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Mini Review

Particle Number vs. Cholesterol Mass: The Emerging Role of ApoB in Refining Cardiovascular Risk Stratification

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Abstract: Cardiovascular diseases (CVDs) remain the leading cause of global mortality and disease burden, with a growing cohort of patients presenting with acute coronary syndrome despite lacking standard modifiable risk factors. This persistent residual risk dictates a shift toward more accurate biomarkers. Historically, lipid management has centered on LDL-C, a measure of cholesterol mass. However, LDL-C fails to account for particle heterogeneity, which is critical since the number of atherogenic apolipoprotein-B (apoB) containing particles, not their cholesterol mass, seems to drive plaque retention. This mini review scopes the contemporary evidence supporting the utility of apoB as a superior metric for risk stratification and therapeutic targeting. Evidence from Mendelian Randomization (MR) studies suggests a causal association between apoB and CVD risk. Furthermore, both observational and discordance analyses demonstrate that apoB, by representing a direct count of all circulating atherogenic particles, is a more accurate predictor of CVD risk than traditional markers like LDL-C and non-HDL-C, suggesting its superiority for identifying high-risk individuals. Despite its established analytical advantages, apoB testing remains vastly underutilized in routine clinical practice, often downgraded to a secondary status in global guidelines. Implementation is significantly hampered by the lack of universal assay harmonization and historical health insurance payment policies that categorize the test as optional. As evidence increasingly identifies apoB as a superior predictor of cardiovascular risk compared to LDL-C and non-HDL-C, its adoption as a high-value alternative target warrants serious consideration.

Keywords: apoB; LDL-C; non-HDL-C; cardiovascular disease

1. Introduction

Cardiovascular diseases (CVDs) remain the leading global health challenge. The Global Burden of Disease (GBD) study estimated that in 2023, CVDs were responsible for 19.2 million deaths and 437 million Disability-Adjusted Life Years (DALYs), marking them the leading cause of disease burden worldwide [1]. The development of atherosclerotic cardiovascular disease (ASCVD), particularly coronary artery disease (CAD), is classically attributed to Standard Modifiable Cardiovascular Risk Factors (SMuRFs), such as hypertension, diabetes, dyslipidaemia, and current smoking. Indeed, a total of 79.6% of the CVD burden is estimated to be attributable to modifiable risk factors, with high systolic blood pressure, dietary risks, high low-density lipoprotein cholesterol (LDL-C), and air pollution being the primary drivers in 2023 [1].

Despite the efficacy of targeting SMuRFs, a substantial number of patients experiencing a first acute myocardial infarction (MI) do not present with any of these standard factors. The global proportion of SMuRF-less patients with a first presentation of Acute Coronary Syndrome (ACS) was recently estimated to be 11.56% [2]. This growing prevalence of SMuRF-less ACS, coupled with a persistent rate of recurrent events in optimally

treated patients, highlights the concept of residual cardiovascular risk and underscores the critical need for novel biomarkers for early identification and refined risk stratification.

It is now an established fact that increased plasma concentrations of cholesterol-rich apolipoprotein-B (apoB)-containing lipoproteins are causatively linked to ASCVD [3]. All atherogenic lipoproteins—including very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, and lipoprotein(a) [Lp(a)]—contain a single apoB molecule. Consequently, the measurement of apoB provides a direct assessment of the number of circulating atherogenic lipoprotein particles, as opposed to mass-based measures like LDL-C [4]. These apoB-containing particles, except for the largest ones (diameter > 70 nm), can cross the endothelial barrier into the subendothelial intima, initiating plaque formation [5].

Historically, LDL-C has been the primary measure for risk evaluation and the main target for lipid-lowering therapy (LLT) [6]. While LDL-C remains a strong causal risk factor and the focus of LLT [7], it does not fully capture the burden of atherogenic lipoproteins in all patients [6]. This limitation has prompted the use of alternative metrics. Among these, non-HDL-C, which measures the total cholesterol mass within apoB particles [8], and apoB itself has gained recognition, particularly in major guidelines such as the 2019 European Society of Cardiology (ESC) guidelines. The ESC guidelines recommend the use of apoB for risk assessment, especially in individuals with conditions like high triglycerides (TG), diabetes mellitus (DM), obesity, metabolic syndrome, or very low LDL-C [9].

Given the limitations of cholesterol-mass measures, this mini review scopes the contemporary evidence for apoB in cardiovascular risk stratification, focusing on three key areas: its superiority over traditional lipid markers, its role in lipid discordance and residual risk, and the practical challenges and implications of apoB's greater adoption as a high-value alternative target in clinical practice.

