



## Review Article

# LDL-C, NON-HDL-C and APO-B for cardiovascular risk assessment: Looking for the ideal marker



Dr Jyoti Aggarwal <sup>a,\*</sup>, Mr Gobardhan Kathariya <sup>b</sup>, Dr Puneet K. Verma <sup>c</sup>

<sup>a</sup> Department of Biochemistry, MMMSR, Mullana, Ambala, India

<sup>b</sup> Department of Biochemistry, MMMCH, Solan, India

<sup>c</sup> ACE Heart and Vascular Institute, Mohali, Punjab, India

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## ABSTRACT

The traditional approach to the management of coronary artery disease (CAD) focuses mainly on low density lipoprotein cholesterol (LDL-C) which is often considered a crucial risk factor for the progression of atherosclerosis. Despite its extensive use in predicting CAD risk, it has become a sub-optimal marker owing to several limitations. Recently, non-high density lipoprotein cholesterol (non-HDL-C) and apolipoprotein-B (Apo-B) have been substantiated to be more reliable predictors of CAD risk. On the basis of available evidence, it is fair to say that non-HDL-C is a more realistic primary target of therapy and can be used for initial screening. In the current scenario, India being a developing country, the population would not be burdened with additional cost of Apo-B estimation as non-HDL-C can be estimated in the non-fasting state which makes it both patient and clinician friendly. Considering this fact, the aim of the present review article is to highlight the reliability and efficacy of non-HDL-Cholesterol and hence make recommendations to incorporate non-HDL-C in routine lipid panel for better assessment of CAD.

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## 1. Introduction

Coronary Artery Disease (CAD) presents a significant health burden worldwide and is one of the prominent causes of mortality and morbidity across the globe. The main cause of progression of the CAD is atherosclerosis. Cholesterol (in free and esterified forms) is one of the key components of the atherosclerotic plaque. Dyslipidemia is a widely established independent major risk factor for CAD.<sup>1</sup> The traditional approach to CAD risk assessment includes measurement of serum levels of fasting total cholesterol (TC), HDL cholesterol (HDL-C), triglycerides (TG) and calculated LDL cholesterol (LDL-C). As per the guidelines from National Cholesterol Education Program (NCEP)<sup>2</sup> low-density lipoprotein cholesterol (LDL-C) is still considered as a primary target of lipid lowering therapy for cardiovascular diseases.

### 1.1. LDL-C: A sub-optimal marker

The role of LDL-C is to transport cholesterol from liver to various extra hepatic tissues. It is a low density lipoprotein molecule rich in

cholesterol and cholesteryl esters. Conventionally, the traditional approach to the management of CAD risk focuses mainly on LDL-C which is the predominant atherogenic lipoprotein particle in the circulation. Some primary prevention trials also showed that lowering LDL-C levels with lipid lowering drugs like statins reduced the risk of coronary events.<sup>3,4</sup>

LDL-C is most often measured indirectly, using a calculation based on other blood lipid analysis. Historically, the Friedewald calculation has been the most common approach in the estimation of LDL-C. This equation, developed in the 1970s, incorporates total cholesterol, HDL-cholesterol (HDL-C), and triglyceride concentrations (TC-[HDL-C + TG/5]). Similarly, direct LDL-C assays which are currently available are dependent on proprietary chemical based methods and not on ultracentrifugation. This is why they are not necessarily reliable in prediction of CAD risk.<sup>5</sup> Direct LDL-C measures are not standardized and in some cases the values can be even less accurate than Friedewald-equation.<sup>6</sup> Rifai N et al even pointed out that the chemical-precipitation method for direct-LDL-C has no appreciable advantages in precision, accuracy as well as sensitivity.<sup>7</sup>

Despite its extensive use in the prediction of coronary artery disease risk and in clinical decision making, the LDL-C has now become a sub-optimal marker owing to some prominent limitations.

\* Corresponding author.

E-mail addresses: [jotsagg@yahoo.com](mailto:jotsagg@yahoo.com) (D.J. Aggarwal), [kathariyadeepak@gmail.com](mailto:kathariyadeepak@gmail.com) (M.G. Kathariya), [puneet\\_verma@hotmail.com](mailto:puneet_verma@hotmail.com) (D.P.K. Verma).

