Indian Journal of Pharmacy Practice., 2023; 16(4):294-302.
https://www.ijopp.org

Review Article

# Non-HDL Estimation Methods: Advancing Cardiovascular Disease Prediction

**Md Akbar[1], Deepak Jha[2,*], Hasan Ali[3], Tasneem Ahmad[1]**

[1]School of Pharmacy, Al-Karim University, Katihar, Bihar, INDIA.
[2]Department of Pharmacy Practice, ASPM's K. T. Patil College of Pharmacy, Dharashiv, Maharashtra, INDIA.
[3]Department of Pharmacy, Meerut Institute of Technology, Meerut, Uttar Pradesh, INDIA.

## ABSTRACT

Cardiovascular Disease (CVD) remains a global health concern, with dyslipidemia playing a significant role in its development. Traditional approaches to assessing CVD risk have primarily focused on individual lipid components, notably Low-Density Lipoprotein cholesterol (LDL-c). However, these approaches exhibit limitations, particularly when applied to populations with hypertriglyceridemia and metabolic disorders. An alternative, non-High-Density Lipoprotein cholesterol (non-HDL-c), which is calculated as the difference between total cholesterol and High-Density Lipoprotein cholesterol (HDL-c), has emerged as a superior biomarker for evaluating CVD risk. Non-HDL-c encompasses all lipoproteins associated with atherosclerosis, including those rich in triglycerides, offering a more comprehensive perspective on atherogenic burden. This biomarker possesses several advantages, including a robust correlation with atherosclerosis, consistent measurements under diverse laboratory conditions, and suitability for non-fasting samples. Most importantly, non-HDL-c exhibits superior predictive capabilities for cardiovascular events when compared to LDL-c. This review underscores the evolution of lipid assessment, elucidates the pathophysiological foundations of non-HDL-c, and underscores its central role in contemporary cardiovascular risk evaluation. Furthermore, it delves into the potential of non-HDL-c in guiding treatment decisions and enhancing patient outcomes, thus emphasizing its crucial role in the battle against CVD.

**Keywords:** Cardiovascular disease, Dyslipidemia, Non-high-density lipoprotein cholesterol, Atherosclerosis, Risk assessment, Cholesterol management.

**Correspondence:**
**Mr. Deepak Jha**
Department of Pharmacy Practice,
ASPM's K. T. Patil College of Pharmacy,
Dharashiv-413501, Maharashtra, INDIA.
Email: drdbjmw@gmail.com

**Received:** 28-08-2023;
**Revised:** 16-09-2023;
**Accepted:** 04-10-2023.

## INTRODUCTION

Cardiovascular Disease (CVD) stands as the foremost global contributor to both mortality and morbidity. As of 2019, the World Health Organization (WHO) recorded approximately 17.9 million deaths attributable to this condition worldwide.[1] Dyslipidemia, a significant inflammatory risk factor, contributes to Coronary Heart Disease (CHD) development.[2] In recent decades, our comprehension of the function of lipoproteins in CVD metabolism has significantly broadened.[3] Initially, Total Cholesterol (TC) was linked to arterial plaque formation, later refined into the concepts of "bad" and "good" cholesterol. The inclusion of Triglycerides (TG) improved our understanding, aiding in predicting plaque-related diseases. These components constitute the core elements of the lipid panel used in clinical lipidology. How we present lipoprotein concentrations effectively communicates data's relative importance to physicians. Explicitly noting levels of Low-Density Lipoprotein cholesterol (LDL-c) has become increasingly significant as both a marker of cardiovascular risk and a target for treatment. Our understanding of the "optimal" LDL-c has transformed, leading to alterations in reference ranges. At times, the TC to High-Density Lipoprotein cholesterol (HDL-c) ratio has been employed, with some adopting it as a primary indicator of heart disease risk. Current understanding reveals that the relationship between lipoprotein pathology and atherosclerosis is more complex than initially believed.[4,5] However; this novel knowledge is not consistently incorporated into education or practice. The dimensions and concentrations of lipoprotein particles, including the "particle counts" for various lipoprotein categories, as well as the levels of specific apolipoprotein, are now being acknowledged as clinical parameters with significant potential. However, their utilization is primarily restricted to research or specialized lipid clinics, primarily due to cost, restricted accessibility, and an incomplete grasp of their clinical significance.

Non-High-Density Lipoprotein cholesterol (non-HDL-c) is ready for clinical integration and should be part of every lipid

**DOI:** 10.5530/ijopp.16.4.52

profile conducted by both commercial and clinical laboratories. A standard lipid panel derives this value by subtracting HDL-c from TC. The connection between elevated blood cholesterol and CVD is well-established through consistent findings from multiple studies.[6,7] Measuring non-HDL-c concentration offers a straightforward means of assessing the total load of proatherogenic lipoproteins, including Apolipoprotein B (ApoB). This category encompasses lipoprotein (a), Very Low-Density Lipoproteins (VLDL), Intermediate-Density Lipoproteins (IDL), and their metabolic remnants.[8] In addition to assessing cholesterol levels within Low-Density Lipoprotein (LDL) particles, current guidelines in both the United States and Europe recommend the evaluation of non-HDL-c. This is calculated by subtracting HDL-c from TC and is a crucial component of cardiovascular risk assessment.[9,10]

Accumulating evidence highlights the effectiveness of therapy aimed at reducing lipid levels in preventing CVD among individuals at high risk.[9-14] Therefore, this review centers on a straightforward method for assessing the extended-term risk associated with non-HDL-c and its connection to CVD.

