Re-Evaluating Therapeutic Target Goals for Statin-Treated Patients

Time for Revolutionary Changes?*

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“God, give us grace to accept with serenity the things that cannot be changed, courage to change the things which should be changed, and the wisdom to distinguish the one from the other.”
—Reinhold Niebuhr (1892–1971) (1)

Ever since Anitschkow’s pioneering experiments on the role of cholesterol in the causation of atherosclerotic plaques in rabbits (2), this intriguing molecule has been at the heart of debate and controversy (3). Initially, the total cholesterol level was used as a measure of risk, then a distinction between α- and β-lipoproteins emerged. As the role of specific lipoproteins became clear, attention focused on the cholesterol content of low-density lipoprotein (LDL), which constitutes the major cholesterol-carrying lipoprotein in serum. The National Cholesterol Education Program’s Adult Treatment Program (ATP), first published in 1988, recommended using the LDL cholesterol level as the marker for initiating treatment as well as for gauging therapeutic target goals (4). The well orchestrated campaign that followed these guidelines familiarized the medical community with LDL cholesterol. Since then numerous clinical studies have confirmed the value of nutritional and pharmacologic treatment of hypercholesterolemia, and the development of newer and more potent drugs resulted in a progressive lowering of the recommended LDL cholesterol target levels for patients at high risk of coronary heart disease (CHD) (5–8).

However, despite the abundant data relating LDL to atherosclerosis, it became clear that focusing solely on the lipoprotein cholesterol content may have its flaws. The predictive power of the LDL cholesterol level for CHD has been challenged, and it has been advocated that the number of atherogenic lipoprotein particles is more predictive of CHD than their cholesterol content (9–11). This distinction is relevant, because the 2 parameters are not always in accord. Because direct measurement of LDL cholesterol levels is cumbersome and expensive, most clinical laboratories report the calculated LDL cholesterol values using the Friedwald formula (12). Although this approach appears to be reasonable in normotriglyceridemic patients, the structural composition of the LDL molecule becomes distorted in hypertriglyceridemia and certain related conditions (13–15). As a result, the relationship between the calculated LDL cholesterol level and the number of LDL particles is modified. In addition, several triglyceride-rich lipoprotein particles, including very-low-density lipoprotein (VLDL) remnants and intermediate-density lipoprotein (IDL), appear to be atherogenic (16,17). Whereas IDL is included within the calculated LDL cholesterol, VLDL is excluded.

Many (11,18–23), but not all (24–26), studies indicate that the apolipoprotein (apo) B level, which represents the total number of atherogenic lipoprotein particles (each particle contains a single apoB molecule), better correlates with CHD than the LDL cholesterol level in untreated as well as statin-treated individuals. Similarly, a growing number of studies suggest that the non–high-density lipoprotein cholesterol (HDL-C) level, which represents the cholesterol carried in all atherogenic apoB-containing lipoproteins, is also superior to LDL cholesterol level in predicting CHD (11,20,27–31). This is especially true in diabetic and/or hypertriglyceridemic individuals. Finally, the whole concept of monitoring treatment success by laboratory parameters has recently been challenged, claiming that the statin dose is more relevant than the LDL cholesterol level achieved (32). Despite these claims, LDL cholesterol has retained its role as the primary indicator for initiating treatment and targeting therapeutic goals in both the ATP III as well as the joint European guidelines (6). The major reason for this approach was the feeling that LDL is deeply rooted in the minds of most physicians as the primary therapeutic target, and replacing it with apoB in the absence of stronger evidence might generate considerable confusion (8,33). The ATP III guidelines did adopt non–HDL-C as a secondary end point, but only in patients with triglyceride levels in the range of 200 to 499 mg/dl and after achieving target LDL cholesterol goals. Although formal data on the acceptability of this 2-step approach by the medical community are lacking, it has been shown that achievement of the recommended non–HDL-C goals is less than optimal (34), suggesting that the adoption of non–HDL-C as a target goal by physicians, patients, and laboratories is still faltering. A recent consensus statement from the American Diabetes Association and the American College of Cardiology Foundation to guide the therapy of patients with cardio-metabolic risk suggested using apoB as a therapeutic guide in addition to LDL and non–HDL-C (8).