2. Why Particle Number Matters

2.1. The Limitations of LDL-C

LDL is not a structurally homogeneous entity but consists of diverse particles varying in size and density, including large buoyant (lbLDL, Pattern A) and small dense (sdLDL, Pattern B) subclasses [10]. While LDL-C has long been the standard risk measure, it is a measure of cholesterol mass and is not synonymous with the LDL particle number itself. The cholesterol content of each particle can vary more than two-fold among individuals. Consequently, while one person may have large, cholesterol-enriched LDL particles, another may have smaller, cholesterol-depleted LDL particles. Even at the same LDL-C concentration, the second person will have a significantly higher number of LDL particles [11].

This variability is clinically critical because sdLDL has a greater atherogenic potential than other LDL subfractions, and the sdLDL proportion is a better marker for cardiovascular disease prediction than total LDL-C [12]. The disparity between LDL mass and particle number limits risk assessment because many patients have LDL-C levels in the same range as those who do not [13]. Furthermore, LDL-C, even at levels currently considered normal, is independently associated with the presence and extent of early systemic atherosclerosis without major cardiovascular risk factors [14]. These findings suggest that the retention of particles, not the cholesterol mass, is the central mechanism of plaque formation.

2.2. ApoB as a Direct Measure of Particle Number

To directly assess this atherogenic burden, the focus shifts to total apoB. ApoB-100 is an essential structural protein found on all atherogenic lipoproteins (VLDL, IDL, LDL, and Lp(a)), and there is precisely one apoB molecule per atherogenic particle [13]. Thus, the plasma apoB concentration provides a direct count of the total number of circulating atherogenic lipoprotein particles, independent of their heterogeneous cholesterol and triglyceride content [15]. ApoB, therefore, unifies, amplifies, and simplifies the information from the conventional lipid markers as to the true atherogenic risk attributable to the apoB-containing lipoproteins.

2.3. Atherogenicity of ApoB-Containing Lipoproteins

Emerging evidence suggests that the atherogenic potential of apoB-containing lipoproteins varies significantly across and within different lipoprotein classes. Advanced structural analyses have demonstrated that subtle variations in particle size, lipid composition, and spatial organization dictate the conformation and dynamics of apoB on the particle surface. These structural differences directly influence particle stability, receptor interactions, and overall proatherogenic potential [5]. Notably, not all apoB-containing species carry the same risk as triglyceride-rich lipoproteins (TRLs), their remnants, and Lp(a) are more atherogenic on a per-particle basis

than LDL [16]. Nevertheless, detailed qualitative characterization of lipoproteins remains impractical for routine clinical settings. To bridge this gap, new metrics like risk-weighted apoB (RW-apoB) have been recently proposed. This approach utilizes measured plasma total apoB but applies specific weightings to the fractions associated with TRLs and Lp(a), thereby aiming to provide a more accurate reflection of an individual's cardiovascular risk compared to standard apoB measurements alone [17].

3. Evidence for the Superiority of ApoB in Risk Stratification

3.1. Evidence from Mendelian Randomization (MR) Studies

Large-scale Mendelian Randomization (MR) studies, which analyze genetic variation to establish causal links, suggests a dominant role of apoB. A major analysis of lipoprotein lipid-related traits found that the relationships between other lipid entities (LDL-C and TG) and the risk of CHD attenuated to the null when the effects of apoB were considered. In contrast, the relationship between apoB and CHD risk remained robust after adjusting for all other traits [18]. Similarly, in another MR analysis, apoB was strongly prioritized as risk factor for CAD [19], suggesting that apoB is the key determinant of CVD risk among lipid-related measurements.

The causal dominance of apoB extends to therapeutic intervention. For novel lipid-modifying agents, such as cholesteryl ester transfer protein (CETP) inhibitors, MR analyses suggest that the causal effect on the risk of cardiovascular events appears to be determined by changes in the concentration of apoB-containing lipoproteins rather than changes in LDL-C or HDL-C level [20]. Furthermore, current clinical analyses indicate that significant reductions in mortality and cardiovascular events are proportional to the absolute reduction in apoB [21]. These data strongly support the notion that the clinical benefit of any lipid-lowering therapy should be proportional to the achieved reduction in apoB concentration, regardless of the corresponding changes in LDL-C or triglycerides [22].

Beyond cardiovascular events, the impact of apoB is general influencing systemic disease risk and overall longevity. Studies have implicated apoB in several major diseases, including heart disease, stroke, and diabetes. A higher apoB was also associated with a shorter parental lifespan, an effect that was strengthened when LDL-C and TG were included in multivariable MR models. This suggests that apoB is the dominant driving force influencing lifespan among these three lipid features. Therefore, these insights suggest that apoB reduction should be the primary goal of lipid lowering, offering not only a reduction in the risks of common diseases but also the potential to extend life by months to years [23].

