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STATE-OF-THE-ART PAPER

Non–High-Density Lipoprotein Cholesterol Versus Apolipoprotein B in Cardiovascular Risk Stratification

Do the Math

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With the emergence of new lipid risk markers and a growing cardiometabolic risk burden in the United States, there is a need to better integrate residual risk into cardiovascular disease (CVD) risk stratification. In anticipation of the Adult Treatment Panel IV (ATP IV) guidelines from the National Cholesterol Education Program (NCEP), there exists controversy regarding the comparative performance of the 2 foremost markers, apolipoprotein B (apoB) and non–high-density lipoprotein cholesterol (non–HDL-C), as they relate to the current standard of risk assessment and treatment: low-density lipoprotein cholesterol (LDL-C). Although some emerging markers may demonstrate better performance compared with LDL-C, certain fundamental characteristics intrinsic to a beneficial biomarker must be met prior to routine use. Collectively, studies have found that non–HDL-C and apoB perform better than LDL-C in CVD risk prediction, both on- and off-treatment, as well as in subclinical CVD risk prediction. The performance of non–HDL-C compared with apoB, however, has been a point of ongoing debate. Although both offer the practical benefits of accuracy independent of triglyceride level and prandial state, non–HDL-C proves to be the better marker of choice at this time, given established cutpoints with safe and achievable goals, no additional cost, and quick time to result with an easy mathematical calculation. The purpose of this review is to assess the performance of these parameters in this context and to discuss the considerations of implementation into clinical practice. (J Am Coll Cardiol 2011;58:457–63) © 2011 by the American College of Cardiology Foundation

Less is more.
—Ludwig Mies van der Rohe (1)

Current guidelines from the National Cholesterol Education Program (NCEP) rely on low-density lipoprotein cholesterol (LDL-C) as the primary therapeutic target in the prevention of cardiovascular disease (CVD) (2). Although LDL-C is well established as an important prognostic marker of coronary heart disease (CHD), population trends suggest the need for better risk stratification. Epidemiological considerations include the recurrence of acute coronary syndromes in up to one-half of patients with "normal" cholesterol levels, and the occurrence of coronary events despite the aggressive use of statins (3). Although statin therapy provides a significant relative risk reduction of 30%, many CHD patients are still having events with LDL-C at goal (2,4,5). In the United States, more than 50% of acute coronary syndromes are recurrent in nature despite a 6-fold increase in the control of LDL-C among hypercholesterolemic patients (3). Taken together, these findings suggest opportunities for further risk reduction of this population. Emerging research has identified potential surrogate lipid markers for assessing cardiovascular risk, including apolipoprotein B (apoB), small dense LDL, LDL particle number, and non–high-density lipoprotein cholesterol (non–HDL-C). The aim of this review is to compare the current standard-of-care lipid marker—LDL-C—to the 2 foremost emerging markers in CVD risk stratification, non–HDL-C and apoB.

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The Conventional Marker of Risk: LDL-C

A conventional lipid panel reports several parameters, including total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Of these, the NCEP (2) and the American Heart Association (3) recommend using LDL-C as a primary target of therapy in conjunction with assessing cardiovascular risk factors. Guidelines over the past 3 decades have maintained that LDL-C should be the main target of treatment based on several large trials (6–9), with the corollary that intensifi-

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Abbreviations and Acronyms

AACC = American Association of Clinical Chemistry
ACC = American College of Cardiology
ADA = American Diabetes Association
apoB = apolipoprotein B
CHD = coronary heart disease
CI = confidence interval
CVD = cardiovascular disease
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio
LDL-C = low-density lipoprotein cholesterol
NCEP = National Cholesterol Education Program
NRI = net reclassification index
TC = total cholesterol
TG = triglycerides
VLDL-C = very low-density lipoprotein cholesterol

cation of therapy to further lower LDL-C in secondary prevention patients is now warranted (10).

Although LDL-C is a well-founded target, emerging findings suggest that it has become a suboptimal marker of risk for a number of reasons (11,12). Population trends in the United States by the National Health and Nutrition Examination Survey (NHANES) and the American Heart Association report that the prevalence of each individual characteristic of the metabolic syndrome has increased over the past decade and is projected to continue increasing at a rapid rate (Table 1) (3,13–15). These characteristics lead to a larger free fatty acid burden on hepatocytes, as well as down-regulation of lipoprotein lipase (LPL) through relative insulin inefficiency (16). Such changes result in a preponderance of very low-density lipoprotein cholesterol (VLDL) and other lipoproteins, which are better accounted for by non–HDL-C and apoB compared with LDL-C. Importantly, the value routinely reported as LDL-C by laboratories is calculated using the Friedewald equation, which is known to lose accuracy with elevated triglycerides or with an LDL-C <100 mg/dl (17,18). Given the growing cardiometabolic burden in the United States, targets of therapy other than LDL-C need to be considered.