### Understanding Lipoproteins and Cardiovascular Disease

Lipoproteins play a vital role in transporting cholesterol and TG to peripheral tissues for cellular membrane maintenance and metabolic processes. These lipoproteins differ in their apolipoprotein compositions and the proportions of cholesterol and TG they carry.[15,16] Historically, the link between atherosclerosis and LDL-c has been predominantly linked to compact, dense particles that effectively convey cholesterol into arteries, subsequently undergoing oxidation.[17,18] However, as TG levels rise, other lipoproteins become more prominent contributors to atherosclerosis.[19,20] Significantly, VLDL, a lipoprotein rich in TG and containing ApoB, stands out as a contributor to atherosclerosis formation. It is synthesized in response to the arrival of free fatty acids in the hepatic environment. VLDL concentrations can be approximated through routine TG measurements. Epidemiological studies support TG and VLDL as predictors of CVD, with reducing TG improving CVD outcomes.[21-23] The breakdown of VLDL into IDLs by lipoprotein lipase leads to the increase of IDL subfractions in the presence of excess TG. Similar to LDL, smaller VLDL and IDL particles can infiltrate the vessel wall, transporting cholesterol to growing plaques. The consideration of lipoprotein(a) (Lp[a]) is also essential. Lp(a) bears resemblance to LDL and exhibits a strong affinity for vessel walls, being relatively less influenced by insulin resistance and TG levels; however, it can trigger thrombosis. The non-HDL-c test gains favor as it consolidates all lipoprotein concentrations associated with atherosclerosis into a comprehensive risk assessment. This metric encompasses the full spectrum of ApoB-containing lipoproteins mentioned earlier, encompassing VLDL, IDL, chylomicron remnants, Lp(a), and LDL. Non-HDL-c potentially outperforms LDL-c as a CVD predictor due to its holistic evaluation of all atherogenic particles, grounded in robust biological underpinnings. As TG levels increase, the correlation between non-HDL-c and ApoB surpasses that of LDL-c, a trend that aligns with expectations.[23,24] Various institutions recommended the adoption of non-HDL-c prior to extensive longitudinal epidemiological support.[25,26] The non-HDL-c test accounts for lipoproteins rich in TG, a factor expected to gain significance due to age-related factors, obesity, insulin resistance, and elevated blood sugar levels within the population.[4] Advancing age and weight gain often exacerbate insulin resistance, augmenting the flow of fatty acids to the liver and consequently elevating VLDL production. Specifically, individuals with metabolic syndrome and Type 2 Diabetes Mellitus (T2DM) often demonstrate heightened non-HDL-c levels.[27,28] Non-HDL-c serves as an indirect indicator of high level of LDL atherogenicity. The concept that small, dense LDLs could exhibit greater atherogenicity than their larger counterparts has been raised. When insulin resistance is present along with elevated levels of TG and Very Low-Density Lipoprotein cholesterol (VLDL-c), the esters of LDL-c can undergo conversion into VLDL and TG.[29] This transformation leads to the creation of small, dense LDL particles, often observed in individuals with elevated non-HDL-c levels. Additionally, incorporating cholesterol into VLDL aids in preventing the separation of LDL-c and LDL particle count.[30]

## EXPLORING LIPOPROTEIN SUBCLASSES

### Decoding lipoprotein sizes: From chylomicrons to high-density lipoproteins

The heterogeneity in lipoprotein particle composition is intricately linked to shifts in lipoprotein atherogenicity.[31,32] Small, dense lipoprotein particles, owing to their fast oxidation and high susceptibility to being taken up by vascular wall macrophages, are considered more prone to atherogenesis.[33] Various laboratory techniques are employed to discern LDL subfractions, each aimed at isolating LDL particles from plasma samples. These methods encompass the vertical auto profile, fragmented gradient gel documentation system, and nuclear magnetic resonance spectroscopy. Nonetheless, the conclusive determination of the comparative therapeutic benefits of these methods in contrast to traditional lipid and lipoprotein assessments remains pending. Although small, dense LDL particles are often elevated in individuals with CHD, it's noteworthy that plasma TG levels are the primary modulators of LDL particle size. Moreover, an extensive body of research has demonstrated that LDL particle size inconsistently predicts CHD risk.[34] Clinical observations have highlighted that individuals with TG concentrations of 150 mg per deciliter (mg/dL) commonly exhibit an elevated prevalence of small, dense LDL particles accompanied by diminished LDL particle size.[35] In the course of this evolutionary progression, LDL particles can originate from VLDL particles.

This transformation is made possible through the action of hepatic lipase, which removes TG-rich remnants from large VLDL particles, ultimately leading to the creation of small, dense LDL particles.[36] Consequently, a substantial positive correlation exists between TG and VLDL levels and the presence of tiny LDL particles.[35] Numerous prospective, retrospective, and case-control studies have established an association between the existence of compact, dense LDL particles and an increased likelihood of CHD. However, other investigations have revealed that while this subtype's circulation might reflect an inflammatory milieu (characterized by TG fluctuations, HDL particles, and other cardio metabolic risk biomarkers), it may not independently signify the presence of Coronary Artery Disease (CAD)[31,37] Given the atherogenic nature of both larger and smaller LDL subclasses, the apoB content (and/or the apoB-containing lipoprotein atherogenicity-enhancing influence of apolipoprotein CIII) could emerge as a more effective predictor of CHD risk within this framework.[31] A critical question arises regarding whether apoB or non-HDL-c stands as a more potent CHD risk predictor, given the existing body of evidence endorsing apoB as a CHD marker.[38,39]

In Figure 1, we have presented a schematic representation of diverse lipoprotein types, their sizes, and densities, aiding in the visual comprehension of their arrangement.[66]

## Chylomicrons

Chylomicrons constitute TG-rich particles originating from the intestine, facilitating the conveyance of dietary TGs and cholesterol to peripheral tissues and the liver. Within these particles, a collection of apolipoprotein is present, encompassing A-I, A-II, A-IV, A-V, B-48, C-II, C-III, and E. Significantly, the primary structural component is apoB-48, and every chylomicron particle contains just one apoB-48 molecule. The dimensions of chylomicrons display variability linked to the quantity of ingested fat. A diet high in fat amplifies the conveyance of TGs, leading to the emergence of larger chylomicron particles. On the contrary, when fasting, the TG load decreases, leading to the creation of smaller chylomicron particles.[40]

## Remnants of chylomicrons

The removal of TG from chylomicrons by peripheral tissues produces small particles known as chylomicron residues. These particles are proatherogenic and contain more cholesterol than chylomicrons.[41]