- The Friedewald-calculated LDL-C gives inaccurate results, predominantly in case of hypertriglyceridemia as already reported by Japan Atherosclerotic Society (JAS) 2012 guidelines. Even in healthy individuals LDL-C has been giving erroneous results in the range of 13.3–13.5 %.<sup>8</sup>
- LDL-C concentration reflects only the amount of cholesterol present in LDL particles (by-products of fat transport that remain in circulation for an extended period of time and are formed when triglycerides are removed from VLDL by the lipoprotein lipase enzyme) while it does not include the participation of other lipoprotein fractions ( e.g. Lp(a), VLDL) that are crucial to the development of atherosclerosis.
- Besides these limitations, the estimation of LDL-C requires fasting serum sample thus causing inconvenience to both patients and clinicians and also delayed reporting.

Moreover, coronary events continue to occur in the population despite the use of LDL-C targeted therapy which suggests that LDL-C might not be the best predictor of CAD risk and thus, highlighting the need to reconstitute cardiovascular risk reduction algorithms beyond the focus on LDL-C levels.<sup>9</sup> In a large randomized controlled trial, Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT/TIMI 22), it was shown that 22.7 % of the patients had a recurrent coronary event at 2 years of follow-up despite attaining low levels of LDL-C and optimal medical care.<sup>10</sup>

### 1.2. Apo-B: An emerging risk marker

The limitations of LDL-C have made it a questionable standalone marker for CAD risk assessment. Therefore, modern diagnosis of the lipid related abnormalities including CAD should be based on such parameters which are unaffected by these limitations. Emerging studies have suggested some of the potential surrogate lipid markers for better assessment of CAD risk which includes apolipoprotein B as well as non-high density lipoprotein cholesterol (non-HDL-C). Both non-HDL-cholesterol and Apo-B have high correlation with CAD risk, especially when LDL-cholesterol appears to be within the normal range (Fig. 1).

Apolipoprotein B is a non-exchangeable apolipoprotein exclusively associated with plasma lipoproteins. It is a key structural component of all the atherogenic lipoprotein particles and found in all  $\beta$ -lipoproteins including small dense LDL. Apolipoprotein B is the major apolipoprotein of LDL, which has been implicated in the development of atherosclerosis and at the same time it is also essential for the binding of LDL particles to the LDL receptor for cellular uptake and degradation of LDL. Apolipoprotein B is able to directly measure the aggregate number of all the atherogenic lipoproteins as each of the atherogenic particles contains some apoB<sub>100</sub> molecule.<sup>11</sup> It has been found that increased levels of Apo-B in plasma is directly related to the development of CAD. There are several reports which indicate that Apo-B is better predictor of coronary risk than LDL-C. Jae-Hong Ryoo et al.<sup>12</sup> found Apo-B to be independently related to the risk of CAD using Framingham risk score (FRS) in healthy Korean males and Walldius G et al.<sup>13</sup> also suggested that Apo-B may not only be a better predictor of risk but also a better monitor of therapy than LDL-C alone. Similarly, Shai et al.<sup>14</sup> estimated the relative risk for lipids and apolipoproteins as predictors of CAD in 32,826 US women and found that Apo-B levels were more strongly associated with increased CAD incidence.

Sniderman et al.<sup>15</sup> found that Apo-B is superior over non-HDL-C and suggested its incorporation into routine clinical practice. Sweetnam et al.<sup>16</sup> in 2008 conducted a prospective study and a strong relationship was found between the levels of Apo-B and the incidence of the CAD. Similarly, Sabino et al.<sup>17</sup> found that hypertension, Apo-B levels as well as Apo-B/ Apo-A<sub>1</sub> ratio independently

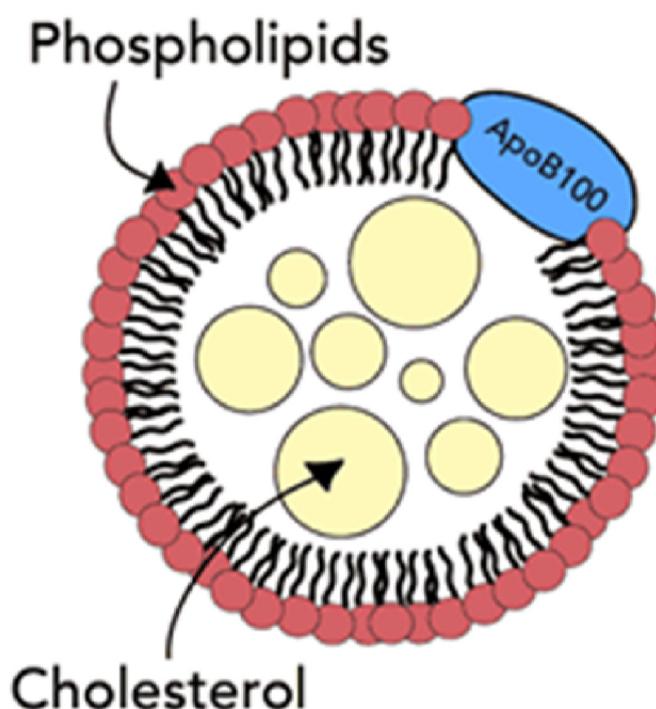


Fig. 1. ApoB100 associated in lipoprotein. Source: Apolipoprotein B level (Richardson, 2020).