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In the current issue of the Journal, Ballantyne et al. (35) provide additional fuel for the debate by examining the relationship between apoB, LDL cholesterol, and non–HDL-C levels before and after 16 weeks of statin therapy in 1,993 high-risk dyslipidemic individuals enrolled in the MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy II) trial. More specifically, they evaluated the levels of LDL cholesterol and non–HDL-C that corresponded to an apoB level of 90 mg/dl, which had been proposed as the target apoB level in high-risk individuals (8,33). They found that in untreated patients, this apoB level roughly corresponds to an LDL cholesterol level of <100 mg/dl and a non–HDL-C level of <130 mg/dl, which is in agreement with current ATP III–recommended target values in high-risk individuals. However, statin therapy altered this relationship so that it was necessary to reduce non–HDL-C to <100 mg/dl and LDL-C to <70 mg/dl (in high-triglyceride patients) or <80 mg/dl (in low-triglyceride patients) to achieve the apoB target of <90 mg/dl. This results from the fact that statin therapy reduces the cholesterol content in LDL to a greater extent than the reduction in apoB (36) and implies that relying on LDL cholesterol as the therapeutic target might overestimate treatment effect. The authors interpret these results as evidence that in statin-treated patients the optimal target goals should be <70 to <80 mg/dl for LDL cholesterol and <100 mg/dl for non–HDL-C. Current ATP III guidelines recommend these levels as “optional” target goals only for individuals with cardiovascular disease who continue to harbor risk factors (such as diabetes, cigarette smoking, or multiple risk factors for metabolic syndrome) that render them at very high risk for recurrent events or after an acute coronary syndrome, but they maintain less ambitious goals for “standard” high-risk individuals. Therefore, if the gold standard target goal is truly an apoB level of <90 mg/dl, the “very-high-risk target goals” should be adopted for all CHD and CHD-equivalent patients. However, the choice of 90 mg/dl as the apoB target goal does not seem to be based on robust clinical evidence but rather on limited epidemiologic, post hoc analyses, and “expert opinion” (33,37,38). Achieving these goals is feasible in less than one-half of high-risk patients, even with the most potent currently available statins (39), and the potential for any added benefit gained by such treatment should be carefully weighed against the incremental cost, potential for adverse effects, and possible frustration of those unable to achieve these goals (40).

Another issue highlighted by the authors is the less-than-optimal correlation between LDL cholesterol and apoB levels in both untreated as well as statin–treated patients. Once again the question is raised: is LDL cholesterol the best marker for gauging CHD risk and therapeutic goals? The use of all 3 parameters (LDL cholesterol, non–HDL-C, and apoB), as suggested by Brunzell et al. (8) for patients with cardiometabolic risk, might be suitable for experts working in specialized lipid or diabetes clinics, but I have doubts whether this approach would be widely adopted by most primary care practitioners. If we were to accept the paradigm that the number of all atherogenic particles is a more important determinant of cardiovascular risk than the LDL cholesterol content (9), then the use of apoB as the primary measure of risk in all patients would make sense. Although some experts support this approach enthusiastically (9,23), others object to it on the grounds of assay standardization and availability. Ballantyne et al. (35) suggest using non–HDL-C as a surrogate for apoB. Although these 2 entities represent different aspects of the atherogenic lipoproteins, they are highly correlated both before and during statin treatment. The use of a single parameter in all patients (irrespective of triglyceride levels) for estimating risk, deciding on the need for therapy, and gauging therapeutic goals has the potential to simplify the current 2-step approach and improve physician adherence to the guidelines. The assay can be performed in the nonfasting state, and all laboratories can (and should) report its value without additional cost. Finally, the name should be changed from “non–HDL-C,” which defines the atherogenic elements in a negative way, to a more appealing title, such as “atherogenic B lipoprotein” cholesterol.

A concluding comment is warranted about guidelines. For the practicing clinician who attempts to stay abreast of evidence–based patient management, it is both frustrating and confusing to witness the same research data being translated into different treatment recommendations by renowned committee experts (6–8,37). Although appreciable effort has been made to achieve consensus among various organizations within each guideline committee, less consensus is apparent between guidelines on the same topic. Whereas diversity of opinion is a crucial component of well-balanced committees, the final output should provide physicians with a clear set of simple recommendations that can overcome the numerous barriers to guideline implementation (41). A unified approach across the Atlantic Ocean could facilitate this goal.

Are we ready for these revolutionary changes?

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