Emerging Markers of Risk: ApoB and Non–HDL-C

With the intent of assessing complete lipid atherogenic risk burden—rather than a partial one, such as LDL-C—the ideal parameter is one that accounts for all atherogenic cholesterol particles, including LDL-C, Lp(a), intermediate-density lipoprotein cholesterol, chylomicron remnants, and VLDL-C (19,20). The dynamic flux of lipoproteins between subtypes under direction of LPL and cholesterol ester transfer protein (CETP) makes direct assessment of total atherogenic burden a challenge, which is significantly improved by apoB and non–HDL-C (19,21). Apolipoprotein B is able to directly measure the aggregate number of all atherogenic lipoproteins because each atherogenic particle contains 1 $apoB_{100}$ molecule.

Non–HDL-C is an established secondary target of therapy per the NCEP ATP III guidelines that remains underutilized in the clinical setting (22). With conventional analysis, non–HDL-C is able to quantify total atherogenic burden by measuring the aggregate amount of "cholesterol" in all contributive particles. Non–HDL-C is a quick and simple calculation of TC minus HDL-C (TC − HDL-C), and can be obtained in the non-fasting state without affecting results.

Moving beyond LDL-centric management. Although LDL-C has been the primary measure used to estimate CVD risk by guidelines for over 3 decades, there are now many studies demonstrating consistent outperformance by non–HDL-C (23–29). In the Lipid Research Clinics Program Follow-Up study (11), 4,462 primary prevention individuals (age: 40 to 64 years) were followed over an average of 19 years. In this study, Cui et al. (11) found that non–HDL-C was a stronger predictor of all-cause mortality, as well as CVD mortality compared with LDL-C (chi-square for non–HDL-C: 24.3, and chi-square for LDL-C: 5.0). The BARI (Bypass Angioplasty Revascularization Investigation) study (25) followed 1,514 secondary prevention patients with multivessel disease for 5 years and found that non–HDL-C was a significant, independent predictor of nonfatal myocardial infarction (MI) (relative risk [RR]: 1.049, $p < 0.05$, per 10 mg/dl increase) with dose-dependent effects on multivariate analysis. Furthermore, LDL-C was not a significant predictor of either of these endpoints or all-cause mortality (25).

Although current recommendations are limited to therapeutic targeting of non–HDL-C in patients who have a TG level ≥200 mg/dl (or ≥2.26 mmol/l), non–HDL-C has been proven to perform better than LDL-C at all TG levels. In the SHEP (Systolic Hypertension in the Elderly Program) (26), for example, 4,736 primary and secondary prevention patients (mean age 72 years) were assessed for CHD risk. In this study, non–HDL-C was found to be an independent predictor of CHD regardless of TG level, whereas LDL-C lost predictive value with TG >400 mg/dl (26). Similarly, in the EPIC-Norfolk study (30), non–HDL-C was the strongest predictor of future CHD (men and women, age 45 to 79 years) across all other lipid-stratified levels, including patients with a TG <200 mg/dl. The ERFC (Emerging Risk Factors Collaboration) (31)

Table 1 United States: A Growing Cardiometabolic Phenotype

	1994–2002	2003–2010	Δ (%)
MetS	23.7%	34.0%	**+10.3**
High TG	27.0%	33.0%	**+6.0**
High TG and low HDL-C	2.1%	4.8%	**+2.7**
Type II diabetes mellitus	7.9%	10.7%	**+2.8**
Impaired fasting glucose	6.1%	25.9%	**+19.8**
Obesity	19.8%	33.7%	**+13.9**

Boldface values highlight the percent change in each individual characteristic of the metabolic syndrome. Percentage prevalence of cardiometabolic profile characteristics in adults ≥20 years of age in the United States. Individual characteristics include those of metabolic syndrome (MetS): high triglycerides (TG) (≥150 mg/dl), low high-density lipoprotein cholesterol (HDL-C) (<40 mg/dl in men, <50 mg/dl in women), impaired fasting glucose (fasting plasma glucose: 100 mg/dl to 125 mg/dl), type 2 diabetes mellitus, and obesity (body mass index ≥30 kg/m^2). Table is based on data from Lloyd-Jones et al. (3), Flegal et al. (13), Gardner et al. (14), and Mokdad et al. (15).