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An evidence-based analysis of the National Lipid Association recommendations concerning non-HDL-C and apoB

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BACKGROUND: The National Lipid Association (NLA) selected non-HDL-C as its prime index of the cardiovascular risk associated with the apoB lipoproteins. ApoB was recommended only as an optional secondary target after low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (HDL-C) targets were achieved.

OBJECTIVE: The aims of this analysis were to determine whether (1) all relevant uses of apoB were considered by the NLA; (2) all the relevant evidence was considered by the NLA panel; and (3) all the evidence that was considered was interpreted correctly.

RESULTS: (1) The utility of apoB in the diagnosis of the atherogenic dyslipoproteinemias was not considered. (2) All the relevant observational studies were not identified, and some that were cited were incorrectly interpreted. In particular, an equal hazard ratio for two markers in a group does not mean they will predict risk equally in individuals within the group in whom they are discordant. This matters because discordance analysis consistently demonstrates apoB and LDL particle number are more accurate measures of cardiovascular risk than LDL-C/non-HDL-C. (3) The target levels of apoB selected by the NLA are too high relative to the levels selected for LDL-C and non-HDL-C.

CONCLUSIONS: The review of the evidence by the NLA was incomplete. More complete examination of the evidence indicates that apoB is a more accurate marker of cardiovascular risk than non-HDL-C and that the practice of lipidology would be improved by inclusion of apoB along with lipoprotein lipids in routine clinical care.

Introduction

All treatment guideline groups state their recommendations are evidence based. That is the source of their authority. However, correctly identifying and appropriately evaluating all the relevant evidence is challenging. Thus, multiple cholesterol treatment guideline groups have produced recommendations that differ substantially, although

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they were based on the same evidence.[1] The evidence does not speak for itself.

Nevertheless, given the rate at which information accumulates and the complex forms in which it appears, the guideline process has become essential to medical care. Therefore, we need to understand how it can be improved. That is the purpose of this review, which will examine the evidence on which the recent recommendations of the National Lipid Association (NLA) regarding non–high-density lipoprotein cholesterol (HDL-C) and apoB were based.[2]

The NLA recommended that non-HDL-C be the primary index of the risk attributable to the apoB lipoproteins and the primary index of the adequacy of lipid-lowering therapy. They concluded that non-HDL-C and apoB were both more accurate markers of risk than LDL-C, and that non-HDL-C and apoB were equivalent measures of cardiovascular risk. Given its greater availability and that no extra expense is required for its determination, non-HDL-C was judged superior to apoB.[2] The NLA further determined that the superiority of non-HDL-C over LDL-C was due to VLDL-C. ApoB was recommended as an optional secondary target to assess the adequacy of LDL lowering therapy after non-HDL-C and LDL-C targets were achieved. No other role for apoB was suggested.[2]

Given that the selection of non-HDL-C as the primary index of the atherogenic lipoproteins was one of the principal changes in care advocated by the NLA, examining the quality of their review of the evidence is a fair test of the validity of the process. The only assumption this analysis makes is that the report represents an accurate and complete record of their deliberations.

Role of apoB in diagnosis of the atherogenic dyslipoproteinemias

Diagnosis of the atherogenic dyslipoproteinemias is not considered in the NLA report. For the present exercise, only one clinical consequence of this omission will be noted: remnant lipoprotein disorder (RLD or type III hyperlipoproteinemia or familial dysbetalipoproteinemia).[3,4] RLD becomes manifest typically after early midlife. However, once it appears, the anatomic progression of atherosclerotic disease can be explosive, so explosive that the clinical consequences, both in the coronary and peripheral arterial trees, become evident often within only a few years after the onset of the dyslipoproteinemia. The natural history of RLD is remarkably condensed. However, RLD is treatable. Accordingly, the clinical consequences should be preventable. Presently, RLD cannot be diagnosed in routine clinical care, including care in almost all specialized lipid clinics. The tools that were used previously, ultracentrifugation and/or electrophoresis, are not available. Yet, the diagnosis could be made, simply and inexpensively, by any clinical chemistry laboratory based on measurement of triglyceride, cholesterol, and apoB.[5–7] Indeed, except for Lp(a), diagnosis of all the apoB atherogenic dyslipoproteinemias is possible based on the plasma levels of triglyceride, cholesterol, and apoB.[5]

Clinical significance

Accurate diagnosis is one of the cornerstones of clinical care but the NLA panel did not demonstrate they were aware of and valued this aspect of care.