## Very low-density lipoproteins

These TG-rich particles are synthesized by the liver and consist of apolipoprotein B-100, C-I, C-II, C-III, and E. Apo B-100 serves as the predominant structural component, with each VLDL particle carrying a single Apo B-100 molecule. Similar to chylomicrons, the size of VLDL particles can vary depending on the amount of TG within each particle. The dimensions of VLDL particles increase as the liver produces more TG. Notably, chylomicrons surpass VLDL particles in terms of size.[42]

## Intermediate-density lipoproteins

The process of extracting TGs from VLDL by adipose tissue and muscle leads to the emergence of IDL particles distinguished by their elevated cholesterol content. Consisting of apolipoprotein B-100 and E, IDL particles play a crucial role in the progression of atherosclerosis.[42]

## Low-density lipoproteins

These particles consist of a significant portion of the bloodstream's cholesterol content comprising cholesterol-rich VLDL and IDL components. The most common apolipoprotein is B-100, with each LDL particle containing one Apo B-100 molecule. Inside LDL, a range of particles can be found, characterized by differences in both size and density. The presence of excessive small, dense LDL particles has been linked to hypertriglyceridemia, low HDL levels, obesity, T2DM, such as individuals with metabolic syndrome, as well as viral and inflammatory disorders. A consensus attributes a greater pro-atherogenic potential to compact LDL particles compared to their larger counterparts. The smaller, denser LDL particles exhibit diminished affinity for the LDL receptor, prolonging their circulation. Furthermore, they exhibit easier infiltration into artery walls and stronger binding to intra-arterial proteoglycans, leading to their entrapment within the arterial wall. Furthermore, these more compact and denser LDL particles have an increased susceptibility to oxidation, which could lead to a greater likelihood of being absorbed by macrophages.[38,43-46]

## High-density lipoproteins

HDL particles have a critical function in promoting the reverse transport of cholesterol from peripheral tissues to the liver, which contributes to their potential as anti-atherogenic agents. Beyond this, HDL particles exhibit a multifaceted range of qualities including antioxidant, anti-inflammatory, anti-thrombotic, and anti-apoptotic properties, collectively serving to deter atherosclerosis. In comparison to LDL particles, HDL particles contain elevated quantities of cholesterol and phospholipids. These particles are associated with a repertoire of apolipoprotein, including A-I, A-II, A-IV, C-I, C-II, C-III, and E. Apo A-I takes

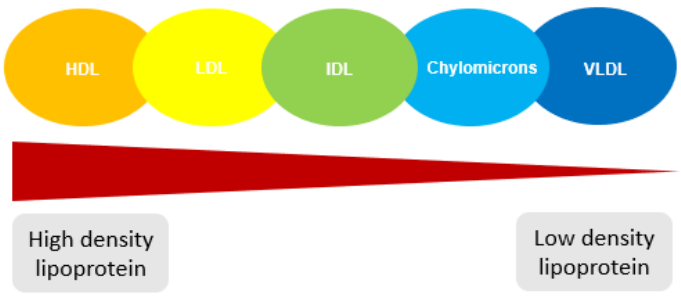


**Figure 1:** Schematically illustrates various lipoprotein types, sizes, and densities for easy visualization.[66]

precedence as the principal structural protein within HDL, with each HDL particle possibly encapsulating multiple Apo A-I molecules. HDL particles demonstrate extensive variation, lending them to classification based on factors such as density, size, charge, or apolipoprotein composition.[47]

## Drawbacks of Traditional Lipid Estimation in Cardiovascular Risk Assessment

Low-density lipoprotein cholesterol is a key target in cholesterol management for CVD and occupies the central role in the conventional approach to addressing dyslipidemia. Historically, the Friedewald equation has been the standard method for calculating LDL-c levels within the standard lipid panel. Despite its widespread application in predicting cardiovascular events, LDL-c's efficacy has diminished due to several limitations. Firstly, LDL-c solely quantifies the cholesterol content within LDL particles. Secondly, this equation yields inaccurate results in cases of dyslipidemia, specifically when TG exceeds 200 mg/dL. This concern is acknowledged by guidelines such as the Japan Atherosclerotic Society 2012 and various contemporary investigations.[38,44-46] Remarkably, LDL-c measurements can display inaccuracies, even in individuals with good health, showing a variance of 13.3-13.5%.[48]

## Embracing Non-high-density-Lipoprotein Cholesterol: Advantages and Innovation

The incorporation of non-fasting samples for the assessment of non-HDL-c levels offers a patient-friendly approach that expedites treatment decisions. This approach is in line with the 2018 recommendations, which emphasized the practicality of using non-fasting samples in healthcare decision-making, thus highlighting non-HDL-c as a crucial focus for therapeutic purposes.[47]

Non-HDL-c yields several distinct advantages as a lipid parameter. Primarily, it boasts a well-defined pathophysiological connection to the development of atherosclerosis, rendering it instrumental in comprehending the underlying disease mechanism. Moreover, non-HDL-c outperforms other commonly used lipid tests when it comes to predicting both subclinical atherosclerosis and adverse clinical outcomes, solidifying its position as a more reliable indicator of cardiovascular risk. Notably, Non-HDL-c remains unaffected by fluctuations in laboratory conditions, ensuring consistent and accurate results. Moreover, the calculation of non-HDL-c can be swiftly performed using standard lipid panels without incurring additional costs, and its assessment necessitates no special patient preparation, as it can be accurately measured from non-fasting samples. Additionally, its importance is already acknowledged within national cholesterol treatment guidelines, including the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Programme (NCEP) and the American Diabetes Association/American College of Cardiology (ADA/ACC). Lastly, the management of non-HDL-c can be effectively undertaken with readily available lipid-lowering medications. Incorporating regular reporting of non-HDL-c has the capacity to greatly improve patient outcomes by enhancing the identification of cardiovascular risk, providing guidance for treatment decisions, and simplifying the monitoring of treatment effectiveness.[47]

