three main levels: 1) it decreases the synthesis of the microsomal triglyceride transfer protein (MTTP), essential to assemble very low-density

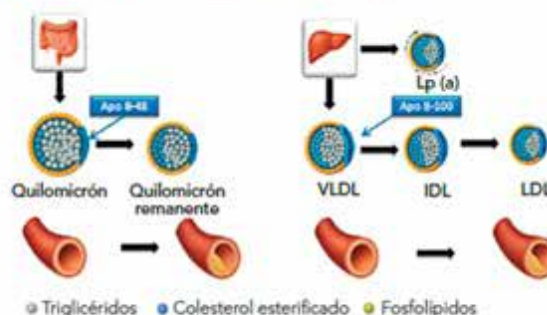
A Lipoproteínas que contienen ApoB



C ApoB refleja mejor el número de partículas aterogénicas



B Síntesis y secreción de lipoproteínas ApoB 48



D Metas actuales en relación con el RCV

Riesgo de ECVA	LDLc mg/dl	C-noHDL mg/dl	ApoB mg/dl (NLA)	ApoB mg/dl (ESC-EAS)
Riesgo muy alto	55	85	60	65
Riesgo alto	70	100	70	80
Riesgo moderado	100	130	90	100

NLA, National Lipid Association; ESC-EAS, European Society of Cardiology – European Atherosclerosis Society

CENTRAL FIGURE.

All lipoproteins with atherogenic potential share an essential structural component: a single apolipoprotein B (ApoB) molecule. As each atherogenic particle contains an ApoB molecule, its plasma concentration accurately reflects the total number of circulating atherogenic lipoproteins. B. ApoB-100 is present in VLDL, IDL, LDL and lipoprotein(a) [Lp(a)]; while ApoB-48 is found in chylomicrons and their remnants. ApoB-48 is synthesized in the small intestine, and ApoB-100, the main LDL protein, is predominantly produced in the liver. C. Two individuals may have the same level of LDL-C, but a different level of ApoB. Consequently, ApoB concentration is a more accurate and reliable marker than LDL-C to estimate cardiovascular risk. D. Therapeutic goals for LDL-C, non-HDL cholesterol (non-HDL-C) and ApoB (expressed in mg/dl), according to cardiovascular risk category.

lipoproteins (VLDL); 2) it stimulates ApoB degradation through the ubiquitin-proteasome system, responsible for its intracellular removal; 3) it favors ApoB degradation through the phagolysosomal system, another mechanism of cell degradation.^{5,6}

WHAT ARE THE METHODS AVAILABLE FOR ITS QUANTIFICATION?

Measuring a lipid component, such as the cholesterol of lipoproteins, may be more practical and slightly more economical. However, due to variability in the content of cholesterol between the particles of each lipoprotein family, the standardization of methods to quantify LDL-C or HDL cholesterol (HDL-C) is more complex than the selective measurement of a specific and structurally constant protein molecule, such as ApoB.⁷ Furthermore, ApoB behaves like a robust marker, since it can be measured accurately throughout the range of concentrations, both in normal and pathological conditions, not being affected by the possible pathophysiological variations.

The methods used by clinical laboratories for the measurement of ApoB are completely automatable, and are based on immunoturbidimetric and immunonephelometric techniques. These should meet the standards established by the World Health Organization (WHO) and the International Federation of Clinical Chemistry (IFCC) by using calibrators traceable to international reference materials, currently SP3.⁸ Both methods use specific antibodies like ApoB.

The basis of immunoturbidimetry is the formation of immune complexes with the antibody addressed against the ApoB to be measured. Then, light diffraction is measured in a given angle, which is altered by the immune complexes formed. In the case of immunonephelometry, it could be of "endpoint" when light diffraction is measured in a given angle, altered by the immune complexes formed, or "kinetic" when the dispersed light emission velocity change is measured, according to immune complexes formation velocity.