Comparison of non-HDL-C and LDL-C as markers of cardiovascular risk by the NLA

> "However, a substantial body of evidence has since accumulated to support the view that non-HDL-C is more strongly related to risk for ASCVD than LDL-C and that this relationship is evident in those with and without hypertriglyceridemia"[2]

There is substantial evidence that non-HDL-C is a better marker of cardiovascular risk than LDL-C. However, at multiple points, the NLA report states that VLDL-C accounts for the superiority of non-HDL-C over LDL-C as a marker of cardiovascular risk and that, this constitutes evidence in favor of therapies to reduce VLDL-C. Indeed, the panel identifies four mechanisms that might account for the atherogenic properties of VLDL particles. Nevertheless, although VLDL-C may be the most obvious explanation for the superiority of non-HDL-C over LDL-C, it is not the only one. An alternative hypothesis is that the superiority of non-HDL-C over LDL-C is due, at least in part, to non-HDL-C being a more accurate index of LDL particle number than LDL-C. This hypothesis and the evidence supporting it[8] are not cited in the NLA report.

Indeed, the results of the discordance analysis by Mora et al,[9] which was cited in the NLA report, provide direct evidence against the assumption by the NLA that VLDL-C must entirely account for the superiority of non-HDL-C over LDL-C. In the Mora study, cardiovascular risk was greater in the low LDL-C/high non-HDL-C subgroup than in the low non-HDL-C/low LDL-C subgroup (Table 1). VLDL-C was, in fact, substantially greater in the former than the latter: 51 mg/dL vs 28 mg/dL, $P < .001$, a difference that could contribute to the difference in cardiovascular risk between the two groups as claimed by NLA. However, it is not the only difference between the groups. LDL particle number is also much greater in the high-risk low LDL-C/high non-HDL-C compared to the latter (1356 vs 977 nmol/L $P < .001$; Table 1).

Even when VLDL levels produce substantial hypertriglyceridemia, LDL particles make up the great majority of apoB particles—more than 85%.[11–13] Moreover, hypertriglyceridemia with an elevated apoB is associated with greater atherogenic risk than hypertriglyceridemia

Table 1 LDL-C/non-HDL-C discordance analysis of the Women's Health Study[9]

Markers	Low LDL-C/low non-HDL-C low risk	Low LDL-C/high non-HDL-C high risk	Absolute difference	% Difference	*P**
Number of Subjects	12,026	1569			
TG (mg/dL)	95 (70–134)	249 (186–348)	154	162.1	<.001
LDL-C (mg/dL)	98 (86–109)	113 (105–118)	15	15.3	<.001
Non-HDL-C (mg/dL)	126 (111–138)	164 (158–175)	38	30.2	<.001
VLDL-C (mg/dL)	28	51	23	82.1	<.001
apoB (mg/dL)	83 (72–92)	112 (100–122)	29	34.9	<.001
LDL particle number	977 (824–1128)	1356 (1169–1552)	379	38.8	<.001
LDL size	21.1 (20.8–21.6)	20.4 (19.8–21.0)	−0.7	−3.3	<.001
Cholesterol/LDL particle	2526 (2206–2947)	2098 (1799–2459)	−464	−18.1	<.001

**P* values were calculated assuming the standard deviation of the subjects in the Women's Heart Study were the same as in female subjects of the Insulin Resistance Atherosclerosis Study.[10]

with a normal apoB.[14–19] In patients with hypertriglyceridemia, the absolute increase in LDL particle number is much greater than the absolute increase in VLDL particles. In addition, cholesterol-depleted LDL particles may be more atherogenic than cholesterol-replete LDL particles, further increasing the risk associated with LDL particles. LDL particles, therefore, presumably account for an important portion, perhaps the majority, of the risk associated with hypertriglyceridemia and increased non-HDL-C.

Clinical significance

LDL-lowering therapy is proven to lower cardiovascular risk, whereas measures to lower VLDL-C have not yet proven successful. In only considering VLDL-C as a possible explanation for the increased risk in hypertriglyceridemia, the NLA report did not point out the hazard to cardiovascular health produced by LDL particles in hypertriglyceridemia, and therefore, the need to continue to focus on aggressively lowering atherogenic LDL particles in these subjects.

Comparison of non-HDL-C and apoB as markers of cardiovascular risk by the NLA

> "Non-HDL-C is favored over apoB by the NLA Expert Panel because it is universally available, requiring no additional expense compared with the standard lipid profile, and because apoB has not been consistently superior to non-HDL-C in predicting ASCVD event rate risk (Figure 10)."[2]

Of the three studies cited in support of their recommendation, one, the Emerging Risk Factor Collaboration (ERFC),[20,21] was a collaborative prospective participant level observational study; one was a meta-analysis of the relation of the three markers to residual risk in multiple major statin trials[22]; and one was a meta-analysis of the relation of the three markers to benefit from a variety of lipid therapies.[23] The results of the ERFC study were highlighted with the reproduction of Figure 3 from that report.[20] This figure demonstrates that non-HDL-C is equivalent to apoB as a marker of cardiovascular events, apparently providing strong support for the conclusion of equivalence. Not noted, however, was that in ERFC,[20,21] TC was just as accurate a marker of cardiovascular risk as non-HDL-C, apoB, and LDL-C. However, as will be demonstrated shortly, this finding is inconsistent with much prior evidence and raises questions about the analytical reliability of these measures in ERFC.

