The New Lipid Profile: From Cholesterol Quantity to Lipoprotein Particle Count

O Novo Perfil Lipídico: Da quantidade de colesterol ao número de partículas lipoprotéicas

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Since the introduction of the term "cholesterol" into laboratory medicine in the early 20th century, the lipid profile has become one of the cornerstones of preventive cardiology. The measurement of total cholesterol, followed by the identification of HDL and LDL fractions, shaped clinical reasoning and underpinned therapeutic strategies that have significantly reduced cardiovascular mortality over recent decades. However, as knowledge of lipoprotein biology has expanded, it has become evident that cholesterol concentration alone does not fully reflect atherogenic risk. Thus, the lipid profile, originally conceived as a quantitative tool for lipid mass, is evolving toward measurements that reflect the number and nature of the particles that truly cause vascular injury.

In recent decades, the lipid profile has served as the backbone of cardiovascular risk assessment. Low-density lipoprotein cholesterol (LDL-C), the primary marker used in clinical practice, has been established as an essential parameter for the diagnosis and monitoring of dyslipidemias. Nonetheless, in light of emerging genetic and pathophysiological evidence, it is increasingly clear that LDL-C, while useful, is an incomplete marker of total atherogenicity.

The 2025 Brazilian Guideline on Dyslipidemias and Prevention of Atherosclerosis[1] introduces a paradigm shift by incorporating apolipoprotein B (ApoB) and lipoprotein(a) [Lp(a)] as central components of the expanded lipid profile. This reformulation reflects a transition from lipid mass measurement to the direct quantification of circulating atherogenic particles, a shift that redefines not only how risk is measured but also how it is biologically understood.

The update also redefines reference values and therapeutic targets for LDL-C and non-HDL cholesterol, reflecting a more aggressive and stratified approach to cardiovascular risk. For individuals at low risk, the LDL-C target is now set below 115 mg/dL, while the non-HDL cholesterol target for the same risk category is below 145 mg/dL. Additionally, an 'extreme risk' category has been introduced for patients with a history of multiple major atherosclerotic cardiovascular events or a single major event combined with two or more high-risk conditions (Table 1).

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Table 1

Reference Values for the Lipid Profile and Therapeutic Targets

Parameter	Fasting (12 hours)	Non-fasting	Reference Values
Total cholesterol	< 190 mg/dL	< 190 mg/dL	
Triglycerides	< 150 mg/dL	< 175 mg/dL	
HDL cholesterol	> 40 mg/dL	> 40 mg/dL	
Parameter	**Fasting (12 hours)**	**Non-fasting**	**Risk category**
LDL cholesterol	< 115 mg/dL < 100 mg/dL < 70 mg/dL < 50 mg/dL < 40 mg/dL	< 115 mg/dL < 100 mg/dL < 70 mg/dL < 50 mg/dL < 40 mg/dL	Low Intermediate High Very High Extreme
Non-HDL cholesterol	< 145 mg/dL < 130 mg/dL < 100 mg/dL < 80 mg/dL < 70 mg/dL	< 145 mg/dL < 130 mg/dL < 100 mg/dL < 80 mg/dL < 70 mg/dL	Low Intermediate High Very High Extreme
Apolipoprotein B	< 100 mg/dL < 90 mg/dL < 70 mg/dL < 55 mg/dL < 45 mg/dL	< 100 mg/dL < 90 mg/dL < 70 mg/dL < 55 mg/dL < 45 mg/dL	Low Intermediate High Very High Extreme
Lipoprotein(a)	< 75 nmol/L (< 30 mg/dL)	< 75 nmol/L (< 30 mg/dL)	Value used for cardiovascular risk stratification. No defined therapeutic target.

The laboratory report should state whether the patient was fasting (12 hours) or non-fasting, as per the physician's instructions. Reference and therapeutic target values must be included in laboratory reports to standardize the management of dyslipidemias. For lipoprotein(a), the use of isoform-independent assays is recommended, with results expressed in nmol/L. The unit mg/dL may be used only when no alternative is available, although it is not the preferred method. Abbreviations: HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Non–HDL-C: non–high-density lipoprotein cholesterol.

Source: Adapted from Rached FH et al. (2025).[1]

ApoB: The Marker of Particles That Truly Cause Vascular Injury

Each atherogenic particle — LDL, VLDL, IDL, and Lp(a) — contains a single ApoB molecule. This characteristic gives ApoB a conceptual advantage: it directly quantifies the total number of particles capable of penetrating the arterial wall and initiating plaque formation. Recent studies have reinforced that plasma ApoB concentration is a more accurate marker of cardiovascular risk than LDL-C or non-HDL cholesterol, particularly in individuals with mixed dyslipidemia, insulin resistance, or hypertriglyceridemia.[2,3] In such cases, LDL-C levels may appear normal, masking a high concentration of atherogenic particles.