The equipment necessary to measure ApoB, as well as quality specifications and experience required, are available in a great number of clinical laboratories. Furthermore, several diagnosis companies manufacture assays approved for measurement. The standard methods mentioned are equivalent to other procedures validated and robust, such as nuclear magnetic resonance, whose equipment is addressed to specialized laboratories and that is also used to analyze lipoprotein subfractions.⁹ Since the 1990s, the IFCC has promoted the standardization of ApoB measurement, establishing a temporary reference method based on the measure, by immunonephelometry, of the total protein of LDL previously isolated by ultracentrifugation. In recent years, the IFCC has started evaluating the liquid chromatography-tandem mass spectrometry (LC-MS/MS) as a candidate to a definitive reference method, which would enable a real standardization of ApoB measurement, turning it into the first truly standardized marker of lipopro-

teins.^{7,10} For the time being, different consensus groups, organizers of the External Quality Assessment organizers, the Lipid Standardization Program of the Center for Disease Control and Prevention (CDC) of the US and other clinical chemistry experts have confirmed that the ApoB standardization program developed by the WHO/IFCC meets the necessary requirements to be applied in clinical care.¹⁰

All methods measure total ApoB (ApoB100+ApoB48); however, postprandial contribution of ApoB48 in relation to ApoB100 is minimal and insignificant, except when triglycerides exceed 400 mg/dl, so ApoB can be measured not requiring fasting in most cases. Serum samples can be frozen and then unfrozen for measurement.¹⁰

WHAT IS THE RELATIONSHIP BETWEEN APOB AND CARDIOVASCULAR RISK ACCORDING TO EPIDEMIOLOGICAL STUDIES AND MENDELIAN RANDOMIZATION?

From what was commented earlier, it is reasonable to propose that elevated levels of ApoB are associated to a greater cardiovascular risk. However, although this idea seems logical from common sense, it is necessary to back it up with scientific evidence.

Evidence from population studies shows that high levels of ApoB are associated with an increase in the risk of developing cardiovascular events. Johannesen et al. carried out an analysis on the Copenhagen General Population Study, where they included 53484 women and 41624 men who did not receive statins, and evaluated the relationship between high levels of ApoB and incidence of cardiovascular events.¹¹ After a median follow-up of 9.6 years, they showed a concentration-dependent association between elevated levels of ApoB and the risk of presenting acute myocardial infarction and atherosclerotic cardiovascular disease. This study proved that ApoB presents a significant predictive value beyond LDL-C throughout the concentration spectrum of this lipoprotein, both in men and in women. Before this study, Sniderman et al. published a meta-analysis of observational studies that included 233455 patients, where they proved that ApoB is a better predictor of cardiovascular risk than LDL-C and non-HDL-C.¹² The relative risk ratio for ApoB was 1.43 (95% confidence interval [CI]: 1.35-1.51), in comparison with 1.25 for LDL-C (95% CI: 1.18-1.33) and 1.34 for non-HDL-C (95% CI 1.24-1.44).

In the same line, Mendelian randomization studies have shown that people carriers of genetic variants associated to elevated levels of ApoB present a greater risk of developing cardiovascular events in comparison with those who don't. particularly, an analysis of the UK Biobank showed that ApoB was associated in a multivariate analysis, with nearly double the risk of cardiovascular disease (odds ratio [OR]: 1.92; 95% CI: 1.31-2.81; $p < 0.001$).¹³ On the other hand, another Mendelian randomization study showed that in cases of mismatch between levels of LDL-C and ApoB, the latter correlates more accurately with cardiovascular risk.¹⁴

WHAT IS THE ASSOCIATION BETWEEN APOB LEVELS DURING TREATMENT AND CARDIOVASCULAR RISK ACCORDING TO CLINICAL TRIALS?

As most controlled and randomized clinical trials included patients according to cardiovascular risk and LDL-C, the evidence available specifically on ApoB is more limited. Moreover, these trials generally evaluated therapeutic schemes, not establishing specific aims of ApoB as treatment target. However, the analysis of many of these studies reveals a direct correlation between the ApoB levels reached during treatment and the future incidence of major cardiovascular events.

Multiple clinical trials with statins have shown that the in-treatment value of ApoB has an independent predictive value, regardless of having been observed both in scenarios of primary and secondary prevention.^{15,16} A meta-analysis, including seven randomized clinical studies with statins, showed that a mean reduction of risk of CAD per each decrease in standard deviation (27 mm/dl) in ApoB levels was 24.4%, representing a greater risk reduction in comparison with LDL-C (20.1%) or non-HDL-C (20%).¹⁷ In this analysis, the mean concentration of ApoB per year in the treated group was 85 mg/dl, with a range of values between 71 and 105 mg/dl.