ERFC is a noteworthy study, both in scope and concept. The strength of ERFC is that it was a participant level analysis, and that individual data from each study were revalidated before inclusion. However, exclusion of cases with incomplete or contradictory data cannot overcome core limitations in design or execution of the studies that make up ERFC. In particular, multiple nonstandardized, nonexternally validated methods were used to measure apoB in many of the studies. Furthermore, many studies that were included in ERFC are unpublished and so their design and methods cannot be evaluated. With randomized clinical trials, the default bias is that negative studies tend not to be published. With prospective observational studies, no such default bias has been demonstrated. Indeed, a substantial per cent of the subjects from many studies that were included in the original studies that were published were subsequently excluded from the ERFC analysis based on inadequate data, *prima facie* evidence of poor execution. For these reasons and others, the results of ERFC should not be taken as incontrovertible evidence of the equality of non-HDL-C and add apoB.[21]

To be sure, as listed in Table 2, six published high-quality studies, that were not cited, do demonstrate equivalence between apoB and non-HDL-C as cardiovascular risk markers for groups and therefore appear to support the conclusion by NLA.[25,27,29,31,33,35] On the other hand, one study that reported a favorable result for apoB vs

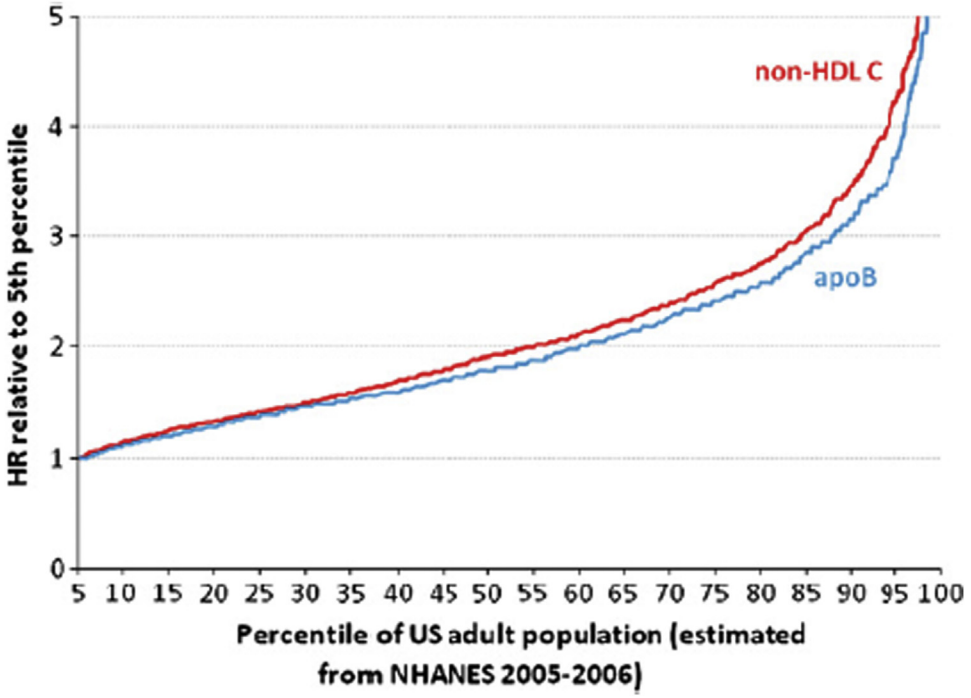

Figure 1 The actual hazard ratios for non-HDL-C and apoB at different levels throughout the population. The values used are taken from the Emerging Risk Factor Study and are virtually identical. HDL-C, high-density lipoprotein cholesterol; apoB, apolipoprotein B.

non-HDL-C was cited within the NLA report.[32] However, this was not identified as a positive result for apoB but rather as support for the use of non-HDL-C. Seven prospective observational and cross-sectional studies that did report apoB to be superior to non-HDL-C were not cited.[26,28,30,34,36–38] It is noteworthy that ERFC is the only study to report that all the markers including TC were equivalent. Moreover, as will be demonstrated below,