## Guidelines for Non-high-density-lipoprotein Cholesterol Levels

When plasma TG concentrations surpass 500 mg/dL, the primary treatment focus is on TG management to avoid pancreatitis. The emphasis on lowering LDL-c becomes relevant only after TG levels attain 500 mg/dL. In scenarios where TG plasma concentrations persist in the elevated range (ranging from 200 to 499 mg/dL), an intervention strategy incorporating lifestyle modifications and/or the utilization of hydroxy-3-methylglutaryl (HMG-CoA) coenzyme reductase inhibitors, commonly known as statins, can be employed. Statins, such as HMG-CoA Q10, function by inhibiting reductase. This class of medication serves as an adjunct to therapy by effectively reducing non-HDL-c levels. It's noteworthy that non-HDL-c targets are established to be 30 mg/dL higher than LDL-c targets, as indicated in Figure 2.[17]

When statin therapy fails to reach the desired non-HDL-c targets, healthcare providers may contemplate the addition of fibric acid or niacin supplements. Specifically, vitamin B3 (niacin) is recommended to significantly lower non-HDL-c levels, even in scenarios where LDL-c levels are not elevated. As another option, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP)-III recommends considering omega-3 fatty acids as a substitute for niacin or fibric acids.[17] Omega-3 fatty acids are effective agents for reducing TG levels and have demonstrated therapeutic merits in myocardial infarction, alongside antithrombotic and anti-inflammatory properties.[49] In clinical practice, the co-administration of omega-3 fatty acids with simvastatin has demonstrated enhanced effectiveness in reducing non-HDL cholesterol (non-HDL-c) levels and additional lipid and lipoprotein indicators when compared to the use of simvastatin alone.[50]

As per the NCEP ATP III recommendations, non-HDL-c assumes a secondary target of therapy for individuals with TG levels ranging from 200 to 499 mg/dL. This additional focus on non-HDL-c aligns with the primary objective of reducing LDL-c levels. Considering that a typical VLDL-c level is approximately 30 mg/dL, the treatment objective for non-HDL-c is set to be 30 mg/dL higher than the LDL-c target. In accordance with this guideline, individuals classified as being at an extremely high risk are advised to achieve LDL-c levels of 70 mg/dL. Conversely, individuals not deemed at very high risk are not mandated to strive for the optional target of 70 mg/dL for LDL-c.[17,51]

## Non-high-density-lipoprotein Cholesterol as a Biomarker for Cardiovascular Disease

Non-high-density-lipoprotein cholesterol has gained recognition as an alternative and more effective biomarker for addressing CAD risk, owing to its unique benefits in comparison to LDL-c. The atherogenic fraction of non-HDL-c encompasses chylomicrons, Lp(a), and their derivatives, including IDL, VLDL, and LDL, making it a comprehensive reflection of atherogenic lipoproteins.[52] Through the subtraction of estimated HDL-c from the TC level, non-HDL-c can be independently calculated, yielding a TC measurement that excludes the HDL-c component. Contemporary lipid profile analysis and cardiovascular event prediction should encompass biomarkers that fully capture the contribution of all plasma lipid components implicated in the development of atherosclerosis. Non-HDL-c encompasses the total cholesterol content found in all lipoproteins except HDL, which includes chylomicrons, VLDL, IDL, LDL, and Lp(a).[53]

The calculation of non-HDL-c concentration employs a straightforward equation:

$$\text{Non-HDL-c} = \text{TC} - \text{HDL-c}$$

Other lipid components such as LDL-c and VLDL-c can be calculated using the Friedewald method:[54]

$$\text{LDL-c} = \text{TC} - (\text{HDL-c} + \text{TG}/5)$$

$$\text{VLDL-c} = \text{TG level}/5$$

Despite the pivotal role that non-HDL-c plays in assessing plaque development and cardiac disease, its utilization remains relatively understated. However, it's noteworthy that both the American and European Cardiological Societies underscore the significance of this parameter. According to NCEP ATP III guidelines, it is suggested that non-HDL-c levels should typically be approximately 30 mg/dL higher than LDL-c levels. The routine calculation of non-HDL-c in lipid panels is advised, and it is regarded as a secondary treatment target for CVD therapy in individuals with hyperlipidemia. This complements the primary emphasis on LDL-c.[55]

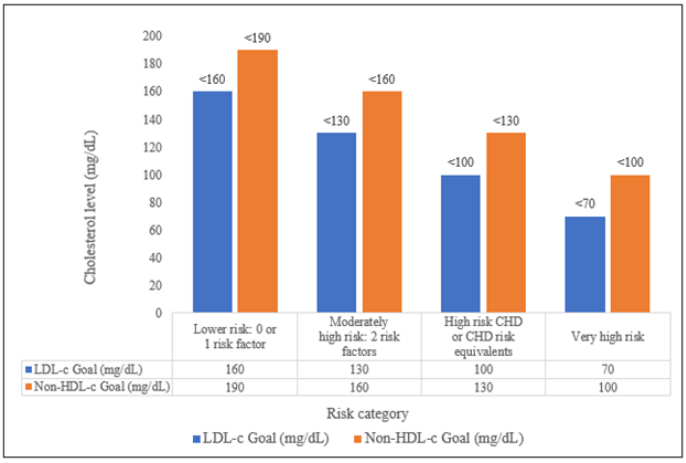


**Figure 2:** Target Cholesterol Levels for Different Risk Categories in Patients*.[17,51]

## Predicting Cardiovascular Risk with Non-high-density Lipoprotein Cholesterol

Non-high-density lipoprotein cholesterol (non-HDL-c) exhibits superior predictive capabilities for cardiovascular events compared to LDL-c. This is emphasized by evidence from various population-based studies.