In the IMPROVE-IT study, the addition of ezetimibe to simvastatin, in comparison with just simvastatin, in patients with acute coronary syndrome, was associated to a 15% reduction in the ApoB levels (in-treatment median of 67 mg/dl), and with a 6.4% decrease in the incidence of cardiovascular events combined within 6 years of follow-up.¹⁸ Both in this study and in the FOURIER, which evaluated the effect of evolocumab in comparison with placebo in patients in secondary prevention treated with statins, the level of ApoB reached during treatment was the best predictor of myocardial infarction.¹⁹ Similarly, in the ODYSSEY OUTCOMES trial, that researched the impact of alirocumab in 18000 patients with acute coronary syndrome in comparison with placebo, it was observed that a greater basal level of ApoB was associated with a greater rate of combined cardiovascular events, as well as with greater relative and absolute reduction of events in the group treated with alirocumab.²⁰ Likewise, low levels of ApoB during treatment (<35 mg/dl) were highly predictive of a greater reduction in clinical events. As to in-treatment ApoB levels, values of 38 mg/dl were recorded in FOURIER and of 49 mg/dl in ODYSSEY OUTCOMES, which was associated with a 15% reduction in combined cardiovascular events in both studies, with follow-ups of 2.2 and 2.8 years, respectively. In the REVEAL study, which evaluated the CETP inhibitor, anacetrapib, compared with placebo in patients in secondary prevention treated with statins, a reduction in ApoB of 12 mg/dl (18%) was associated with 9% decrease in the incidence of cardiovascular events.²¹ Similarly, in the REDUCE-IT trial, that used purified eicosapentaenoic acid (EPA), a 10% reduction in ApoB levels was associated with 25% decrease in cardiovascular events.²² On the contrary, in

the STRENGTH study, which used a combination of EPA and docosahexaenoic acid (DHA), there was no significant reduction of ApoB or cardiovascular events observed, reinforcing the coherence of the association between ApoB decrease and cardiovascular risk decrease.²³

A meta-analysis that included 29 clinical studies, with a total of 332912 patients, evaluated whether a reduction of cardiovascular events associated to ApoB decrease depended on the type of drug used.²⁴ Although the magnitude in events reduction was greater in studies with statins, these trials had a weighed mean follow-up longer in comparison with those made with other treatments, such as with PCSK9 inhibitors. A comparative analysis between the FOURIER and the SPIRE studies, that used monoclonal antibodies inhibitors of PCSK9 and the meta-analysis of the CTT group (*Cholesterol Treatment Trialists' Collaboration*), which included the main trials with statins, concluded that a reduction in cardiovascular events, observed with PCSK9 inhibitors, was coherent with the expected reduction during the first two years of treatment with statins.²⁵

In brief, the evidence available is consistent in proving that, regardless of the drug used, ApoB reduction per se is associated with a significant decrease in the risk of future cardiovascular events. Although the results of clinical trials may vary according to the time of exposure to the treatment, the clinical context of patients and the characteristics of the population included, evidence backs robustly that ApoB reduction during treatment constitutes a central therapeutic goal, associated consistently with a decrease in the risk of cardiovascular events.

WHAT IS THE CORRELATION AND AGREEMENT BETWEEN APOB, NON-HDL-C AND LDL-C?

The concepts of agreement and correlation are widely used to assess the association between variables, but, although related, they represent different approaches.²⁶ Correlation focuses on the relationship between the changes observed in two variables; i.e., how one varies according to the other. Instead, agreement focuses on the degree of coincidence between the two measurement or classification methods of a single variable. Thus, while correlation measures association, agreement assesses the degree of agreement between results.