The new Brazilian guideline recommends ApoB measurement as a complementary or substitute tool for LDL-C, especially in patients at intermediate risk, undergoing lipid-lowering therapy, or in cases of clinical discordance between the lipid profile and calculated risk. This recommendation aligns with recent positions from the European Atherosclerosis Society and the American Association of Clinical Endocrinology,[4] establishing ApoB as the true 'common denominator' of plasma atherogenicity.

Lipoprotein(a): The Hidden Genetic Risk

Among the most notable advances in the 2025 Brazilian guideline update[1] is the formal inclusion of Lp(a) as an essential component of the lipid profile. Structurally similar to LDL, Lp(a) differs by carrying an additional glycoprotein, apolipoprotein(a) [apo(a)], bound to its ApoB100. This configuration confers unique proinflammatory, proatherogenic, and antifibrinolytic properties.

Recent genetic evidence demonstrates that Lp(a) is a causal, independent, and hereditary risk factor for atherosclerotic cardiovascular disease and aortic valve stenosis.[5,6] Mendelian randomization analyses have shown that a 50 nmol/L increase in Lp(a)-ApoB raises the risk of coronary artery disease by 28%, whereas the same increase in LDL-ApoB raises the risk by only 4%, indicating approximately sixfold greater atherogenicity per particle.

The clinical impact is undeniable: individuals with elevated Lp(a) levels remain at high residual risk even after strict LDL-C control, suggesting that cholesterol reduction alone is insufficient for a significant portion of the population. It is estimated that one in five individuals has Lp(a) levels above 50 mg/dL, a threshold associated with an increased risk of myocardial infarction and aortic stenosis.[7,8]

In light of this evidence, a one-time measurement of Lp(a) is now recommended for all adults, regardless of baseline risk, along with cascade family screening in cases of markedly elevated levels. This universal approach is consistent with the guidelines of the National Lipid Association (2024),[9] and the European Atherosclerosis Society (2022).[10]

From Cholesterol to Particles: A New Clinical Paradigm

The cumulative body of evidence leads to the conclusion that lipid-mediated cardiovascular risk depends not only on the amount of circulating cholesterol but also on the total number of particles that transport it. Large-scale cohort studies[2,11] have demonstrated that ApoB-containing particles, regardless of their type (VLDL, IDL, LDL), carry a risk that is proportional to their number.

This paradigm shift is reinforced by the recognition that discordance between LDL-C and ApoB is both common and clinically meaningful. Patients with LDL-C values within target ranges but elevated ApoB levels exhibit a risk comparable to that observed in individuals with high LDL-C, a finding that challenges the traditional practice of basing therapy solely on plasma cholesterol concentrations.

Lp(a), in turn, adds a component of genetic and residual risk that is not captured by other lipid measurements. The coexistence of elevated Lp(a) and increased ApoB amplifies the risk of atherothrombotic events, even in individuals without marked elevation of LDL-C.[12]

Therapeutic Challenges and Perspectives

Despite diagnostic advances, therapeutic options for Lp(a) remain limited. Statins, well-established agents in cardiovascular prevention, do not reduce Lp(a) levels and may, in some cases, increase them. PCSK9 inhibitors such as evolocumab and alirocumab have shown modest reductions (≈25%) in Lp(a) levels, whereas novel RNA-based therapies (pelacarsen, olpasiran, zerlasiran) have demonstrated reductions exceeding 90% in phase 2 clinical trials, with outcome results expected by 2026.[13,14]

These agents herald a new therapeutic era in which intervention aims not merely to lower cholesterol but to modulate the number and type of atherogenic particles. Meanwhile, clinical management should prioritize the aggressive control of all modifiable factors, including LDL-C, blood pressure, glycemia, and inflammation, along with early genetic risk stratification.

The Role of the Laboratory in Defining More Effective Biomarkers

The concept of the expanded lipid profile is not merely an addition of new tests; it represents a conceptual redefinition of atherogenic risk. The incorporation of ApoB and Lp(a) into the routine laboratory panel has the potential to enhance diagnostic precision, reclassify risk categories, and guide truly personalized therapeutic strategies.

As highlighted by Sniderman et al. (2025),[3] "ApoB quantifies the total number of particles capable of causing harm, whereas Lp(a) identifies those that do so with greater intensity."Together, they form the core of a modern lipid profile, one centered on particle biology rather than solely on the biochemistry of cholesterol.

The current challenge lies in translating this knowledge from guidelines into practice, by fostering clinical and laboratory education, improving laboratory accessibility, and implementing screening policies that democratize the use of these biomarkers.

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