3.2. Evidence from Randomized Clinical Trials (RCTs)

The assessment of which lipid marker best associates with the cardiovascular benefit of statin therapy presents conflicting evidence. One meta-analysis of seven major placebo-controlled statin trials, using both frequentist and Bayesian methods, concluded that the relative risk reduction (RRR) of cardiovascular events achieved by statin therapy is most closely related to the decrease in apoB [24]. This finding positioned reductions in apoB as the superior marker, demonstrating the greatest association with risk reduction compared to changes in non-HDL-C and LDL-C, which were found to be statistically indistinguishable in their relationship to risk reduction. This superiority was deemed expected because statins generally lower LDL-C and non-HDL-C to a greater extent than they lower apoB. Therefore, the study strongly suggested that reductions in apoB are a more informative marker of the adequacy and effectiveness of statin therapy than changes in the cholesterol markers [24].

However, a separate Bayesian random-effects meta-analysis of 12 statin trials reached a different conclusion, reporting that apoB was not a consistently superior marker of benefit. This analysis found that decreases in apoB and non-HDL-C similarly predicted cardiovascular disease risk. While apoB did improve the prediction of CHD risk when added to the decrease in non-HDL-C/LDL-C, it did not improve the prediction of stroke risk. Ultimately, this study concluded that, across all drug classes, apoB decreases did not consistently improve risk prediction over decreases in LDL-C and non-HDL-C. Specifically for statins, apoB decreases added information only for predicting CHD, but not for stroke or overall cardiovascular disease risk decrease [25].

3.3. Evidence from Observational Studies

Both apoB and non-HDL-C have been recognized as superior to LDL-C as markers for assessing cardiovascular risk [26]. However, the relative performance of non-HDL-C and apoB remains a subject of continuing controversy. Evidence from a meta-analysis of 12 independent epidemiological studies reporting RRRs for both markers indicated a specific hierarchy, where apoB emerged as the most accurate marker of cardiovascular risk, non-HDL-C was intermediate, and LDL-C was the worst [27]. Conversely, the Emerging Risk Factors Collaboration (ERFC) meta-analysis found that the hazard ratios for both apoB and non-HDL-C, as well as non-

HDL-C and LDL-C, were indistinguishable [28]. The relative strength of these markers also appears to vary in specific patient populations; for instance, a meta-analysis evaluating statin-treated patients found that on-treatment levels of LDL-C, non-HDL-C, and apoB were all associated with risk, but the strength of this association was greater for non-HDL-C than for either LDL-C or apoB [29]. The debate continues, with subsequent studies showing that non-HDL-C and apoB were comparable in predicting the risk of future CHD [30], while others continue to indicate that apoB is a more precise biomarker of CVD risk than both LDL-C and non-HDL-C [31].

While apoB and other lipid markers are known to be associated with cardiovascular risk, their added value in improving risk prediction scores that already include traditional factors remains a subject of investigation. In individuals without known CVD, a study examining the addition of markers such as the combination of apoB and A1, Lp(a), or lipoprotein-associated phospholipase A2 mass to conventional risk scores (which already include age, systolic blood pressure, smoking status, history of diabetes, total cholesterol, and HDL-C) found only a slight improvement in CVD prediction [32].

Similarly, results from the UK Biobank indicated that, in a low-risk cohort, the measurement of total cholesterol and HDL-C (even in the nonfasted state) is sufficient to capture the lipid-associated risk in CVD prediction. The addition or substitution of other lipids or apolipoproteins (including apoB, apolipoprotein A1, or direct/calculated LDL-C) to classical CVD risk factors showed no meaningful or appreciable improvement in prediction. These similar findings were also reproduced in those already taking statins at baseline [33].

Furthermore, specifically integrating apoB into the European SCORE2 algorithm did not significantly improve the model's performance metrics, compared with the SCORE2 model alone [34]. This limited added value could be attributed to the overlap between apoB information and the traditional lipid markers already included in the SCORE2 model, which reduces apoB's capacity to contribute novel predictive information [34]. It is also argued that the conventional method for testing the clinical utility of a novel marker, such as calculating the Area Under the Curve (AUC), may yield invalid conclusions if the novel marker is correlated with other markers already present in the prediction algorithm [35].