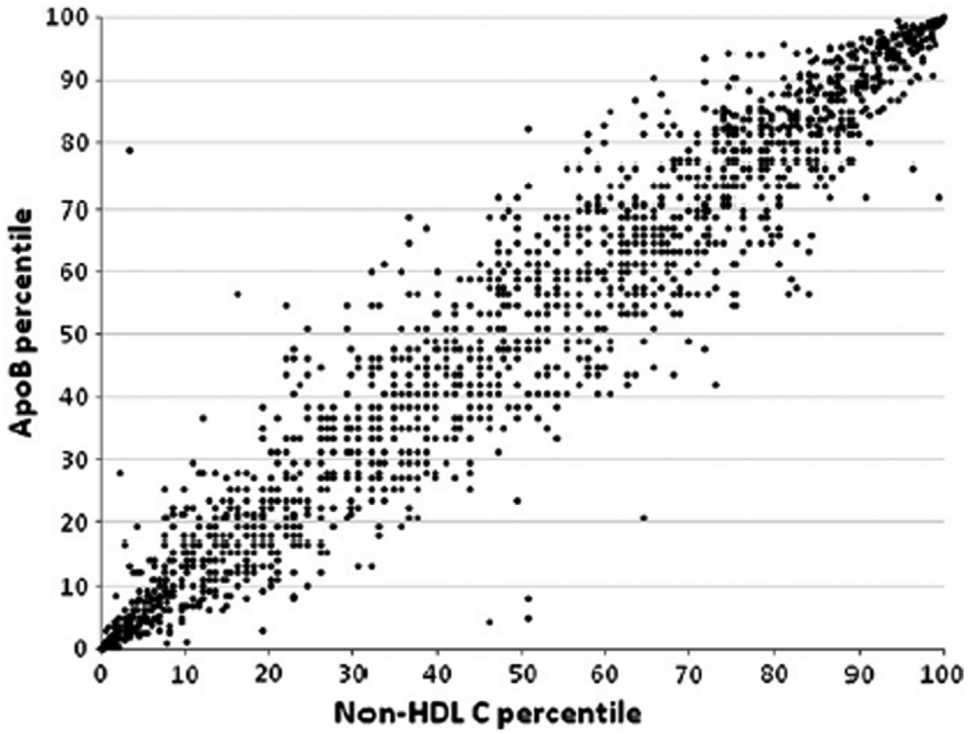

Figure 2 Scatter plot of percentile of apoB vs percentile of non-HDL-C in NHANES 2005 to 2006.[24] HDL-C, high-density lipoprotein cholesterol; apoB, apolipoprotein B.

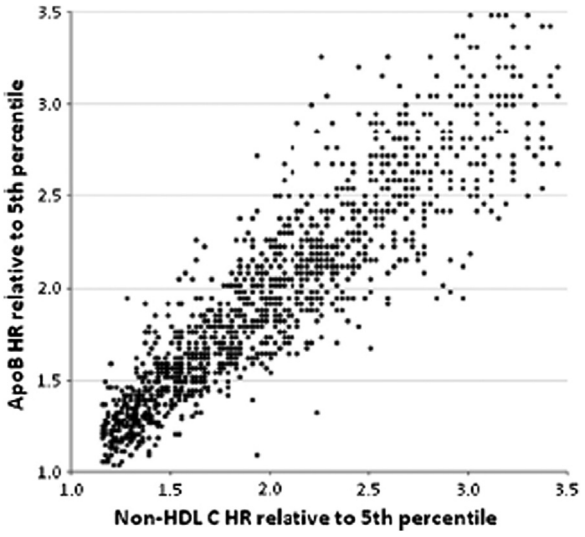

Figure 3 Scatter plot of individual apoB hazard ratio vs individual non-HDL-C HR in NHANES 2005–2006 subjects with non-HDL-C values between the 10th and 90th percentile.[24] HDL-C, high-density lipoprotein cholesterol; apoB, apolipoprotein B.

the studies that demonstrated apoB and non-HDL-C to be overall equivalent markers of risk in the total study group do not establish they are equivalent markers in all the individuals in the study. Indeed, the contrary is the case, and this will also apply to ERFC.

Finally, the two published meta-analyses that are relevant were also not cited. One is the only meta-analysis of prospective observational studies. This study demonstrated that non-HDL-C was superior to LDL-C, and that apoB was superior to non-HDL-C and LDL-C.[39] This meta-analysis included 233,455 subjects with 22,950 events, whereas ERFC included 91,307 subjects and 4499 events.[20] The other meta-analysis demonstrated that apoB was superior to LDL-C and non-HDL-C as a marker of the benefit from the statin therapy.[40] This study estimated that a 40% reduction in apoB would result in 500,000 fewer cardiovascular clinical events over 10 years than a 40% reduction in LDL-C and 200,000 fewer cardiovascular events than a 40% reduction in non-HDL-C. These results are not cited in the NLA report.

Clinical significance

All the relevant evidence was not considered by the NLA. Their conclusions, therefore, are not based on the totality of the evidence.