Numerous studies have analyzed the correlation and agreement between the different lipid markers. A study analyzed the lipid profiles of participants with no cardiovascular diseases, belonging to the UK Biobank (n=308182), the Women's Health Study (n=26204) and the Framingham Heart Study (n=2839).²⁷ The analysis showed a good correlation between the different lipid markers. In particular, the correlation between ApoB and LDL-C showed "r" values between 0.80 and 0.96, while the correlation between ApoB and non-HDL-C presented "r" values between 0.85 and 0.96.

It has been well established that there is a mismatch between LDL-C and non-HDL-C for a single value of ApoB.²⁸ A post-hoc analysis on the InPractice data, including pa-

tients with cardiovascular disease, treated with different lipid-lowering schemes, showed that agreement between ApoB and non-HDL-C ranges between 60.6% and 62.4%. Likewise, kappa analysis confirmed a moderate agreement between LDL-C and ApoB levels in all treatment groups, with values ranging between 0.54 and 0.59²⁹.

Data from the United Kingdom indicate that, in spite of the high correlations between ApoB and non-HDL-C (≥ 0.95) at population level (and a slightly lower correlation between ApoB and LDL-C), there is wide variability of ApoB for a given value of non-HDL-C or LDL-C.³⁰ Additionally, using population percentiles of LDL-C, non-HDL-C and ApoB in untreated adults in the National Health and Nutrition Examination Survey (NHANES) 2005-2016, for a non-HDL-C value of 100 mg/dl (approximately in percentile 10-20 of the population), the range of values of ApoB was 52 to 78 mg/dl (approximately from percentile 5 to 30).³⁰ Similarly, for a non-HDL-C value of 160 mg/dl (percentile 70-80), the values of ApoB were between 88 and 112 mg/dl (percentile 40-80). Similar findings were observed when comparing LDL-C with ApoB.

Agreement/mismatch can be defined in multiple ways: mismatch by cutoff points, mismatch by percentiles or mismatch by residuals.³¹ Regardless of the method, agreement and mismatch represent different proportions between parameters compared. Mismatch by cutoff points seems to be the most intuitive and clinically applicable method; the results of these analyses suggest that elevated levels of LDL-C, non-HDL-C or ApoB in individuals not treated with lipid-lowering medication entail a greater risk of cardiovascular disease. Instead, in people that do receive the treatment, elevated levels of non-HDL-C and ApoB seem to indicate residual risk better.

WHO DO APOB, NON-HDL-C AND LDL-C COMPARE AS CARDIOVASCULAR RISK MARKERS?

Although there is a high correlation between ApoB, LDL-C and non-HDL-C levels, different clinical situations may generate mismatches between these values and its predictive capacity for cardiovascular risk.^{30,31} In this scenario, it is important to take into account the following aspects: 1) while ApoB reflects the number of atherogenic particles, the measurement of LDL-C and non-HDL-C quantifies cholesterol mass; and 2) especially in a comparison with LDL-C, which is the main therapeutic goal to reduce cardiovascular risk, its measurement emerges often from the estimation by formulas that, as it is well known, are inaccurate. From a pathophysiological point of view, it could be proposed that if each particle containing ApoB would transport a constant amount of cholesterol, the different lipid markers (ApoB, LDL-C and non-HDL-C) would have a similar predictive value.^{32,33} However, current evidence suggests there is considerable variability in cholesterol content by the ApoB particle. This variability is determined, mainly, by lipid exchange processes between lipoproteins, which depend on multiple factors,

such as for instance, triglyceride concentration.^{34,35} As a result, conditions such as hypertriglyceridemia, obesity and resistance to insulin may generate discrepancies between these measurements, which is translated into an increase in the number of LDL particles (higher ApoB concentration), but with a reduced cholesterol content (lower concentration of LDL-C).³⁵

Different studies have analyzed the differential predictive capacity of these three markers. Considering different cohorts and points of analysis, evidence backs that ApoB concentration is more closely associated with the risk of atherosclerotic cardiovascular disease than LDL-C and non-HDL-C.^{32,36,37,38} However, patients treated with statins constitute a particular population, as these drugs reduce LDL-C preferentially, generating differences in relation to ApoB and non-HDL-C levels.