As an example, in 2001 research conducted by Cui and colleagues, which included a 20-year follow-up of participants in the Lipid Research Clinics Program Follow-up Investigation, it was found that non-HDL-c exhibited a stronger predictive value for cardiovascular-related deaths compared to LDL-c. In this study, which involved 2,406 men and 2,056 women with coronary disease, a fixed 30% increase in non-HDL-c was notably associated with statistically significant cardiovascular mortality, whereas an increase of 15% and 8% in LDL-c, respectively, did not show a similar connection.[38]

In the year 2003, a study conducted by Lu and colleagues examined a group of 4,549 individuals with diabetes who were part of the Strong Heart Study. The findings of this study revealed that the hazard ratios in the top tertile for non-HDL lipoproteins were higher than those for triglycerides, LDL-c, and the total HDL-c ratio in both genders. Importantly, this predictive trend remained consistent across a range of TG concentrations.[56]

In a crucial study conducted by Ridker and colleagues in 2005, an analysis was conducted among initially healthy participants from the Women's Health Study. This analysis compared conventional cholesterol measurements, non-HDL-c, and specific apolipoprotein. It was observed that individuals in the extreme quintiles of non-HDL-c showed superior predictive performance compared to other single lipid measures and were on par with ApoB. In contrast, the top quartile of LDL-c displayed a less pronounced predictive value.[57]

Moreover, recent research conducted within the Framingham Cohort Study reaffirms the significance of non-HDL-c. In the study by Lui and colleagues, it was observed that even after making multiple adjustments, there was no remaining link between LDL-c and CVD risk once non-HDL-c was taken into account. However, a robust and positive association between non-HDL-c and CHD risk remained evident.[39]

In 2008, Orakzai and colleagues conducted a study involving 1,611 consecutive asymptomatic individuals. Their findings revealed that, in the absence of calcium, the statistical significance of the association between non-HDL-c and the presence of coronary artery calcium persisted. These results emphasize that non-HDL-c serves as a strong predictor of coronary atherosclerosis, as assessed through coronary artery calcium measurements.[58]

Studies increasingly suggest that total LDL particle levels may better predict cardiovascular risk than LDL-c levels.[59] Statins primarily reduces LDL-c while having little effect on particle size. Therefore, residual risk following cholesterol reduction may not be adequately captured by LDL-c testing alone. ApoB present in all atherogenic lipoprotein particles and every LDL particle, regardless of size, is emerging as a potential superior predictor of ongoing cardiovascular risk after statin-induced lipid reduction.[31,60]

As a result, non-HDL-c testing, which includes all lipoproteins, including ApoB, continues to be the preferred option for general use.

## DISCUSSION AND FUTURE DIRECTIONS

Our results emphasize the importance of non-HDL-c in addressing lipid disorders, particularly among young individuals who have underlying obesity conditions.[61] Individuals with elevated levels of non-HDL-c, exceeding 123 mg/dL, demonstrated significant elevations in serum TC, LDL-c, TG, the TC:HDL-c ratio, the TG:HDL-c ratio, and a decrease in HDL-c levels. The influence of increased TG levels on LDL-c, as demonstrated by the Friedewald formula, highlights the relevance of non-HDL-c in predicting CVD risk and atherosclerosis development in individuals with dyslipidemia.[62] This is particularly pertinent in conditions like diabetes and obesity, where elevated TG levels contribute to increased LDL-c and reduced HDL-c levels. Several investigations, including the Copenhagen City Heart Study, the Health Professionals Follow-up Study, and Safari, have consistently shown that non-HDL-c is more strongly correlated with ApoB than LDL-c, strengthening its importance as a risk factor. As a diagnostic marker, HDL-c exhibits diagnostic value comparable to or even surpassing that of ApoB.[10,63,64]

Non-HDL-c plays a crucial role in assessing and managing CVD risk in individuals undergoing pharmacological treatment for lipid-related issues. A comprehensive evidence-based assessment of lipid-lowering medications revealed a nearly equal ratio of reduction in non-HDL-c to reduction in CHD risk with lipid-modifying agents.[65] Therefore, emphasis should be placed on reducing both LDL-c and non-HDL-c in the prevention and treatment of CVD. Existing clinical evidence corroborates the relationship between non-HDL-c levels and atherosclerosis imaging techniques. Orakzai *et al.* explored the association between blood lipid levels and coronary artery calcification, an early marker of subclinical atherosclerosis. This further highlights the importance of non-HDL-c in evaluating and managing CVD risk in patients receiving pharmacological lipid therapy. The evidence emphasizes that a dual focus on LDL-c and non-HDL-c is crucial for optimizing cardiovascular risk reduction.[58]

Looking ahead, non-HDL-c's role is expected to expand in cardiovascular risk assessment and management. Advances in clinical research, coupled with growing awareness of the limitations of traditional lipid measurements, are likely to drive its adoption into routine clinical practice. As non-HDL-c emerges as a more comprehensive marker of atherogenic lipoproteins, efforts should be directed toward integrating it into clinical guidelines and treatment strategies. Incorporating non-HDL-c as a primary target in therapy decisions and risk assessment has the potential to enhance patient outcomes by enabling more accurate risk stratification and informed treatment choices. Moreover, ongoing research exploring the nuances of non-HDL-c in different populations and clinical scenarios will further refine its utility and impact on cardiovascular care.

## CONCLUSION

This review has discussed the evolution of lipid assessment and the pivotal role of non-HDL-c in cardiovascular risk assessment. Non-HDL-c has emerged as a superior and more reliable biomarker compared to traditional LDL-c in the evaluation of CAD risk.

The limitations of LDL-c, stemming from the Friedewald equation and its inability to account for the full spectrum of atherogenic lipoproteins, have necessitated the adoption of alternative lipid markers. Non-HDL-c, calculated as TC minus HDL-c, addresses these limitations by encompassing all cholesterol-containing atherogenic lipoproteins, including TG-rich lipoproteins. This inclusivity provides a more accurate reflection of the true atherogenic burden within the cardiovascular system.

Non-HDL-c's clinical utility extends beyond its superior predictive power. It offers a deeper understanding of athero sclerosis's pathophysiology, making it an invaluable tool for comprehending the disease process. This is particularly important in populations at risk of hypertriglyceridemia, such as those with obesity, insulin resistance, metabolic syndrome, and T2DM, where non-HDL-c outperforms LDL-c by capturing the full scope of atherogenic lipoproteins.

Furthermore, non-HDL-c aligns with evolving guidelines that emphasize the use of non-fasting samples, making it a patient-friendly approach that expedites treatment decisions. Its consistency across diverse laboratory conditions and ease of calculation using standard lipid panels contribute to its practicality in clinical settings.

As we continue to deepen our understanding of lipoprotein metabolism and its intricate connection to CVD, non-HDL-c stands as a critical and indispensable biomarker. Its routine inclusion in lipid panels and its incorporation into cardiovascular risk assessment guidelines are essential steps toward improving patient outcomes, guiding treatment decisions, and advancing our collective efforts in the fight against heart disease.