Table 2 ApoB, non-HDL-C, and LDL-C as markers of cardiovascular risk

Non-HDL-C = ApoB but >LDL-C*	ApoB > LDL-C + Non-HDL-C†	TC = Non-HDL-C = LDL-C = apoB‡
AMORIS Holme et al J Intern Med 2008, 264 30[25]	INTERHEART McQueen et al Lancet 2008, 372 224[26]	ERFC Di Angelantonio et al JAMA 2009, 302 1993[20] Di Angelantonio et al JAMA 2012, 307 2499[21]
EPIC-NORFOLK Sondermeijer and Rana Eur J Clin Invest 2013, 43 1009[27] Ndumele et al Eur J Prevent Cardiol 2014, 21 866[29]	Carlo Monferrato Bruno et al Diabetalogia 2006, 49 937[28] Chin-Shan Cohort Chien et al J Lipid Res 2007, 48 2499[30]	
MONIKA/KORA Meisinger et al Eur Heart J 2005, 26 271[31]	Health Professionals Pischon et al Circulation 2005, 112 3375[32]	
COPENHAGEN City Heart Benn et al ATVB 2007, 27 661[33]	ISIS Parish et al Eur Heart J 2009, 30 2137[34]	
Women's Health Study Ridker et al JAMA 2005, 294 326[35]	Framingham Heart Study Ingelsson et al JAMA 2006, 295 2859[36]	
	Schmidt et al Angiology 2013, 65 901[37]	
	MESA Steffen et al ATVB 2015, 35 448[38]	
	Sniderman et al Circ Cardiovasc Qual Outcomes 2011, 4 337[39]	

*Studies in which non-HDL-C and apoB were equivalent risk markers for cardiovascular risk but both were superior to LDL-C.
†Studies in which apoB was superior to both LDL-C and non-HDL-C as a marker of cardiovascular risk.
‡The only study in which total cholesterol (TC) is equivalent as a marker of cardiovascular risk to LDL-C, non-HDL-C and apoB.

If the HRs of non-HDL-C and apoB are equal in a study, does that mean non-HDL-C and apoB predict risk equally in all the individuals in that study?

The NLA concluded that if the HRs of non-HDL-C and apoB are equivalent in a study, they are of equal value clinically. This seems no more than common sense. However, in the case of the cholesterol and particle number markers for cardiovascular risk, common sense may be common but is not necessarily correct. The explanation has been given in full elsewhere.[41] Nevertheless, because it is critical for the issue at hand, the major points will be recapitulated.

A HR is the increase in the risk of a clinical event per one standard deviation increase in the concentration of LDL-C, non-HDL-C, or apoB in the population. Because the number of standard deviations in a population for any normally distributed marker is the same, the predictive power of these different markers in groups can be compared based on their HRs. ERFC reported that the HRs of non-HDL-C and apoB were effectively identical.[20] The higher the level of non-HDL-C or apoB, the higher is the risk. Therefore, the risk predicted by a marker in an individual depends on the HR of the marker and the level of the marker in the individual (Figure 1).

However, the critical point for clinical care is whether the two markers will predict risk similarly in all the individuals within a study. This would only be the case if the composition of the apoB particles was fixed. Yet, a mass of evidence has established that the amount of cholesterol per apoB particle varies substantially. Figure 2 illustrates this variance by plotting the levels of non-HDL-C as percentiles vs the levels of apoB in the NHANES survey, which is designed to be representative of the American population. It is evident from the figure that in a substantial minority of subjects, the percentile level of cholesterol is higher than the level of apoB, whereas in a substantial minority, the converse is the case.

In patients with cholesterol-enriched apoB particles, as illustrated, the population percentile of cholesterol will be greater than the population percentile of apoB. Accordingly, even if the HRs are identical, the risk predicted by the cholesterol marker—LDL-C or non-HDL-C—for the individual will be greater than the risk predicted by apoB or LDL PN. Conversely, in patients with cholesterol-depleted apoB particles, even if the HRs of apoB and the cholesterol markers were the same, the risk predicted by apoB/LDL PN vs LDL-C/non-HDL-C would not be. These effects are illustrated in Figure 3, which plot the actual hazard ratio calculated for both non-HDL-C and apoB for each individual. There is considerable dispersion around any line of identity, and this dispersion reflects discordance between the risk predicted by apoB vs the risk predicted by non-HDL-C. Note that this dispersion exists although the HRs for the two markers for the group are the same because it is driven by differences in the mass of cholesterol per apoB particle observed in individuals. The consequence is that in many individuals the two markers predict risk differently.

But this is logically impossible: there can be only one risk attributable to LDL in any individual. Risk cannot simultaneously be high in an individual based on the mass of cholesterol but low based on the number of particles. Individual risk may be high, low, or intermediate. But it can only be a single value not multiple values.