3.4. Evidence from Discordance Analyses

LDL-C, non-HDL-C, and apoB exhibit high correlations, or multicollinearity, meaning that an elevation in one typically corresponds to an elevation in the others, and vice versa. This large agreement, or concordance, between the parameters tends to obscure any potential relationship linked to disagreement, or discordance, when using conventional statistical methods designed for unrelated variables [36]. Discordance between lipid parameters such as apoB and LDL-C is common [37]. Consequently, discordance analyses have emerged as a required method, comparing ASCVD risk in groups with discordant lipid parameters to those with concordant parameters, thus allowing for the examination of risk associated with disagreement among the lipid markers [36].

A recent systematic review compiling all such discordance studies compared the predictive powers of LDL-C and non-HDL-C against LDL particle number (LDL P) or apoB. The review concluded that discordance analysis provides robust evidence that apoB is a more accurate marker of cardiovascular risk than either LDL-C or non-HDL-C, despite the high intercorrelation among these variables. Therefore, neither LDL-C nor non-HDL-C is considered an adequate clinical surrogate for apoB [8].

4. Clinical Utility and Implementation in Risk Management

4.1. Current Guideline Status and Practical Barriers

Current guidelines acknowledge the role of apoB in atherosclerosis and risk prediction and have incorporated it into recommendations, though with varying emphasis and target cut points. Guideline-based targets for LDL-C show significant variation, influenced by publication year, iterative trial data, and fundamental differences among guidelines. Even when the same LDL-C target is used (e.g., <70 mg/dL), the corresponding recommended apoB level often differs, which reflects the lack of a universally accepted conversion between apoB and LDL-C and differing approaches to setting an apoB target [4].

The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidaemias, note that apoB may be a superior measure of an individual's exposure to proatherogenic lipoproteins and, therefore, may be especially useful for risk assessment in individuals where LDL-C measurement underestimates this burden, such as in individuals with high triglycerides, diabetes mellitus, obesity, or very low LDL-C [9]. The 2021 ESC guidelines on cardiovascular disease prevention in clinical practice noted that the information provided by apoB is similar to that of calculated LDL-C [38], whereas in the 2019 ACC/AHA guidelines on the primary prevention of cardiovascular disease, apoB is used as risk-enhancing factor [39].

The major limitation preventing guidelines from clearly preferring one measurement over the other is the lack of direct evidence from RCTs [40]. However, some experts consider a dedicated RCT proving apoB's superiority over LDL-C unnecessary for its adoption into routine care, noting that non-HDL-C was adopted without such a requirement [41]. Nevertheless, designing a fair RCT to directly compare apoB versus LDL-C/non-HDL-C as primary treatment targets is deemed impossible due to the intrinsic biological response to lipid-lowering therapy. If an equivalent statin dose were given to groups randomized to an LDL-C target and an apoB target, the resulting on-treatment apoB level would signal less intensive therapy compared to the LDL-C, thus making the comparison unfair. Conversely, treating the apoB group to achieve the same population percentile reduction as the LDL-C group would necessitate more intensive therapy, invalidating the comparison [42].

4.2. ApoB vs. Non-HDL-C: The Preferred Target

Despite these trial limitations, a review utilizing a SWOT analysis (short for strengths, weaknesses, opportunities, threats) suggests that apoB should be the preferred alternate target, if available, because it is the pathophysiologically more accurate marker, as the risk of ASCVD is more closely related to the number of apoB particles that become trapped in the arterial wall than the mass of cholesterol they contain. ApoB is particularly prioritized over non-HDL-C for follow-up in treated patients with conditions like mild-to-moderate hypertriglyceridemia (175–880 mg/dL), diabetes, obesity, metabolic syndrome, chronic kidney disease, or very low LDL-C (<70 mg/dL). However, non-HDL-C remains a valuable surrogate and significantly complements LDL-C when apoB is unavailable [43].

4.3. Limitations for Use of apoB

While apoB measurement offers certain advantages, its utility is limited in some settings. For instance, in cases of severe hypertriglyceridemia resulting in chylomicronemia, the immediate and overriding concern is reducing chylomicron and TG levels to prevent pancreatitis, a risk not fully reflected by apoB [44]. Another example is dysbetalipoproteinemia (Type III hyperlipoproteinemia). Dysbetalipoproteinemia is a disease of remnant lipoprotein metabolism associated with increased total cholesterol and TG levels and premature atherogenesis but is associated with low LDL-C and apoB [45]. Moreover, although Lp(a) particles contain apoB and are therefore included in apoB measurements, elevated Lp(a) may not substantially raise total apoB. Furthermore, apoB underestimates risk in patients with high Lp(a) [46]. Therefore, Lp(a) should still be measured separately when clinically indicated. Lipoprotein X (LpX) is an abnormal lipoprotein lacking apoB and is typically absent from healthy plasma. However, its levels increase significantly in patients with cholestatic liver disease or rare genetic conditions like lecithin-cholesterol acyltransferase (LCAT) deficiency [47]. In this complex lipid disorder, as well as in cases of severely low HDL-C, relying solely on apoB measurements may result in an incomplete assessment of total lipoprotein-associated cardiovascular risk [44].