In conclusion, non-HDL-c represents a paradigm shift in cardiovascular risk assessment—a shift that not only improves the

accuracy of risk prediction but also enhances our understanding of the underlying mechanisms of CAD. Its adoption is pivotal in the quest for more effective strategies to prevent and manage this leading cause of morbidity and mortality worldwide.

## ACKNOWLEDGEMENT

The authors acknowledge the assistance received from the institute's principal and management.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**ACC:** American College of Cardiology; **ADA:** American Diabetes Association; **ApoB:** Apolipoprotein B; **ATP III:** Adult Treatment Panel III; **BARI:** Bypass Angioplasty Revascularization Investigation; **CAD:** Coronary artery disease; **CHD:** Coronary heart disease; **CVD:** Cardiovascular disease; **HDL-c:** High-density lipoprotein cholesterol; **HMG:** Hydroxy-3-methylglutaryl coenzyme; **IDL:** Intermediate-density lipoproteins; **LDL:** Low-density lipoprotein; **LDL-c:** Low-density lipoprotein cholesterol; **Lp(a):** Lipoprotein(a); **mg/dL:** Milligrams per deciliter; **NCEP:** National Cholesterol Education Program; **non-HDL-c:** Non-high-density lipoprotein cholesterol; **TC:** Total cholesterol; **TG:** Triglycerides; **T2DM:** Type 2 diabetes mellitus; **VLDL:** Very low-density lipoproteins; **VLDL-c:** Very low-density lipoprotein cholesterol; **WHO:** World Health Organization.

## SUMMARY

Cardiovascular disease remains a global health challenge, with dyslipidemia playing a significant role in its development. The conventional assessment of CVD risk primarily focused on LDL-c. However, recent advancements have highlighted the limitations of this approach. This comprehensive review emphasizes the importance of non-HDL-c as a superior biomarker for assessing CVD risk.

Non-HDL-c encompasses all atherogenic lipoproteins, offering a more accurate reflection of the atherogenic burden within the cardiovascular system. It overcomes the limitations of LDL-c, such as the Friedewald equation's accuracy issues, particularly in cases of hypertriglyceridemia. Non-HDL-c also provides a deeper understanding of atherosclerosis pathophysiology and its connection to conditions like obesity, insulin resistance, metabolic syndrome, and T2DM.

This review underscores the practicality of non-HDL-c, as it can be measured from non-fasting samples and remains consistent across various laboratory conditions. It aligns with evolving guidelines and complements LDL-c as a secondary treatment target for CVD therapy. Studies show that non-HDL-c offers superior predictive capabilities for cardiovascular events compared to LDL-c.

Further, we concluded that non-HDL-c represents a paradigm shift in cardiovascular risk assessment, offering more accurate risk prediction and a deeper understanding of CAD mechanisms. Its routine inclusion in lipid panels and integration into risk assessment guidelines are essential steps toward improving patient outcomes and advancing CVD management strategies.

## REFERENCES

1. World Health Organization [cited Jan 14, 2023]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
2. Gupta R, Rao RS, Misra A, Sharma SK. Recent trends in epidemiology of dyslipidemias in India. Indian Heart J. 2017;69(3):382-92. doi: 10.1016/j.ihj.2017.02.020, PMID 28648438.
3. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, *et al.* Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. J Am Coll Cardiol. 2008;51(15):1512-24. doi: 10.1016/j.jacc.2008.02.034, PMID 18402913.
4. Mudd JO, Borlaug BA, Johnston PV, Kral BG, Rouf R, Blumenthal RS, *et al.* Beyond low-density lipoprotein cholesterol: defining the role of low-density lipoprotein heterogeneity in coronary artery disease. J Am Coll Cardiol. 2007;50(18):1735-41. doi: 10.1016/j.jacc.2007.07.045, PMID 17964036.
5. Kannel WB, CASTELLI WP, GORDON T. Cholesterol in the prediction of atherosclerotic disease: new perspectives based on the Framingham study. Ann Intern Med. 1979;90(1):85-91. doi: 10.7326/0003-4819-90-1-85, PMID 217290.
6. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, *et al.* Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459-72. doi: 10.1093/eurheartj/ehx144, PMID 28444290.
7. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, *et al.* Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993-2000. doi: 10.1001/jama.2009.1619, PMID 19903920.
8. Authors/Task Force Members, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Atherosclerosis. 2019;290:140-205. doi: 10.1016/j.atherosclerosis.2019.08.014, PMID 31591002.
9. Grundy SM, Vega GL, Tomassini JE, Tershakovec AM. Correlation of non–high-density lipoprotein cholesterol and low-density lipoprotein cholesterol with apolipoprotein B during simvastatin+ fenofibrate therapy in patients with combined hyperlipidemia (A subanalysis of the Safari trial). Am J Cardiol. 2009;104(4):548-53. doi: 10.1016/j.amjcard.2009.04.018, PMID 19660610.
10. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, *et al.* Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478-90a. doi: 10.1093/eurheartj/eht273, PMID 23956253.
11. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials. Lancet. 2010;376(9753):1670-81. doi: 10.1016/S0140-6736(10)61350-5, PMID 21067804.
12. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, *et al.* Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016;316(12):1289-97. doi: 10.1001/jama.2016.13985, PMID 27673306.
13. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, *et al.* Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713-22. doi: 10.1056/NEJMoa1615664, PMID 28304224.
14. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. Am J Cardiol. 2002; 90(8A):22i-9i. doi: 10.1016/s0002-9149(02)02632-2, PMID 12419478.
15. Kwiterovich Jr PO. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. Am J Cardiol. 2002; 90(8A):30i-47i. doi: 10.1016/s0002-9149(02)02749-2, PMID 12419479.
16. National Cholesterol Education Program (US). Expert Panel on Detection, Treatment of High Blood Cholesterol in Adults. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) [program]; 2002.
17. Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff Jr DC, *et al.* LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of

Atherosclerosis (MESA). Atherosclerosis. 2007;192(1):211-7. doi: 10.1016/j.atherosclerosis.2006.05.007, PMID 16765964.

18. Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. Circulation. 1990;82(2):495-506. doi: 10.1161/01.cir.82.2.495, PMID 2372896.
19. Grundy SM. Non–high-density lipoprotein cholesterol level as potential risk predictor and therapy target. Arch Intern Med. 2001;161(11):1379-80. doi: 10.1001/archinte.161.11.1379, PMID 11386886.
20. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, *et al.* Triglycerides and the risk of coronary heart disease: 10 158 incident cases among 262 525 participants in 29 Western prospective studies. Circulation. 2007;115(4):450-8. doi: 10.1161/CIRCULATIONAHA.106.637793, PMID 17190864.
21. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non–high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. Am J Cardiol. 2006;98(10):1363-8. doi: 10.1016/j.amjcard.2006.06.032, PMID 17134630.
22. Ballantyne CM, Andrews TC, Hsia JA, Kramer JH, Shear C, ACCESS Study Group. Atorvastatin Comparative Cholesterol Efficacy and Safety Study. Correlation of non-high-density lipoprotein cholesterol with apolipoprotein B: effect of 5 hydroxymethylglutaryl coenzyme A reductase inhibitors on non-high-density lipoprotein cholesterol levels. Am J Cardiol. 2001;88(3):265-9. doi: 10.1016/s0002-9149(01)01638-1, PMID 11472705.
23. Abate N, Vega GL, Grundy SM. Variability in cholesterol content and physical properties of lipoproteins containing apolipoprotein B-100. Atherosclerosis. 1993;104(1-2):159-71. doi: 10.1016/0021-9150(93)90187-y, PMID 8141840.
24. Garg A, Grundy SM. Management of dyslipidemia in NIDDM. Diabetes Care. 1990;13(2):153-69. doi: 10.2337/diacare.13.2.153, PMID 2190770.
25. Frost PH, Havel RJ. Rationale for use of non–high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. Am J Cardiol. 1998; 81(4A):26B-31B. doi: 10.1016/s0002-9149(98)00034-4, PMID 9526810.
26. Sniderman AD, Scantlebury T, Cianflone K. Hypertriglyceridemic hyperapob: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. Ann Intern Med. 2001;135(6):447-59. doi: 10.7326/0003-4819-135-6-200109180-00014, PMID 11560458.
27. Sattar N, Williams K, Sniderman AD, D'Agostino Jr R, Haffner SM. Comparison of the associations of apolipoprotein B and non-high-density lipoprotein cholesterol with other cardiovascular risk factors in patients with the metabolic syndrome in the insulin Resistance Atherosclerosis Study. Circulation. 2004;110(17):2687-93. doi: 10.1161/01.CIR.0000145660.60487.94, PMID 15492304.
28. Krauss RM, Siri PW. Metabolic abnormalities: triglyceride and low-density lipoprotein. Endocrinol Metab Clin North Am. 2004;33(2):405-15. doi: 10.1016/j.ecl.2004.03.016, PMID 15158526.
29. Sacks FM. The apolipoprotein story. Atheroscler Suppl. 2006;7(4):23-7. doi: 10.1016/j.atherosclerosissup.2006.05.004, PMID 16822722.
30. Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. Circulation. 2004; 109(23_suppl_1):III-2. doi: 10.1161/01.CIR.0000131511.50734.44, PMID 15198959.
31. Chapman MJ, Guérin M, Bruckert E. Atherogenic, dense low-density lipoproteins. Pathophysiology and new therapeutic approaches. Eur Heart J. 1998; 19;Suppl A:A24-30. PMID 9519339.
32. Campos H, Moye LA, Glasser SP, Stampfer MJ, Sacks FM. Low-density lipoprotein size, pravastatin treatment, and coronary events. JAMA. 2001;286(12):1468-74. doi: 10.1001/jama.286.12.1468, PMID 11572739.
33. McNamara JR, Jenner JL, Li Z, Wilson PW, Schaefer EJ. Change in LDL particle size is associated with change in plasma triglyceride concentration. Arterioscler Thromb. 1992;12(11):1284-90. doi: 10.1161/01.atv.12.11.1284, PMID 1420088.
34. Brewer Jr HB. Hypertriglyceridemia: changes in the plasma lipoproteins associated with an increased risk of cardiovascular disease. Am J Cardiol. 1999; 83(9B):3F-12F. doi: 10.1016/s0002-9149(99)00308-2, PMID 10357568.
35. Kawakami A, Aikawa M, Alcaide P, Luscinskas FW, Libby P, Sacks FM. Apolipoprotein CIII induces expression of vascular cell adhesion molecule-1 in vascular endothelial cells and increases adhesion of monocytic cells. Circulation. 2006;114(7):681-7. doi: 10.1161/CIRCULATIONAHA.106.622514, PMID 16894036.
36. Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, *et al.* Non–high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med. 2001;161(11):1413-9. doi: 10.1001/archinte.161.11.1413, PMID 11386890.
37. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ, *et al.* Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. JAMA. 2007;298(7):776-85. doi: 10.1001/jama.298.7.776, PMID 17699011.
38. Wang Z, Shufesky WJ, Montecalvo A, Divito SJ, Larregina AT, Morelli AE. *In situ*-targeting of dendritic cells with donor-derived apoptotic cells restrains indirect allorecognition and ameliorates allograft vasculopathy. PLOS ONE. 2009;4(3):e4940. doi: 10.1371/journal.pone.0004940, PMID 19333400.
39. Gardner RS, Mayes PA. Comparison of the metabolism of chylomicrons and chylomicron remnants by the perfused liver. Biochem J. 1978;170(1):47-55. doi: 10.1042/bj1700047, PMID 629782.
40. Jayaraman S, Baveghems C, Chavez OR, Rivas-Urbina A, Sánchez-Quesada JL, Gursky O. Effects of triacylglycerol on the structural remodeling of human plasma very low- and low-density lipoproteins. Biochim Biophys Acta Mol Cell Biol Lipids. 2019;1864(7):1061-71. doi: 10.1016/j.bbalip.2019.03.001, PMID 30844432.
41. Ginsberg HN, Packard CJ, Chapman MJ, Borén J, Aguilar-Salinas CA, Averna M, *et al.* Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society. Eur Heart J. 2021;42(47):4791-806. doi: 10.1093/eurheartj/ehab551, PMID 34472586.
42. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, *et al.* Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan-2012 version. J Atheroscler Thromb. 2013;20(6):517-23. doi: 10.5551/jat.15792, PMID 23665881.
43. Aggarwal J, Reddy S, Nagtilak S. Non-HDL-C: an alternate to LDL-C for the diagnosis of cardiovascular disease. IOSR JDMS. 2016;15(2):1-4.
44. Kumar VB, Guntakalla YR, Thomas Z, Rajasekaran UR, Gnanasekaran P. Role of nonhigh Density lipoprotein cholesterol (Non-HDL-C) in predicting coronary artery disease. Indian J Pharm Pract. 2015;8(4):166-70.
45. Estrada-Luna D, Ortiz-Rodriguez MA, Medina-Briseño L, Carreón-Torres E, Izquierdo-Vega JA, Sharma A, *et al.* Current therapies focused on high-density lipoproteins associated with cardiovascular disease. Molecules. 2018;23(11):2730. doi: 10.3390/molecules23112730, PMID 30360466.
46. Miller WG, Myers GL, Sakurabayashi I, Bachmann LM, Caudill SP, Dziekonski A, *et al.* Seven direct methods for measuring HDL and LDL cholesterol compared with ultracentrifugation reference measurement procedures. Clin Chem. 2010;56(6):977-86. doi: 10.1373/clinchem.2009.142810, PMID 20378768.
47. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, *et al.* AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation; 2018. p. 2019;139(25):e1082-143.
48. Nambi V, Ballantyne CM. Combination therapy with statins and omega-3 fatty acids. Am J Cardiol. 2006; 98(4A):34i-8i. doi: 10.1016/j.amjcard.2005.12.025, PMID 16919515.
49. Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, *et al.* Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. Circulation. 2004;110(2):227-39. doi: 10.1161/01.CIR.0000133317.49796.0E, PMID 15249516.
50. Bittner V. Non-HDL cholesterol–measurement, interpretation and significance. Adv Stud Med 2007;7. 2007;1:8-11.
51. Friedward WT. Estimation of plasma low-density lipoprotein cholesterol concentration without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499-502.
52. Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, *et al.* Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2007;29(7):1354-67. doi: 10.1016/j.clinthera.2007.07.018, PMID 17825687.
53. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, *et al.* European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Eur Heart J. 2007;28(19):2375-414. doi: 10.1093/eurheartj/ehm316, PMID 17726041.
54. Bittner V, Hardison R, Kelsey SF, Weiner BH, Jacobs AK, Sopko G, *et al.* Non–high-density lipoprotein cholesterol levels predict five-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI). Circulation. 2002;106(20):2537-42. doi: 10.1161/01.cir.0000038496.57570.06, PMID 12427648.
55. Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ, *et al.* Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. Diabetes Care. 2003;26(1):16-23. doi: 10.2337/diacare.26.1.16, PMID 12502653.
56. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non--HDL cholesterol, apolipoproteins AI and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA. 2005;294(3):326-33. doi: 10.1001/jama.294.3.326, PMID 16030277.
57. Orakzai SH, Nasir K, Blaha M, Blumenthal RS, Raggi P. Non-HDL cholesterol is strongly associated with coronary artery calcification in asymptomatic individuals. Atherosclerosis. 2009;202(1):289-95. doi: 10.1016/j.atherosclerosis.2008.03.014, PMID 18452924.
58. Cromwell WC, Otvos JD. Low-density lipoprotein particle number and risk for cardiovascular disease. Curr Atheroscler Rep. 2004;6(5):381-7. doi: 10.1007/s11883-004-0050-5, PMID 15296705.
59. Ruminska M, Czerwonogrodzka A, Pyrzak B. Evaluation of usefulness of non-HDLc in children and adolescents with abdominal obesity. Pediatr Pol. 2010;1:1-5.
60. Shimano H, Arai H, Harada-Shiba M, Ueshima H, Ohta T, Yamashita S, *et al.* Proposed guidelines for hypertriglyceridemia in Japan with non-HDL cholesterol as the second target. J Atheroscler Thromb. 2008;15(3):116-21. doi: 10.5551/jat.e560, PMID 18603817.

61. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non–high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation. 2005;112(22):3375-83. doi: 10.1161/CIRCULATIONAHA.104.532499, PMID 16316964.
62. Benn M, Nordestgaard BG, Jensen GB, Tybjaerg-Hansen A. Improving prediction of ischemic cardiovascular disease in the general population using apolipoprotein B: the Copenhagen City Heart Study. Arterioscler Thromb Vasc Biol. 2007;27(3):661-70. doi: 10.1161/01.ATV.0000255580.73689.8e, PMID 17170368.
63. Robinson JG, Wang S, Smith BJ, Jacobson TA. Meta-analysis of the relationship between non–high-density lipoprotein cholesterol reduction and coronary heart disease risk. J Am Coll Cardiol. 2009;53(4):316-22. doi: 10.1016/j.jacc.2008.10.024, PMID 19161879.
64. Reese JA, Roman MJ, Deen JF, *et al.* Dyslipidemia in Young American Indians: Strong Heart Family Study. medRxiv [cited Aug 21, 2023] [cited Aug 21, 2023]. Available from: https://www.medrxiv.org/content/10.1101/2023.06.13.23291360v1.
65. Hangargekar P, Jha D, Akbar MA, Pawar S, Joshi A. Exploring non-high-density lipoprotein estimation methods and their clinical significance in cardiovascular disease. Adv Pharma J. 2023;8(2):37-42. doi: 10.31024/apj.2023.8.2.1.
66. Su X, Kong Y, Peng D. Evidence for changing lipid management strategy to focus on non-high density lipoprotein cholesterol. Lipids in health and disease. 2019;18(1):1-7.


**Cite this article:** Akbar M, Jha D, Ali H, Ahmad ST. Non-HDL Estimation Methods: Advancing Cardiovascular Disease Prediction. Indian J Pharmacy Practice. 2023;16(4):294-302.