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Commentary

# Another Step Forward in Refining Risk Stratification

## Moving Past Low-Density Lipoprotein Cholesterol

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*There is nothing wrong with change,*
*if it is in the right direction.*
—Winston Churchill (1)

In 1959, Thomas Dawber published the first in a series of landmark papers from the Framingham cohort, identifying what he coined "risk factors" for the development of heart disease; these included hypertension, high total cholesterol, and smoking (2). For almost 30 years following this seminal observation, total cholesterol had been used as a primary measure of risk, when in 1988, the National Cholesterol Education Program's Adult Treatment Panel (ATP) suggested using low-density lipoprotein cholesterol (LDL-C) as the principal marker for initiating and targeting treatment (3). Since then, numerous studies have confirmed the importance of LDL-C in risk assessment and intervention, with statins have risen to become the most prescribed therapeutic class of agents in the United States (4,5). Although LDL-C reduction with statins have dramatically advanced our treatment of coronary heart disease (CHD), a substantial residual risk of CHD events remains in statin-treated patients, even in patients achieving an LDL-C <70 mg/dl, thus challenging the predictive power of LDL-C level for CHD and highlighting the need to focus on other lipid markers in risk assessment and intervention (6,7). In

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the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial (8), a statin trial focusing on comparative LDL cholesterol treatment objectives post-myocardial infarction, a lower on-treatment triglyceride level of <150 mg/dl was independently associated with reduced CHD risk compared with higher triglyceride levels, suggesting that non–high-density lipoprotein cholesterol (HDL-C) (the sum of LDL-C and very low-density lipoprotein [VLDL] cholesterol) could provide a superior therapeutic target for risk intervention than LDL-C alone.

The evidence highlighting excess residual risk, however, is never more explicit than in patients with diabetes and/or metabolic syndrome, where lipid profiles are generally characterized by relatively low levels of LDL- and HDL-C, but elevated levels of triglycerides and small dense LDL particles (9,10). In a meta-analysis of over 90,000 CHD patients enrolled in 14 statin trials, the residual risk for major vascular events observed in statin-treated diabetics exceeded that of nondiabetic CHD patients treated with placebo, dramatizing the inadequacy of exclusively targeting LDL-C in diabetics (11). This fact is particularly relevant, given the explosive increase in the prevalence of obesity and subsequent metabolic syndrome and diabetes that result from it; today, nearly 70% of U.S. adults are classified as overweight or obese compared with fewer than 25% 40 years ago (12–14). Over that same time frame, the prevalence of diabetes as a percentage of the U.S. population quadrupled, now present in 8.3% of the U.S. population and continuing to rise (15,16).

In recognition of these trends, the ATP III suggested non–HDL-C as a "secondary endpoint," targeting a goal for therapy 30 mg/dl higher than the recommended LDL-C goal, but only in patients with triglyceride levels between 200 to 499 mg/dl and after achieving target LDL-C goals (17). Because non–HDL-C was relegated to a secondary endpoint, and its use as a secondary target was recommended only under specific circumstances, few clinicians became aware of it, and fewer diabetic patients achieved this recommended endpoint (18–20). The resulting treatment gap led to the more recent publication of a joint consensus report from the American Diabetes Association and the American College of Cardiology promoting the concept of global cardiometabolic risk assessment that recognizes many of the manifestations of obesity and metabolic syndrome, including insulin resistance, inflammation, and elevation of triglycerides and apolipoprotein (apo) B (21). The statement further recommends lipid treatment goals for CHD and/or diabetic patients, as well as high-risk patients with 2 or more major CHD risk factors, that extend well beyond

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**Table 1 Suggested Treatment Goals in Patients With CMR and Lipoprotein Abnormalities**

| | LDL-C (mg/dl) | Non–HDL-C (mg/dl) | ApoB (mg/dl) |
|---|---|---|---|
| CHD patients or diabetic patients with 1 or more additional major CHD risk factor | <70 | <100 | <80 |
| 1) High-risk patients without diabetes or CHD but 2 or more major CHD risk factors; or 2) diabetic patients without other major CHD risk factors | <100 | <130 | <90 |

Other major risk factors include smoking, hypertension, and family history of premature CHD. Adapted from Brunzell et al. (21).

apoB = apolipoprotein B; CHD = coronary heart disease; CMR = cardiometabolic risk; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

LDL-C and include apoB and non–HDL-C as combined primary targets of therapy (Table 1).

Many studies now document that apoB levels, which represent the total number of atherogenic lipoprotein particles, better correlates with CHD than does the LDL-C level, both in untreated as well as statin-treated patients (7,22–25). Similarly, non–HDL-C, which represents the cholesterol contained in all atherogenic apo-B–containing lipoproteins, has also been demonstrated to best LDL-cholesterol in predicting CHD (9,18,22,23,26). In this issue of the *Journal*, Ramjee et al. (27) review the data supporting the need to extend lipid risk assessment and intervention beyond LDL-C, and compare the relative strengths and weakness of the 2 prime candidates to replace LDL-C as the principal therapeutic lipid target, namely apoB and non–HDL-C. Although both of these parameters are relatively similar in out-performing LDL-C in risk stratification, the authors point out the practical advantages of using non–HDL-C, namely its low cost (no additional cost), rapid turn-around time, and easier conceptualization by the majority of practicing clinicians, than the introduction of a "new" lipid parameter such as apoB. These practical advantages are not trivial, and they argue strongly for its adoption to replace LDL-C as the principal therapeutic target for lipid intervention (28). Moreover, a recent guideline statement from the American College of Cardiology and the American Heart Association support these conclusions and propose that apo-B, as well as particle size and density, not be measured in cardiovascular risk assessment (Class III, Level of Evidence: C) (29). Although these debates among risk factors are worthwhile and necessary, we should not, however, lose sight of our primary goal: the further reduction and eventual elimination of residual risk in CHD. Taken together, non–HDL-C offers an attractive and inexpensive therapeutic target for risk reduction in all patients at risk for CHD, and with the continued cardiometabolic changes in the population, a more relevant primary target of intervention in the modern era.

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