The high correlation between apolipoprotein B (apoB) and non–high-density lipoprotein cholesterol (non–HDL-C) is the chief argument employed against introducing apoB into clinical practice. However, high correlation does mean that non–HDL-C and apoB will often yield similar clinical information. Nevertheless, the critical issue is not how often the two tests agree, but how often, and how substantially, they differ. In other words, how often would an apoB result change a clinical decision based on a value for non–HDL-C? This article presents a series of examples from prominent published studies in which apoB and non–HDL-C differ so dramatically that diagnosis and therapy would truly differ depending on which index was used by the physician. These examples establish that apoB and non–HDL-C are not clinical equivalents.

Introduction

If medical practice is to remain evidence-based, a seismic shift in the diagnosis and therapeutic monitoring of the atherogenic dyslipoproteinemias must occur. Low-density lipoprotein cholesterol (LDL-C) has been the cornerstone of lipid diagnosis and therapy. LDL-C is so entrenched that it has, effortlessly but erroneously, become a synonym for LDL. For many, LDL-C has become “too big to fail.” Yet LDL-C has fallen behind non–HDL-C and apoB as a marker of the risk of vascular disease and a measure of the adequacy of LDL-lowering therapy in all the recent prospective epidemiologic studies and clinical trials. Unless all of this evidence is to be ignored, LDL-C can no longer be the standard of care. The contest for that position is now between non–HDL-C and apoB. The proponents of non–HDL-C argue that apoB and non–HDL-C are highly correlated and that a number of studies have shown non–HDL-C and apoB have equal predictive value for clinical events. Accordingly, they argue that the additional expense to measure apoB and to educate patients is not justified.

We do not agree. What is the test of a test? When does a test add sufficient value that it should be incorporated into clinical practice? Clearly, it is not necessary that a test change clinical decision making every time in every patient. No test would meet that requirement. Nor is it necessary that one alternative be superior to the other in every patient; that is not the standard either. Moreover, in this specific case, the three parameters of interest (LDL-C, non–HDL-C, and apoB) are highly correlated over their concentrations in plasma, and these high correlations are based on intimate biological connections. It follows that LDL-C, non–HDL-C, and apoB will, in a large proportion of individuals, yield similar information. The answer as to whether apoB should be included in routine care depends on whether, in an acceptable number of instances, additional information of substantial value would be obtained by measuring apoB [1••]. Put simply, the case for apoB depends on the instances when apoB differs in information content and not on those where it is similar. The virtually exclusive focus on head-to-head comparisons in prospective epidemiologic studies and clinical trials has obscured the primacy of this principle. Therefore, this article examines specific clinical trials and specific clinical situations to determine if non–HDL-C can adequately substitute for apoB in these specific circumstances. Based on this evidence, we demonstrate that non–HDL-C is not an adequate clinical surrogate for apoB.

Background

Before we get underway, we must point out that apoB and non–HDL-C measure different things. Each proatherogenic lipoprotein particle contains one molecule of apoB. Therefore, measurement of apoB provides a precise estimate of the number of atherogenic particles whereas non–HDL-C equals the sum of the mass of cholesterol and cholesterol ester within apoB particles. Except for the rare circumstance of familial dysbetalipoproteinemia, LDL particles account for more than 90% of total apoB particles, whereas very low-density lipoprotein (VLDL) particles make up a little less than 10% of the total.
Because non–HDL-C is the arithmetic sum of cholesterol in VLDL and LDL, the assumption is that the cholesterol in VLDL and LDL contribute equally to atherogenic risk. However, VLDL particles are substantially larger than LDL particles; accordingly, they will not enter the arterial wall as readily. Therefore, this assumption is suspect.

It also needs to be appreciated that there is considerable variance in the level of non–HDL-C for any given value of apoB. The National Health and Nutrition Examination Survey (NHANES) [2••] was designed to enable the calculations of statistics that are representative of the American population as a whole. Figure 1 displays the values for non–HDL-C and apoB obtained in the NHANES survey. The two are highly correlated. However, for any given value of one, there is substantial variance for the other. For example, two different individuals may each have a non–HDL-C of 130 mg/dL. One may have an apoB value of 125 mg/dL and the other a value of 92 mg/dL. One will have an elevated apoB and the other a low apoB. Discordance between non–HDL-C and apoB is more pronounced in patients with dyslipoproteinemias [3••]. This variance arises because in any individual it is not certain how much of the cholesterol is in VLDL versus how much is in LDL. That is the reason neither VLDL nor LDL particle number can be accurately calculated from their lipid constituents, and it is the number of atherogenic particles that become trapped within the arterial wall and not the mass of cholesterol they transport in plasma that matters.

Concordance Versus Discordance

By convention, the units of concentrations of LDL-C and non–HDL-C are expressed either as mg/dL or mmol/L, whereas apoB is recorded as mg/dL. The levels of LDL-C, non–HDL-C, and apoB expressed in these units vary throughout any specific population. The deviance of any parameter within a population is given by its percentile within its the population. Thus, the 50th percentile level for any parameter has the same meaning as the 50th percentile for any other. Similarly, a 90th percentile level or a 10th percentile parameter for any parameter expresses identical extent of deviance from the mean of the population. Values for different parameters are concordant if they are at similar percentiles of the population. Values are discordant if they are at significantly different percentiles of the population.

As demonstrated in Figure 1, non–HDL-C and apoB are highly correlated but only moderately concordant. Under most circumstances, LDL particles account for the dominant proportion of the total number of apoB particles. Therefore, discordances between LDL-C and apoB will drive discordances between non–HDL-C and apoB. LDL-C can be discordant with regard to apoB if either the LDL particles are cholesterol enriched or if they are cholesterol depleted. If the former, then LDL-C will overestimate the risk due to LDL; if the latter, then LDL-C will underestimate the risk due to LDL.

Because cholesterol can be transferred to VLDL in return for triglyceride (TG), non–HDL-C may not be as discordant from apoB as LDL-C. This “compensation” is the principal basis for the higher correlation between non–HDL-C and apoB than between LDL-C and apoB. Even so, apoB is more closely related to hyperglycemia, insulin resistance, and inflammation than non–HDL-C [4]. However, in rare instances, non–HDL-C can be positively discordant with regard to apoB if large numbers of cholesterol-enriched chylomicron and VLDL remnant particles are present [5••]. In this specific circumstance, non–HDL-C or total cholesterol (TC), but not apoB, is the valid index of atherogenic risk (see discussion of familial dysbetalipoproteinemia later in the text).

Examples of Substantial Discordance Between Non–HDL-C and apoB

The JUPITER trial

The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) [6••] provides a striking example of the error