4.4. Current Status in apoB Measurement

Despite its established value, the measurement of apoB has not been widely adopted in routine clinical practice. A cross-sectional analysis of over 7 million adults using 2019 United States commercial and Medicare Advantage claims data found that only 0.21% received an apoB measurement [48]. The clinical utility of apo B guidelines relies on having consistent measurements across all laboratory methods. Research by Jing Cao et al. highlights that current harmonization efforts, which use a secondary reference material for manufacturers, have been insufficient in achieving the necessary between-method comparability. Consequently, the absence of full assay harmonization prevents the establishment of a single, universal apoB cutoff for routine clinical use [49,50].

The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) defines four key characteristics for a diagnostic biomarker to become medically useful—analytical performance, clinical performance, clinical effectiveness, and cost-effectiveness. In the case of apoB, the laboratory test has not yet been completely validated for this clinical purpose according to the EFLM criteria [51,52]. However, standardization efforts, centered on the International Federation of Clinical Chemistry (IFCC)/World Health Organization (WHO) SP3 reference material, give apoB measurements the potential to meet stringent analytical performance criteria [52].

Despite this, the apoB measurement offers several significant advantages:

- Analytical Superiority: Standardized, automated, and accurate methods to measure apoB are readily available, and the analytical performance of apoB measurement methods is superior to the measurement or calculation of LDL-C and non-HDL-C [53].

- Non-Fasting Requirement: Fasting is not required for an accurate apoB measurement, improving patient compliance and simplifying the testing process [53].
- Cost Efficiency: The actual cost of producing an apoB result on a modern chemistry analyzer is low, representing only a fraction of the price typically charged (e.g., the 2021 Centers for Medicare and Medicaid Services reimbursement rate for ApoB was $21.09) [54].

5. Future Directions

ApoB testing's widespread adoption in routine clinical practice is hindered by several factors, including the lack of consistent guidance on its interpretation and application [4]. A primary barrier is the historical emphasis on cholesterol as the cornerstone of ASCVD risk management, which has positioned apoB as "optional" due to its added cost and limited clinical accessibility resulting from restrictive health insurance payment policies [55].

Global heterogeneity in healthcare infrastructure is a major barrier to universal adoption of apoB, therefore, LDL-C and non-HDL-C remain the practical options for population-level screening in many regions due to their low cost and ubiquity. Nevertheless, from a technical point of view, apoB testing does not necessarily require specialized equipment as it can be performed on the same chemistry analyzers used for standard lipid panels. Greater use of apoB may help mitigate the high costs caused by low volume and ultimately make reimbursement rates for an extended panel only slightly higher than the standard lipid panel, thereby improving its feasibility in a variety of healthcare settings [56].

Misclassification of apoB as experimental, leading to payment denials, is fundamentally harmful to patient care and can erode patient trust when high copayments are imposed. Recognizing apoB's essential function in both pre- and post-treatment risk stratification (including during LLT) and its diagnostic value, organizations like the National Lipid Association (NLA) advocate for educating clinicians and payers on its indispensable role in cardiovascular risk assessment and management [44].

6. Conclusions

The body of contemporary evidence strongly supports the re-evaluation of apoB as the superior and most pathophysiologically relevant measure of atherogenic burden compared to the traditional cholesterol-mass measures, LDL-C and non-HDL-C. Because all atherogenic lipoproteins contain one apoB molecule, the apoB concentration provides a direct count of circulating atherogenic particles, addressing the critical limitation of LDL-C, whose mass does not always correlate with particle number.

Despite its established analytical superiority (non-fasting, automated, accurate) and relatively low running cost, the routine clinical use of apoB is hindered by a lack of universal harmonization standards and pervasive historical payment policies that classify the test as "optional". Overcoming these barriers, through continued education and standardized measurement protocols, is critical. LDL-C continues to dominate clinical workflows, largely because lipid-lowering outcome trials and treatment algorithms have historically been anchored to LDL-C, and because LDL-C along with non-HDL-C are widely available, low cost, and simple to implement. However, as evidence increasingly identifies apoB as a superior predictor of cardiovascular risk compared to LDL-C and non-HDL-C, its adoption as a high-value alternative target warrants serious consideration.

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