The results of the Copenhagen General Population Study, that included individuals treated with statins, reinforce this conclusion.³⁹ In cases of mismatch between ApoB and LDL-C figures, cardiovascular risk proved to be more consistently related with ApoB levels. Particularly, participants with ApoB levels above the median and LDL-C below the median presented a higher risk of all-cause mortality. In contrast, those with ApoB below the median and LDL-C above the median showed less risk of mortality. Similar results were observed when analyzing the mismatch between ApoB and non-HDL-C. According to the last Expert Consensus of the National Lipid Association (NLA), when there is mismatch between ApoB and LDL-C, between ApoB and non-HDL-C or between LDL-C and non-HDL-C, ApoB is considered the most reliable predictor for cardiovascular risk.⁴⁰

WHAT IS THE DIAGNOSTIC USEFULNESS OF APOB IN USUAL CLINICAL PRACTICE?

ApoB is an excellent biomarker to optimize cardiovascular risk stratification, particularly in patients with “normal” levels of LDL-C, but high cardiovascular risk.^{40,41} This measurement is particularly useful, as it allows evaluating the risk of cardiovascular disease more accurately in these patients. ApoB is equivalent to quantifying the number of atherogenic lipoproteins, as each particle contains a single ApoB molecule, contributing to a more accurate measurement of atherogenic risk.^{42,43}

Given that each LDL particle contains a specific amount of ApoB, in situations where LDL-C values are similar, but ApoB concentrations vary, LDL particle size and density could be different. This has direct implications on particle atherogenicity, which makes ApoB measurement particularly useful when LDL-C is low or “controlled”, conditions where risk could be underestimated. Furthermore, in patients with multiple risk factors, such as hypertriglyceridemia, diabetes, abdominal obesity, resistance to insulin or metabolic syndrome, it is usual to find small and dense LDL particles, which are associated to a greater risk of premature or accelerated atherosclerosis.⁴⁴ For this reason, in

these patients, ApoB measurement provides additional and valuable information for cardiovascular risk stratification. Likewise, ApoB measurement is useful to differentiate between familial hypertriglyceridemia and combined familial hyperlipidemia, as in the former, the value of ApoB is normal, while in the latter it is elevated.^{45,46}

In brief, ApoB is a specific and useful indicator, acting as a supplementary tool for LDL-C measurement. Its measurement allows for a personalized evaluation of cardiovascular risk, associated to lipids and facilitates the establishment of more accurate therapeutic goals, optimizing the strategies to reduce atherosclerotic cardiovascular disease.

Situations where ApoB measurement is particularly useful:

a) Optimizing cardiovascular risk stratification, especially in patients in high or very high risk, presenting “normal” or “controlled” LDL-C figures, according to the established therapeutic targets. In such cases, the presence of elevated ApoB suggests a higher atherogenic residual risk, and it may justify the intensification of therapeutic measures.

b) Improving risk stratification in patients with hypertriglyceridemia, diabetes, obesity, resistance to insulin or metabolic syndrome, where LDL-C estimation by formula is not recommended, while the measured LDL-C value may mask the presence of small and dense particles.

WHAT IS THE IMPACT OF THE MAIN LIPID-LOWERING DRUGS ON APOB LEVELS?

Different lipid-lowering therapies have proven to be efficient in reducing ApoB, contributing to a decrease in cardiovascular risk.

Statins inhibit HMG-CoA reductase, reducing cholesterol synthesis and increasing LDL receptor expression. High-intensity statins can reduce ApoB levels between 30% and 50%.⁴⁷

Ezetimibe inhibits intestinal absorption of cholesterol through the NPC1L1 transporter. When associated with statins, it provides an additional reduction of approximately 20% in ApoB levels.⁴⁸

PCSK9 inhibitors (alirocumab and evolocumab) increase recycling of LDL receptors and facilitate the depuration of particles containing ApoB. These therapies achieve reductions in ApoB of between 45% and 55%.^{19,20}

Similarly, inclisiran, a small interfering RNA (siRNA), inhibits liver synthesis of PCSK9. It is administered twice a year and produces sustained reductions of ApoB of approximately 43%.⁴⁹

Bempedoic acid inhibits ATP citrate lyase, an enzyme acting before HMG-CoA reductase. Whether alone or in combination with ezetimibe, it reduces ApoB levels between 14% and 19%.⁵⁰