Clinical significance

Equal HRs for cholesterol and apoB in a study do not mean that cholesterol and apoB predict risk equally in all the individuals in a study. Because clinical care is about the individual, the conclusion by the NLA that the two markers are necessarily equivalent for clinical care is not correct. To settle which is correct requires testing their predictive powers when they disagree not when they agree. Discordance analysis is a new analytical method, which allows this to be done.

Discordance analysis

Discordance analysis is based on the physiologically driven differences in the composition of apoB particles. In most subjects, whose apoB particles contain an average mass of cholesterol, the concentrations of LDL-C, non-HDL-C, and apoB, relative to each other are the same. Because they are concordant, the predictions of cardiovascular risk each makes must be the same as any of the others. Not so when the cholesterol markers, LDL-C and non-HDL-C, and particle number markers, apoB and LDL PN, are discordant. When increased numbers of cholesterol-depleted particles are present, apoB and/or LDL PN predict increased cardiovascular risk, whereas LDL-C and non-HDL-C do not. Similarly, when normal numbers of cholesterol-rich apoB particles are present, LDL-C and non-HDL-C are high and predict increased cardiovascular risk, whereas apoB and LDL PN predict that cardiovascular risk is not increased.

Discordance analysis tests two markers in subgroups, which have been created to ensure that one predicts increased risk, whereas the other predicts the opposite.[42] Only one can be right. One must be wrong. The outcome, therefore, is unambiguous. Discordance analyses in the Framingham Heart Study,[43] the MESA study[44] and in the Women's Health study[9] have demonstrated that LDL PN predicted cardiovascular risk correctly, whereas LDL-C did not. Discordance analysis in INTERHEART study,[45,46] the Framingham Heart Study,[47] and the Women's Health study[9] has demonstrated that apoB predicts cardiovascular risk correctly and LDL-C does not. Discordance analysis in the INTERHEART study[45,46] and the Framingham Heart Study[47] demonstrated that apoB predicts risk correctly, whereas non-HDL-C does not. Discordance in the CARDIA study demonstrated that apoB at age 25 years is

superior to LDL-C and non-HDL-C at age 25 years to predict the risk of coronary calcification at age 50 years.[48]

The concept of discordance analysis is discussed in the NLA report, and some of the initial publications are noted. A publication summarizing more of the results that were available, and their significance was not noted.[49] The NLA concluded that discordance analysis did not significantly change the balance of the evidence. Potential limitations of discordance analysis are identified by the NLA including the fact that different definitions of discordance have been used. However, the replicability of the core observations in multiple large well-constructed databases should strengthen confidence in the results. Also, the replicability of the results when different definitions of discordance are used in the same data set and among different data sets should strengthen confidence.

The NLA suggests that the numbers of those who are discordant are too small to matter clinically. This is incorrect. A median definition of discordance is the most conservative definition of discordance. That is, this approach produces the smallest discordant groups and correspondingly the largest concordant group. Even with this definition, between 8% and 10% of subjects have high numbers of cholesterol-depleted particles and therefore are at greater risk than either LDL-C or non-HDL-C would indicate, whereas 8%–10% have cholesterol-enriched particle and are at lower cardiovascular risk than either LDL-C or non-HDL-C would indicate. This means that at least 16%–20% of individuals—that is, between 1 in 6 and 1 in 5—have clinically significant discordance by a conservative definition of discordance. This is a substantial portion of the population. Moreover, discordance will be even greater in high cardiovascular risk groups such as individuals with diabetes and patients with the metabolic syndrome in whom correlation between non-HDL-C and apoB is much lower.[50]

The Framingham Heart Study demonstrated that elevated non-HDL-C at age 55 years, particularly if the finding was present on previous examinations, is associated with high intermediate term risk even in those whose 10-year risk threshold was <7.5%.[51] However, the total group with elevated non-HDL-C is composed of a subgroup that is at increased risk and a subgroup that is not at increased risk, and apoB can differentiate the two. From the available data, approximately one in four women and one in five men with elevated non-HDL-C have a normal apoB or LDL particle number.[9,45,46] Although their estimated risk may not be high enough to be selected for statin therapy, they would need to be informed their level of non-HDL-C (or LDL-C) was above normal and, given the link in the public mind between elevated cholesterol and elevated cardiovascular, this would almost certainly raise considerable concern, a concern, which is unfounded for those with normal apoB or LDL PN.

Clinical significance

Discordance analyses have shown that in discordant individuals, the risk predicted by the particle number index is correct, whereas risk predicted by the mass of cholesterol is not. Therefore, the conclusion by the NLA that non-HDL-C is equivalent to apoB as a marker of cardiovascular risk for individuals is contradicted by the evidence. If apoB is high but non-HDL-C is not, cardiovascular risk is high. If non-HDL-C is high but apoB is not, cardiovascular risk is not. Non-HDL-C is not equivalent to apoB as a marker of cardiovascular risk.

