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Non-HDL-C levels and residual cardiovascular risk: Do population-specific precision approaches offer advantages?

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Since the initial discovery of the links between dietary fats, blood lipids and coronary heart disease (CHD) risks nearly eight decades ago [1, 2], extensive research has been conducted in this area and the risk factor role of blood lipids and lipoproteins in the development of atherosclerotic cardiovascular disease (CVD) is firmly established. Significant improvements in our understanding of the physiological role, function, regulation and metabolism of each lipoprotein class during health and disease have permitted the establishment of reference values for normal (optimal or desirable) and pathological concentrations for both pro- and anti-atherogenic lipoprotein classes. These values provide guidance to clinicians when assessing an individual patient's risk of developing CVD and have also been used in guidelines to monitor treatment effects and to establish therapeutic goals. It is increasingly appreciated that lipid and lipoprotein traits differ between population (ethnic/racial) groups and/or geographical locations. For example, at a population level, African-Americans have higher levels of high-density lipoprotein cholesterol (HDL-C) and lower levels of triglycerides compared to Caucasians [3, 4]. These population-specific characteristics in lipid profile may become important in evaluating the dynamic interplay between multiple risk factors, leading to the development of CVD [3].

Based on the findings of a large number of epidemiological, population-based as well as mechanistic and experimental studies, effective lifestyle- and pharmacological-based interventions for reducing circulating levels of atherogenic lipoproteins have been developed. These include, but are not limited to, lifestyle modifications (reducing dietary saturated fat intake, increasing dietary fiber and plant sterols/stanols intakes, staying physically active and exercising regularly) as the corner stone of treatment [5, 6] as well as use of lipid-lowering medications such as 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (i.e., statins). Due to these seminal works and developments as well as the increasing public awareness regarding the importance of maintaining a healthy lifestyle to reduce cardiovascular risk, age-adjusted prevalence of elevated levels of low-density lipoprotein cholesterol (LDL-C) among U.S. adults aged 40–74 yrs has decreased from 59% to 27% from the late 1970s through 2007–2010 [7]. Accordingly, the percentage of U.S.

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adults using lipid-lowering medication increased from 5% to 23% from the late 1980s through 2007–2010 [7]. These shifts have contributed to reduce heart disease and stroke mortality over the last decades [8].

Although LDL-C is well established as a CVD risk factor, dyslipidemia is frequently characterized by a more complex pattern with elevated levels of triglycerides, remnant lipoproteins, lipoprotein(a) and a lipoprotein subfraction pattern considered unfavorable in addition to low levels of HDL-C. Notably, a low level of HDL-C is the most commonly observed type in patients with premature CVD [9] and it has been shown to be a strong independent predictor of incident cardiovascular events [10–12]. Therefore, assessment of an individual's risk of CVD based on LDL-C level alone, a snap shot of a steady-state pool size of a single class of atherogenic lipoproteins, may not always accurately reflect a person's global risk for CVD development. Given these complexities, non-HDL-C, calculated as the difference between HDL-C and total cholesterol concentrations, has been identified as a useful tool to capture a more complex dyslipidemic pattern. Measurement of non-HDL-C concentration may be particularly useful in individuals with high levels of triglycerides, reflecting those in triglyceride-rich lipoproteins such as lipoprotein remnants and VLDL-C. It has been suggested that the non-HDL-C concentration, a sum of all apolipoprotein (apo)-B-containing atherogenic lipoprotein populations, predicts CVD risk at least equivalent to or even more robustly than LDL-C concentration [13–15].

In this context, the study by Brito et al., published in this issue of *Atherosclerosis* offers opportunities for additional population-specific insights into the use of non-HDL-C treatment goals in detecting and reducing residual CVD risk. Their study included about 15,000 subjects, participating in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). The ELSA-Brasil recruited civil servants aged between 35 and 74 years in a spectrum of regions across Brazil (six cities: Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, São Paulo and Vitória). The cohort consisted of approximately equal number of men and women with on average a relatively normal lipid profile. All laboratory parameters were measured in a single laboratory, reducing the potential impact of inter-laboratory variability. First, the authors systematically determined non-HDL-C values corresponding to the same population percentiles of LDL-C treatment goals. Then, using the 2004 National Cholesterol Education Program Adult Treatment Panel III update guideline [16] and percentile-based non-HDL-C goals, they estimated the prevalence of discordance between non-HDL-C and LDL-C, while also taking LDL-C and triglyceride levels into account. The study demonstrated that percentiles-based goals for non-HDL-C were lower (up to 8 mg/dL) than the guideline goals and, in addition, that there was a significant treatment category discordance between LDL-C and non-HDL percentiles with a more pronounced effect noted for low LDL-C (<100 mg/dL) and high triglycerides (>150 mg/dL) levels.

The findings of this study have several clinical implications. First, the recommended method to determine non-HDL-C treatment goals (LDL-C plus 30 mg/dL) in persons with relatively normal triglyceride-rich lipoproteins under fasting conditions may not always accurately reflect real-life situations and could fail to identify a significant number of individuals who are at a residual risk of CVD. Second, the application of non-HDL-C population percentile-based goals reclassified a smaller portion of individuals into a lower therapeutic category

compared with guideline-based goals (16% vs. 27%). Third, the performance of reclassification of individuals into a higher therapeutic category was dependent on LDL-C and triglyceride levels. Among individuals with a low LDL-C level (<70 mg/dL or 70–99 mg/dL) and a moderately elevated triglyceride level (150–199 mg/dL), a greater proportion of individuals met criteria for a higher therapeutic category based on population percentiles rather than by applying guideline recommendations (64% vs. 26% for the group with LDL-C level of <70 mg/dL; 51% vs. 17% for the group with LDL-C level of 70–99 mg/dL). This suggests that using population-specific percentiles might offer advantages in identifying individuals potentially benefiting from continued treatment to prevent future CVD incidents. Fourth, use of population-specific non-HDL goals, matched to the same population percentile of LDL-C goals, may help reduce misclassification risks due to the use of the Friedewald equation for LDL-C level (e.g., underestimation) and therefore help identify all individuals at residual risk for CVD across categories. The study also adds to the ongoing discussion whether to use lipoprotein goal levels or aim for a relative reduction of atherogenic lipoprotein levels as a guiding tool, the latter being a central theme in the recently published American College of Cardiology/American Heart Association guidelines [6]. The findings further illustrate the need to evaluate therapeutic goals among different population groups and the results highlight the importance of using a population-specific model compared to a more generalized model for establishing treatment goals to reduce CVD risk across populations. These approaches are well-aligned with the precision medicine concept and with the 2020 Impact Goals of the American Heart Association to improve the cardiovascular health of all Americans by 20%, while reducing CVD and stroke deaths by 20% by the year of 2020 [17].

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