correlated with brain stroke as well as peripheral atherosclerosis. Similar results were also found in the study conducted by Pischon et al.<sup>18</sup> which demonstrated that Apo-B could predict the occurrence of CAD. Studies conducted by Mashayekhi et al.<sup>19</sup> and Sattar et al.<sup>20</sup> argued in favour of Apo-B for the better assessment of future CAD risk. Similarly, AMORIS (Apolipoprotein Mortality Risk Study)<sup>21</sup> and INTERHEART study<sup>22</sup> have endorsed Apo-B as a better parameter than conventional lipid profile panel in CAD risk prediction.<sup>20</sup>

### 1.3. Non-HDL-C: Promising novel marker

Non-HDL-C was introduced by ATP III guidelines in 2001 (Adult Treatment Panel III) as an alternate target therapy for hypertriglyceridemia patients.<sup>23</sup> In several studies it has been found that non-HDL-C correlates better with the characteristics of the metabolic syndrome. The Lipid Research Clinics Program Follow-up study by Cui et al.<sup>24</sup> including 4,462 subjects observed the importance of non-HDL-C levels in hypertriglyceridemic population. Similarly, Pischon et al.<sup>25</sup> concluded in their study that high levels of non-HDL-C correlated well with severity of coronary atherosclerosis, particularly in hypertriglyceridemic patients.

Levinson SS et al.<sup>26</sup> in their study found that serum non-HDL-C is better correlated with Apo-B than LDL-C. The BARI study (Bypass Angioplasty Revascularization Investigation)<sup>27</sup> found that non-HDL-C was a significant as well as independent predictor of non-fatal myocardial infarction (MI). Similarly, Kathariya et al. in 2020 found non-HDL-C to be much specific and sensitive parameter than Friedewald calculated LDL-C for CAD risk assessment.<sup>28</sup> A study conducted by Ridker et al. which was analysed on the basis of relative hazard ratios, concluded that non-HDL-C was better predictor of future coronary events as compared to Apo-B in women<sup>29</sup> and Grundy et al. proposed non-HDL-C as a surrogate marker for Apo-B.<sup>30</sup>

A number of primary and secondary prevention trials have shown non-HDL to be a better marker of CAD risk than LDL-C in both genders, individuals with and without diabetes and in groups

irrespective of race, gender and diabetes.<sup>31</sup> A relationship between CAD and non-HDL-C was demonstrated in a multivariate logistic regression analysis of data from the Cholesterol lowering Atherosclerosis Study<sup>32</sup> and in this analysis, non-HDL-C was the best predictor of overall change in the extent of coronary artery disease among men who were not using lipid lowering drugs.<sup>33</sup> In addition; recent post-hoc analysis has demonstrated that the on-treatment, level of non-HDL-C is more closely associated with cardiovascular outcome than LDL-C.<sup>34</sup> Liu et al.<sup>35</sup> compared the diagnostic value of non-HDL-C as a prognostic factor of acute coronary events and myocardial infarction among healthy subjects and diabetes and found non-HDL-C to be a better predictive indicator than the traditional lipid markers. In multiple interventional studies with statins it has been concluded that on-treatment levels of LDL-C and non-HDL-C are equally associated with cardiovascular outcomes; some studies even indicated that non-HDL-C is better marker with respect to LDL-C in this regard. For example, Kastelein JJ et al.<sup>36</sup> (2008) concluded that non-HDL-C levels during statin treatment is a better indicator of cardiovascular disease risk. Another study has reported that among statin treated patients the risk of future cardiovascular events could be assessed by the measurement of LDL-C, non-HDL-C and Apo-B but the association was strongest for non-HDL-C. The study by Ballantyne CM et al.<sup>37</sup> compared LDL-C, non-HDL-C and Apo-B levels before and during statin therapy in cohort of high coronary heart disease risk, and observed that non-HDL-C measurement could be an acceptable marker instead of Apo-B. A meta-analysis to determine the relationship of non-HDL-C and risk of coronary heart disease in multiple interventional studies with lipid lowering agents including statins concluded that the lowering of non-HDL-C could be an important target in preventing cardiovascular disease.<sup>38</sup> In large study<sup>39</sup> involving 524,444 individuals in the 44 cohorts in multiple countries the authors used multivariate analysis to conclude that non-HDL-C concentration has strong association in long term cardiovascular risk.

