

ApoB Versus Non-HDL-C: What to Do When They Disagree

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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-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (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.

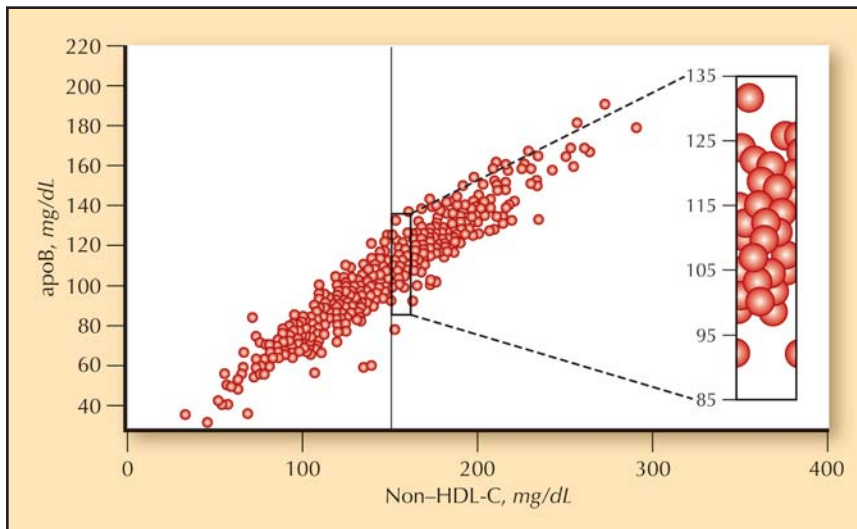


Figure 1. Values for apolipoprotein B (apoB) and non-high-density lipoprotein cholesterol (non-HDL-C) for participants in the National Health and Nutrition Examination Survey NHANES survey. (Data from NHANES Investigators [2••].)

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 even 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

in estimation of risk that can occur if apoB is not taken into account. JUPITER compared the effects of a fixed dose of rosuvastatin versus placebo in patients selected to have a low LDL-C (< 130 mg/dL) and elevated C-reactive protein (CRP, > 4.0 mg/dL). The participants were characterized as low risk based on their LDL but high risk based on their CRP. The LDL-C (108 mg/dL) was at the 25th percentile of the American population based on the fourth cycle of the Framingham study. The non-HDL-C (134 mg/dL) was at the 30th percentile. By contrast, the apoB (109 mg/dL) was at the 60th percentile for men and the 70th percentile for women. The discordance between the levels of LDL-C and non-HDL-C versus apoB is substantial by any measure. The average level of apoB is above the median of the population and, of course, half of the participants had levels above this. Based on LDL-C and non-HDL-C, the physician would conclude LDL was low, but if based on apoB the physician would conclude it was not. The average age of the participants was 66 years. Therefore, they had been exposed to high or moderately high levels of atherogenic particles for long periods of time. Accordingly, the event rate in the placebo group was not surprising, nor was the benefit from statin therapy.

Diagnosis of specific atherogenic dyslipoproteinemias

Only the rare genetic disorders that profoundly impair the normal removal of LDL particles from plasma, such as familial hypercholesterolemia or familial defective apoB, can be recognized from the standard lipid panel. None of the other hallmark atherogenic dyslipoproteinemias can be adequately characterized by measuring only lipids. By contrast, all can be identified and differentiated based on TC, TG, and apoB [7••]. Three dyslipoproteinemias—familial combined hyperlipidemia (FCHL), familial dysbetalipoproteinemia (FDB), and familial hypoalphalipoproteinemia—are briefly discussed here.

Familial combined hyperlipidemia

FCHL is the most common familial atherogenic dyslipoproteinemia and is present in 25% to 40% of patients presenting with premature myocardial infarction. Diagnosis is essential if others within the family who are affected are to be treated before they also suffer a myocardial infarction or die suddenly. The original diagnostic criteria demanded that the patient's family be studied before the diagnosis could be made in the affected individual [8]. This virtually ensured the diagnosis would not be made in clinical practice. Moreover, if the family members were not available, the family was not sufficiently large, or if the children were not old enough, the best of intentions would lead nowhere. Because of this, the matter rested until Veerkamp et al. [9] published a diagnostic algorithm for the FCHL phenotype based on TC, TG, and apoB. Recognition of the hyper-TG and hyper-apoB phenotype that is the hallmark of FCHL is the first step to efficient selection of families for screening. Wiesbauer et al. [10••] identified 38 individuals from 102 consecutive patients presenting with myocardial

infarction under 40 years of age who had an FCHL phenotype. Of the 21 families studied, FCHL was confirmed in 76%. Non-HDL-C cannot substitute for apoB in the diagnostic algorithm. Indeed, non-HDL-C adds nothing of significance to TC. If there were no other reason to measure apoB, diagnosis of FCHL would be sufficient. There are, however, many others.