Evinacumab is a monoclonal antibody inhibiting ANGPTL3, promoting lipolysis and depuration of lipoproteins containing ApoB. In patients with homozygous familial hypercholesterolemia (HoFH), an average reduction of 40.8% has been observed in ApoB levels.⁵¹ On the other hand, lo-

mitapide, an MTTP inhibitor, prevents the assembly of lipoproteins containing ApoB, achieving reductions of between 29 and 56%.⁵²

Finally, obicetrapib, an oral, selective, new-generation inhibitor of the cholesteryl ester transfer protein (CETP), known for its significant effect on atherogenic lipoproteins beyond increasing HDL-C levels, has been shown to reduce ApoB levels by 26.5% in comparison with placebo, according to a recent meta-analysis.⁵³

A summary of the impact of the different drugs on ApoB levels is presented in [Table 1](#).

WHAT ARE THE CURRENT APOB TARGETS?

One of the first recommendations in favor of using ApoB in the United States (2009) came from the American Association of Clinical Chemists, that backed ApoB measurement as a useful tool for the evaluation and follow-up of patients in risk of cardiovascular disease.⁵⁴

Canadian and European guidelines have recommended ApoB measurement in specific populations for several years now. Since 2012, the Canadian Cardiovascular Society (CCS) guideline for the diagnosis and treatment of dyslipidemia acknowledges using ApoB measurement in people with elevated levels of triglycerides, defined as >1.5 mmol/L (131 mg/dl).⁵⁵ Likewise, since 2026, the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) have recommended considering ApoB measurement, when available, in patients with hypertriglyceridemia.⁵⁶

The 2018 multi-society guideline from the American Heart Association (AHA) and the American College of Cardiology (ACC), prepared in collaboration with different leading medical organizations, established that people with triglycerides levels ≥ 200 mg/dl have a “relative indication” for ApoB measurement.⁵⁷ Additionally, the guideline indicates that an ApoB level >130 mg/dl should be considered a “risk enhancing factor” at the time of evaluating the need to start lipid-lowering therapy. However, performing universal tests for ApoB is not advised in the general population.

In 2019, ESC and EAS recommended the measurement of ApoB as an alternative for LDL-C measurement, and even, possibly, being preferred in comparison with non-HDL-C, as main marker for detection, diagnosis and treatment in individuals with elevated triglycerides, diabetes, obesity, metabolic syndrome or very low levels of LDL-C.⁵⁸ The same guideline pointed out that LDL-C levels can underestimate the risk of atherosclerotic cardiovascular disease, by not reflecting accurately the total concentration of cholesterol transported by LDL, or the total number of lipoproteins containing ApoB. On the other hand, the document defined secondary lipid targets for ApoB of <65 mg/dl, <80 mg/dl and <100 mg/dl in patients in very high, high and moderately high risk, respectively. These correspond to LDL-C targets of <55 mg/dl, <70 mg/dl and <100 mg/dl.

The 2020 guideline from the American Association of Clinical Endocrinologists (AACE) and the American Colle-

TABLE 1.

Impact of the main lipid-lowering drugs on apolipoprotein B levels.

Drug	Percentage reduction	Mechanism of action
High intensity statins	↓ 30–50%	They inhibit HMG-CoA reductase, reducing liver synthesis of ApoB by reducing production of VLDL-C. Moreover, the decrease in liver cholesterol stimulates an increase in liver uptake of LDL particles (containing ApoB) from circulation. ApoB reduction is proportional to the power of the statin used.
Ezetimibe	↓ 20%	It inhibits intestinal absorption of cholesterol (inhibiting the NPC1L1 protein) and, when associated with statins, it exerts a synergic effect on reduction of production of particles containing ApoB.
PCSK9 inhibitors (evolocumab, alirocumab)	↓ 45–55%	Monoclonal antibodies that inhibit PCSK9 in extracellular space. They increase recycling of LDL receptors and facilitate depuration of particles containing ApoB.
Bempedoic acid	↓ 14–19%	It inhibits the ATP citrate lyase, which participates in an early state of the production pathway of cholesterol in liver, just before action by the HMG-CoA reductase (target of statins). It reduces liver synthesis of ApoB by reducing production of VLDL-C. Also, the decrease in liver cholesterol stimulates an increase in liver uptake of LDL particles (containing ApoB) from circulation.
Inclisiran	↓ 43%	Small interfering RNA. It inhibits liver synthesis of PCSK9. It increases recycling of LDL receptors and facilitates depuration of particles containing ApoB.
Evinacumab	↓ 40.8%	It inhibits ANGPTL3, an inhibitor of LPL and EL. It promotes lipolysis and depuration of lipoproteins containing ApoB.
Lomitapide	↓ 29-56%	It inhibits MTTP, preventing assembly of lipoproteins containing ApoB.
Obicetrapib	↓ 26.5%	Oral, selective and new-generation inhibitor of CETP. By interfering in the exchange of cholesterol esters from HDL to LDL and VLDL for triglycerides, it modulates the composition and metabolism of these lipoproteins, decreasing ApoB levels indirectly.