Non-HDL-C owing to its distinctive advantages over LDL-C is now considered a surrogate and better marker for CAD risk assessment. The chylomicrons, very low density lipoprotein (VLDL) and their remnants, intermediate density lipoprotein (IDL), low density lipoprotein (LDL) and Lp(a) account for the atherogenic non-HDL-C fraction. The value of non-HDL-C can be obtained by a simple and quick calculation of subtracting High Density Lipoprotein Cholesterol (HDL-C) from Total Cholesterol (TC) i.e. TC minus HDL-C that can be obtained even in the non-fasting state without any effect on the results. It avoids potential inaccuracy caused by inherent intra-individual variability of triglycerides measurement. This enables non-HDL-C to be more patient friendly and enables timely clinical decision making. Moreover, 2018 guidelines have also highlighted the utility of non-fasting sample in prognostication and mapping management.<sup>40</sup> Further, American and European Cardiologists Societies, International Atherosclerosis Society, Expert Dyslipidemia Panel and the National Lipid Association have strongly recommended the incorporation of the non-HDL-C in routine lipid profile panel. The Lipid Association of India<sup>41</sup> has also recommended non-HDL-C as co-primary target in prediction of CAD risk. Unfortunately, the usage of non-HDL-C in routine lipid panel has found very little support of cardiologists in India despite its efficacy in CAD risk prediction validated by several epidemiological studies as well as clinical trials.

#### 1.4. Non-HDL-C or Apo-B: Which is reliable?

Apo-B as well as non-HDL-C has been considered as a better predictor for the assessment of CAD risk over LDL-C, but the relative usefulness of either parameter has not been critically assessed.

Various studies including Health Professionals Follow-up Study, Safari and Copenhagen City Heart Study indicated that non-HDL-C correlates better with Apo-B and its diagnostic value as a risk factor is similar or as high as Apo-B. In contrast some of the studies which were based on relative odds and risk ratios concluded that both non-HDL-C and Apo-B were strong predictor of CAD, but Apo-B was the better maker in men compared to women.<sup>42</sup> AFCAPS/TexCAPS study as well as van Lennep JE et al. found Apo-B as a better predictor of acute coronary events than non-HDL-C.<sup>43</sup>

Aggarwal J et al.<sup>44</sup> compared the predictive value of Apo-B and non-HDL-C on the basis of AUROC analysis and non-significant difference was observed. Therefore, the authors supported the use of non-HDL-C as an initial screening tool for CAD risk. Similarly, Stanley S. Levinson et al.<sup>45</sup> on the basis of ROC analysis found a non-significant difference between Apo-B and non-HDL-C in CAD risk prediction. Further, Sondermeijer et al.<sup>46</sup> concluded that both non-HDL-C as well as Apo-B are equivalent in predicting the future CAD risk. Another study conducted by Hermans et al in 2011 using the validated discriminant ratio demonstrated that in diabetic patients, both non-HDL-C as well as Apo-B performed equally well. The Emerging Risk Factors Collaboration study found that non-HDL-C as well as Apo-B was the most predictive parameters in CAD risk prediction.<sup>47</sup> Thus, both Apo-B as well as non-HDL-C has emerged as predictable markers beyond LDL-C in CAD risk prediction.

Unlike Apo-B, non-HDL-C can be easily determined from the standard lipid profile panel and requires no additional expense and thus, readily available for clinical decision making. Also, the mean time to report for Apo-B is about four times longer than that of non-HDL-C. There are also several other challenges due to which the use of Apo-B as a primary therapeutic target in management of CAD risk is still ignored.

## 2. Conclusion

Both the Apo-B and non-HDL-C are being accepted as parameters of CAD risk stratification beyond LDL-C. The ESC/EAS 2019 Guidelines<sup>48</sup> recommend that, in patients with diabetes, obesity, metabolic syndrome, high triglyceride concentration or very low LDL-C levels, non-HDL-C and Apo-B should be preferred for the assessment of the CAD risk. Further, unlike LDL-C non-HDL-C level can be estimated via non-fasting sample thereby facilitating clinical decision making. This is further endorsed by the 2018 guidelines and allows non-HDL-C to be a primary therapeutic target. Henceforth, in the light of studies conducted by Ramjee et al., Brunner FJ et al., Stanley S. et al., Aggarwal J et al. and many other researchers, we would suggest to incorporate non-HDL-C in the standard lipid profile panel for assessing CAD risk in the vulnerable population.

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