Familial dysbetalipoproteinemia

FDB is characterized by marked hypercholesterolemia and marked hypertriglyceridemia due to the accumulation of chylomicron and VLDL remnants. Homozygosity for apoE2 is a precondition in the vast majority of patients but only a small percent of individuals homozygous for apoE2 develop the clinical syndrome. Moreover, apoE2/E2 patients can develop other dyslipidemias. Diagnosis of FDB is not possible from plasma TC and TG. However, diagnosis can be made based on apoB and the TC/apoB and TG/apoB ratios [5••]. A normal apoB in the face of marked combined hyperlipidemia is the hallmark of FDB. apoB is normal because VLDL remnants are not processed to LDL particles, which have even longer plasma half-lives than VLDL remnants. If LDL particles are not formed, total plasma apoB remains low even though VLDL and chylomicron remnants accumulate. A ratio of TG/apoB of less than 10 (mmol/mg) allows intact chylomicrons to be excluded as the cause of the hypertriglyceridemia and points to the presence of TG-rich remnants. A TC/apoB ratio greater than 6.2 (mmol/mg) indicates that cholesterol-rich buoyant apoB particles are present. Only FDB, and possibly hepatic lipase deficiency (which is even less common than FDB), fulfill these criteria. Using this approach, the diagnosis of FDB can be made in any standard clinical laboratory. The conventional technology (ie, electrophoresis or ultracentrifugation) is not available in many of the most specialized lipid clinics, which means, for practical purposes, the diagnosis of FDB is not made with exactitude even by most specialists. Once again, non-HDL-C cannot substitute for apoB in this algorithm.

Familial hypoalphalipoproteinemia

Familial hypoalphalipoproteinemia is characterized by low HDL-C but normal plasma TG and cholesterol. The inference, of course, is that any excess in the risk of vascular disease is due to the low level of HDL-C. Indeed, such syndromes have been one of the pillars of evidence tying low HDL-C to the pathophysiology of vascular disease. However, in one of the largest series of families investigated for familial dyslipoproteinemia in which the index case presented with coronary disease and low HDL-C, the average apoB in the patients with familial hypoalphalipoproteinemia was elevated well above the 75th percentile, whereas TG, LDL-C, and non-HDL-C were all normal [11]. These data illustrate, once again, that the lipid data without apoB can produce an erroneous diagnostic conclusion. Not all individuals with low HDL-C have an elevated apoB, but the portion that does have it will not be recognized unless apoB is measured.

That is the diagnostic message, but there is a patho-physiologic one as well, which is that apoB and HDL-C are linked. The European Prospective Investigation of Cancer (EPIC)-Norfolk study demonstrated significant inverse relations between both LDL particle number and apoB with HDL size but not HDL particle number [12••]. Thus HDL-C is inversely related to apoB. The metabolic basis for this relationship is not known with certainty but in vitro studies of hamster hepatocytes demonstrated that low HDL in the medium resulted in increased apoB secretion, a relationship that is consistent with the role of intracellular cholesterol ester as a determinant of apoB secretion [13]. The role of HDL-C as an independent determinant of the risk of vascular disease must now be reexamined, and measurement of apoB in patients with low HDL-C should be mandatory. Lowering apoB should be the first objective of therapy in the patient with low HDL-C and elevated apoB.

Determination of the adequacy of LDL-lowering therapy

Statins dominate LDL-lowering therapy. Yet it is still not widely appreciated that they lower LDL-C and non-HDL-C significantly more than they lower apoB or LDL particle number. A meta-analysis of 17,000 patients from seven studies of LDL lowering demonstrated that LDL-C was reduced by 43%, non-HDL-C by 39%, and apoB by 33% [14••]. This necessarily results in an LDL particle number that, on average, is higher than would be anticipated from the concurrent LDL-C or non-HDL-C. Moreover, in many patients, apoB and LDL particle number are already disproportionately elevated compared with LDL-C or non-HDL-C before therapy is initiated. The net result is that the discordance between apoB and non-HDL-C cholesterol lowering can be very pronounced. In the meta-analysis, the average on-treatment LDL-C was reduced to the 20th percentile and the non-HDL-C to the 29th percentile, but apoB was decreased only to the 55th percentile. This discordance points to substantial residual risk in many patients on statin therapy.

Evidence of discordant outcomes is also present in clinical trials. For example, the combined analysis of Treatment to New Targets study and the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (TNT/IDEAL) study found identical hazard ratios for non-HDL-C and apoB and concluded they were of equivalent value [15]. However, non-HDL-C and apoB were not reduced to equivalent levels of the population. In the low-intensity statin-therapy group, non-HDL-C was reduced to the 30th percentile of the American population whereas apoB was reduced only to the 60th. In the high-intensity statin-therapy group, non-HDL-C was reduced to the 5th percentile whereas apoB was reduced to only the 30th percentile. Thus, the two markers were not fully equivalent in the information they provided. apoB was more accurate than non-HDL in pointing to residual risk and the opportunity for further therapy.