ANGPTL3: angiopoietin-like 3; **ApoB**: apolipoprotein B; **CETP**: cholesteryl ester transfer protein; **HMG-CoA**: 3-hydroxy-3-methylglutaryl coenzyme A; **EL**: endothelial lipase; **LPL**: lipoprotein lipase; **MTTP**: microsomal triglyceride transfer protein; **NPC1L1**: Niemann-Pick C1-like 1.

ge of Endocrinology (ACE) emphasized that ApoB measurement can offer a more accurate evaluation for atherogenicity.⁵⁹ The guideline also acknowledged the value of ApoB in the evaluation of lipid-lowering treatment efficacy, as ApoB levels may remain above the target, even after reaching the target values for LDL-C.

In its most recent 2021 guideline, the CCS recommended using ApoB or non-HDL-C instead of LDL-C as preferred lipid measurement for the screening of patients with triglycerides >1.5 mmol/l (133 mg/dl).⁶⁰ The CCS also suggested a threshold of ApoB ≥70 mg/dl as criterion to intensify lipid-lowering treatment in patients with established atherosclerotic cardiovascular disease. The recent scientific statement by the NLA backed measuring ApoB as a reasonable strategy, not just for initial lipid evaluation, but also in patients that are under lipid-lowering treatment.⁴⁰ According to this document, the thresholds to start or intensify pharmacotherapy for ApoB levels are not as properly established as for LDL-C and non-HDL-C levels. Nevertheless, on the basis of population studies and controlled randomized trials on individuals treated with lipid-lowering drugs, it is suggested that ApoB thresholds for patients with very high, high or intermediate cardiovascular risk are 60, 70 and 90 mg/dl, respectively, to correspond with the current treatment thresholds for LDL-C and non-HDL-C.

A study made in Argentina proved that, in a healthy population, percentile 20 of ApoB was 72 mg/dl.⁶¹ It is rele-

vant to point out that this figure is found among the ApoB targets recommended by the ESC/EAS and NLA guidelines for people with high cardiovascular risk. Furthermore, percentile 10 was less than 60 mg/dl, a level that coincides with the lipid targets given by the same recommendations for a population in very high risk. In contrast, an ApoB value of more than 117 mg/dl was observed in 20% of individuals with a greater concentration of atherogenic particles, which may indicate a threshold of greater vascular risk, even in apparently healthy people.⁶¹

WHAT SHOULD WE KNOW ABOUT HYPOBETALIPOPROTEINEMIA?

Familial hypobetalipoproteinemia (FHBL) is characterized by reduced plasma concentration of LDL-C below percentile 5 for gender and age.⁶² More frequently, the monogenic form in adults results from heterozygote variants of loss of function in ApoB, and less frequently in PCSK9, leading to dominant autosomal disorder. The mutations in the ApoB gene lead to production of truncated ApoB proteins (both of ApoB100 and ApoB48), affecting the liver capacity to export lipoproteins, leading to an accumulation of triglycerides in hepatocytes, increasing the risk of developing liver diseases.⁶³ The ApoB48 mutation affects lipid absorption from the intestine, leading to malabsorption of fat and fat-soluble vitamins, and is associated with gastrointestinal, neuromuscular, ophthalmological and hema-

tological complications. The homozygous or compound heterozygous form (HoFHBL1) is rare, and may cause severe complications and phenotypical manifestations similar to abetalipoproteinemia (ABL), an autosomal recessive disorder caused by mutations in the microsomal transfer protein (MTTP). The heterozygous form (HeFHBL1) is relatively common and, in general, asymptomatic, except for moderate hypolipidemia and a tendency to fatty liver disease.⁶²