The relation of on-treatment levels of LDL-C, non-HDL-C and apoB to residual risk and benefit

> "iii) ApoB is a potential contributor to residual ASCVD risk because it may remain elevated in some individuals who have attained their treatment goals for non-HDL-C and LDL-C, particularly in patients with high triglycerides and low HDL-C levels."[2]

In a meta-analysis of 8 statin randomized trials, Boekholdt et al[22] reported that the on-treatment HR of non-HDL-C was significantly higher than LDL-C or apoB. The absolute values, however, were almost identical and the difference, while statistically significant, was not clinically significant. That the predictive powers of the three markers after statin therapy are similar was also reported by the Heart Protection Study.[52] Nevertheless, as established above, even if the overall HRs were the same, this does not mean that the markers predict actual risk similarly if the plasma levels of the cholesterol and particle number markers are significantly discordant. This indeed appears to be the case as demonstrated in Table 3, which lists the plasma levels of LDL-C, non-HDL-C, and apoB and their relative levels in the

Table 3 Achieved plasma levels and population percentiles of LDL-C, Non-HDL-C, and apoB in multiple clinical trials

Studies	LDL-C, mg/dL	PP*	Non-HDL-C, mg/dL	PP	ApoB, mg/dL	PP
TNT	75	10th	101	15th	98	64th
IDEAL	80	14th	102	16th	84	41st
JUPITER	55	6th	76	4th	66	15th
CARDS	72	9th	100	15th	80	35th
HPS	80	14th			78	31st
PROVE-IT	62	4th			67	16th

TNT, treatment to new targets[53]; IDEAL, Incremental decrease in end points through aggressive lipid lowering[54]; JUPITER, justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin[55]; CARDS, primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study[56]; HPS, Heart Protection Study[57]; Prove-IT, pravastatin Or atorvastatin evaluation and infection therapy.[58]

*The level of the marker expressed as a percentile of the population.

population from six recent statin RCTs, which have published data on the three markers.[59]

In all these studies, although least remarkable in JUPITER, the achieved levels of LDL-C and non-HDL-C, expressed as a percentile of the population are substantially lower than for apoB. Thus, overall, the apoB particles must be cholesterol-depleted. This result should not be surprising since cholesterol-depleted apoB particles are more common in those groups selected for statin clinical trials plus the fact that statin therapy reduces the mass of cholesterol within apoB particles more than the number of particles.[7,60]

Clinical significance

In multiple clinical trials, on-treatment levels of apoB, expressed as percentile of the population, are substantially higher than LDL-C or non-HDL-C. Accordingly, apoB will identify those who might benefit from additional therapy more accurately than LDL-C or non-HDL-C.

The relation of LDL-C, non-HDL-C and apoB to the benefits of statin therapy

There are two meta-analyses of the relation of LDL-C, non-HDL-C, and apoB to benefit. Robinson et al[23] reported that apoB was not more closely related to the benefit of lipid therapy than LDL-C or non-HDL-C, whereas Thanassoulis et al[40] reported benefit was significantly more closely related to apoB than to either non-HDL-C or LDL-C. The Robinson study is cited by the NLA, whereas the Thanassoulis study is not. However, we will demonstrate that although the conclusions of the two studies appear to differ diametrically, on closer review, they are not that different. Both point to the superiority of apoB.

Robinson et al[23] used a Bayesian approach, whereas Thanassoulis et al[40] reported that both a frequentist and Bayesian analysis produced the same results. The overall conclusions of the Robinson study are based on the combination of statin and nonstatin studies. The analysis by Thanassoulis includes only statin studies. The nonstatin studies in the Robinson report include a number with only minor changes in LDL and without significant clinical benefit. When only the statin studies were considered, apoB in the Robinson study was more closely related to benefit than non-HDL-C or LDL-C.[23] In this sense, the studies agree and support apoB. Nevertheless, the strength of the association reported in the Thanassoulis study was substantially stronger than in the Robinson study.