Laboratory measurement of apoB and non-HDL-C

Considerable effort was invested initially to demonstrate that HDL-C could be measured and LDL-C calculated with sufficient accuracy for clinical practice. LDL-C was defined operationally as the mass of cholesterol carried by lipoproteins with density between 1.006 and 1.063 g/mL. Even so, multiple samples were required, and even then, after plasma TG were more than modestly elevated, calculation of LDL-C quickly became increasingly problematic. Modern medicine demands clinical chemical methods that are automated and standardized; accordingly direct methods to measure HDL-C and LDL-C have been developed and are being widely applied. Unfortunately all direct methods are susceptible to matrix effects and specificity is easily compromised with minor modifications in reagent composition or interaction with pathologic sera. The consequence, of course, is an inaccurate calculation of non-HDL-C. Standardization demands accurate definition and characterization of the entity to be measured. That poses a challenge for LDL-C and HDL-C because both LDL and HDL consist of a diverse series of particles that are heterogeneous with regard to the mass of cholesterol they contain, making the preparation and definition of a common, unequivocally defined standard for healthy and diseased patients impossible. The problem is compounded by the fact that neither LDL-C nor HDL-C necessarily measures the clinically most relevant impact of the lipoprotein classes they represent. TG have so far posed insuperable difficulties to standardization. In vivo, they are a heterogeneous series of compounds, including free glycerol, whereas the reference system is calibrated only to triolein or tripalmitate. Manufacturers attempt to compensate for these effects but biases cannot be avoided, particularly in pathologic samples. By contrast, apoB and apoA-I present direct and unequivocally defined entities for measurement. Standardization of manufacturers by means of secondary serum reference preparations was achieved in 1994 by the International Foundation of Clinical Chemistry/World Health Organization group [16].

The educational challenge of change

Introducing apoB into routine clinical care would require investment in patient and physician education, as would introducing non-HDL-C into routine clinical care. Both pose challenges but we would wager that apoB is a simpler concept to transmit than non-HDL-C. It is easy to imagine how atherogenic particles damage our arteries. It is not easy to conceptualize a non-number. The failure of non-HDL-C to gain substantial traction in clinical practice in the United States since the endorsement of National Cholesterol Education Adult Treatment Panel III guidelines supports this concern. Moreover, it is far easier to imagine transition strategies that include different entities (LDL-C and apoB) than it is to imagine those that include similar ones (LDL-C and non-HDL-C). Those who favored non-HDL-C over LDL-C from the outset turned out to be correct, but the commitment to LDL-C over the interval has made their favored option more problematic. It is easier to credibly argue that an option that is only recently

available represents progress than to solicit support for one that was there all along. In any event, two cholesterol goals is one too many, but instantaneously eliminating LDL-C from clinical care is not an option.

Conclusions

Most physicians and many clinician scientists do not really understand the subtleties of the sophisticated statistical methods that drive the analyses of the major epidemiologic studies and clinical trials and, therefore, not surprisingly, are uncomfortable when their results conflict or are disputed. That is why the objective of this review has been to present a series of concrete examples, each of which demonstrates, transparently and incontestably, that non-HDL-C is not an adequate measure of apoB. However, we would be the first to insist that there are other examples in which they are of equivalent value. Both outcomes are biologically valid and neither excludes the other. We are used to thinking that if one thing is better than another, it must be better every time and everywhere. Non-HDL-C and apoB do not work that way. They are used for the same purpose but they do not measure the same thing and that is why sometimes they convey the same information and sometimes they do not. They are the same when they are concordant with regard to their levels in the population and they are different when they are discordant. These qualities of concordance/discordance do not reflect the play of chance. Rather, they are determined by differences in the core lipid composition of the apoB particles. Thus, depending on the characteristics of the individuals being studied, apoB will be overall superior or only equivalent to non-HDL-C. However, doctors do not study groups; they diagnose and treat individuals. Also, while there are clues as to whether apoB and non-HDL-C are likely to be discordant, they are only clues and not infallible rules.

The battle between apoB and non-HDL-C comes down to a contest between more versus less. Measuring apoB will add more expense up front, but it will also allow more effective diagnosis and therapy because apoB adds clarity and precision to deciding who needs to be treated and how much treatment they require. Therapies cost multiples more than tests, and events that are prevented cost multiples less than those that are not. It follows that applying therapies more effectively to those who need them more than others will save more lives and money. Therefore, apoB-directed therapy will be more effective and less costly than non-HDL-C-directed therapy. Moreover, diabetes and abdominal obesity, the disorders that promote discordance between apoB and non-HDL-C, are becoming more and more common, so apoB will become more and more useful.

Accurate diagnosis is fundamental to excellence in care. The impact on diagnosis of apoB versus non-HDL-C is frequently an all or none, not a more or less, comparison. Measuring apoB along with cholesterol and TG makes diagnosis of all the atherogenic dyslipoprotein-

emias possible in the office setting. Non-HDL-C adds no information to TC and TG for this purpose. Moreover, it will be less difficult from a technical standpoint to introduce accurate measurement of apoB and apoA-I in developing countries than LDL-C and HDL-C. The concept of atherogenic particle number is easier to explain than a non-number. All in all, non-HDL-C offers much less than it appears to and apoB adds much more than its critics have so far acknowledged.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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