In a recent study about FHBL, more than 140 variants of the APOB gene were identified.⁶² The frequency of truncated ApoB in the general population is 1:3000 (HeFHBL1); while the homozygous form or compound heterozygous (HoFHBL1) has an estimated incidence of less than 1:1,000,000. FHBL can also be caused by mutations in the angiopoietin-like protein 3 gene (ANGPTL3), being called FHBL2 in the latter case.

HeFHBL1 is usually asymptomatic, except for low levels of LDL-C and ApoB, which reach approximately one third of normal levels. Patients may present moderate liver dysfunction, and 5-10% develop severe fatty liver disease, with possible complications like cirrhosis and liver cancer. Some rare cases present neurological complications, possibly due to vitamins E and A deficiency. On the contrary, patients with HoFHBL1 have severe clinical forms and present phenotypical characteristics similar to ABL. Among them, we find neuromuscular disorders (due to vitamin E deficit), ophthalmological disorders (due to vitamin A deficit), gastrointestinal disorders (steatorrhea, deficit in growth due to malabsorption syndrome, fatty liver disease that rarely progresses into cirrhosis and hepatocellular carcinoma), anomalies in bone metabolism (due to vitamin D deficit) and hematological anomalies (acanthocytosis in 50% of the erythrocyte population). Severe cases are diagnosed in early childhood, while moderate cases are usually diagnosed in adults during general medical checkups, due to hypolipidemia.⁶²

The diagnosis of FHBL1 is based on the identification of genetic mutations, extremely low levels of LDL-C and ApoB (less than 15 mg/dl) and the presence of clinical symptoms. Differential diagnoses should be considered, such as hypobetalipoproteinemia, secondary to chronic or terminal diseases like cancer, liver disease, hyperthyroidism, malabsorption of fats due to chronic pancreatitis and malnutrition.⁶²

Recently, polygenic forms have been described of hypobetalipoproteinemia associated with a lower risk of liver lesions and fatty liver disease, in comparison with monogenic forms, which are diagnosed by polygenic risk score and are more prevalent in the general population than previously described monogenic mutations.⁶⁴

There is no specific treatment for FHBL. This is focused on supplementation with high doses of fat-soluble vitamins and essential fatty acids, with the aim of preventing or delaying complications. Furthermore, it is important to guarantee an appropriate caloric ingestion and to restrict the ingestion of fats to prevent delays in growth.

Finally, these low cholesterol syndromes have been associated to less risk of developing cardiovascular diseases, which has opened the door to new therapeutic strategies. One example is mipomersen, an antisense oligonucleotide (ASO), which inhibits the production of ApoB100 and is used in patients with HFHo. Another relevant treatment is lomitapide, which inhibits MTTP production and is used both in the treatment of HFHo and in familial chylomicronemia syndrome (FCS).⁶⁵

CONCLUSIONS

ApoB has consolidated as a key lipid marker in the management of dyslipidemic patients, contributing diagnostic and prognostic information with great clinical value. By reflecting directly the number of circulating atherogenic particles, its quantification allows estimating the total atherogenic potential with greater accuracy. This is evident in the excellent correlation between ApoB and LDL-C, although with a moderate agreement between both parameters. Different epidemiological and genetic pieces of evidence, and those coming from clinical studies back its prognostic value in prevention of atherosclerotic cardiovascular disease. Likewise, there are efficient pharmacological tools to reduce its levels. A routine addition of ApoB in the evaluation of cardiovascular risk could optimize stratification and therapeutic approach, particularly in scenarios where LDL-C concentrations may underestimate residual risk. In this context, the acknowledgement and use of ApoB as an emerging therapeutic goal may contribute to decreasing the overall load of cardiovascular disease in a more effective manner.

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