A more detailed examination of the methods is necessary to explain these differences. Robinson et al[23] used a 3-parameter simple linear model, which included marker change, length of time on treatment, and intercept. They analyzed how well each marker fit the model, not how closely each marker related to benefit in each trial. A linear model with a positive intercept, such as theirs, predicts benefit at zero dose of therapy and zero duration of therapy. An advantage of Cox regression, which was the approach in the Thanassoulis study,[40] is that duration of treatment does not need to be adjusted for as the assumption is that the relative difference between the two groups is the same throughout the study. Finally, the *P* values in the Thanassoulis study were calculated using a paired approach, which reduces the variance of the sample differences. Because change in plasma levels of the cholesterol or apoB levels reflects differences in the same individuals before and after therapy, this is the appropriate approach as opposed to an unpaired analysis, which was used in the Robinson study, which presumes before and after samples are not related to each other. The variance in the latter approach will be much larger than the former and the statistical significance of a difference will be correspondingly reduced. The core finding is that statins reduce LDL-C and non-HDL-C more than they reduce apoB.[7,60] Because apoB is reduced least, benefit must relate most closely to apoB. The analysis and the argument are no more complicated than that. Finally, a meta-analysis of coronary intravascular ultrasound studies, which was also not cited, reported that percent change in apoB was significantly more closely related than LDL-C or non-HDL-C to lesion regression.[61]

Clinical significance

The evidence is consistent that the benefit from statin therapy is more closely related to the decrease in apoB than to the decreases in LDL-C or non-HDL-C. This evidence supports the use of apoB as the preferred target of statin therapy.

Treatment goals

In its report, the NLA stated that "If apoB is used as an optional target for treatment, goals are <90 mg/dl for primary prevention and <80 mg/dl for those with very high risk, although measurement of apoB is generally not necessary until the patient has been treated to his or her goal levels for atherogenic cholesterol (Table 4)."[2] The NLA offers two lines of reasoning to justify their selections of goals. One relates to the levels that were observed in clinical statin trials. "Treatment with statins and other cholesterol-lowering therapies appears to alter the relationship between atherogenic cholesterol and apoB concentrations.[155,189–191] In an analysis of data from the Limiting of Undertreatment of Lipids in ACS with Rosuvastatin (LUNAR), Ballantyne et al[190] reported that during statin therapy an apoB concentration of 80 mg/dl was associated with mean LDL-C and non-HDL-C concentrations of 85 mg/dl and 105 mg/dl, respectively. The corresponding mean values associated with an apoB concentration of 80 mg/dl were 74 mg/dl for LDL-C and 92 mg/dl for non-HDL-C."[2]

Table 4 NLA goals for LDL-C, non-HDL-C, apoB, and equivalent population goal for apoB

Markers	Low risk, mg/dL	Low risk, PP	High risk, mg/dL	High risk, PP	Low risk PP, equivalent apoB	High risk PP, equivalent apoB
LDL-C	100	33rd	70	8th		
Non-HDL-C	130	42nd	100	15th		
apoB	90	51st	80	35th	80 mg/dL	60 mg/dL

PP, percentile population.

These values, however, are not the population equivalent values. They are the observed plasma concentrations for these variables for the subjects that were studied. The population percentile values, which are the comparable values, are the values for the percentile of the population to which these values correspond. These are the 8th, 15th and 35th percentile for LDL-C, non-HDL-C and apoB respectively (Table 4). These results demonstrate that the level of apoB, in the Ballantyne study is actually substantially higher than the other two markers pointing to cholesterol-depleted apoB particles.

"The thresholds chosen by the panel are the same as those recommended previously by the American Diabetes Association/ACC Foundation.[186]" However, the authors of this report also wrote that: "For subjects with mildly or moderately elevated triglyceride levels (>200 mg/dl), we support the ATPIII recommendations to target LDL cholesterol first and then use non-HDL cholesterol as a secondary target for treatment, with a goal 30 mg/dl higher than the patient's LDL cholesterol goal but *we further recommend that the population-equivalent apoB goal be reached.*" (emphasis added)[62] The ADA/ACC Foundation report does not explain why the value of 80 mg/dL for apoB was chosen as its goal because in Table 4, it is not the population equivalent value for LDL-C and non-HDL-C, which based on the NHANES survey would be 79 and 62 mg/dL, respectively.

Thus, with regard to the low-risk goal, the level of apoB chosen by the NLA is at the 51st percentile of the population vs the 33rd percentile for LDL-C. The differences for the high risk goals are even more dramatic. The NLA LDL-C goal is at the 8th percentile of the population, whereas the apoB goal was set at the 35th percentile level. Based on the equivalent level in the population, the appropriate low-risk level for apoB would be 80 mg/dL, whereas the appropriate high-risk level would be 60 mg/dL (Table 4).

Clinical significance

The goals selected by NLA for apoB are much higher than those for LDL-C or non-HDL-C. No rationale is given for this decision, the effect of which would be undertreatment in a substantial number of high-risk individuals.

Limitations of this analysis

There are limitations in this analysis. First, we cannot know the full range of subjects that were discussed by the NLA panel. However, we must presume that the authors of the report included all the material they thought necessary to justify the decisions that they reached just as the authors of original scientific research would include all the observations they have gathered to justify or contradict their conclusions. Second, time has passed since the NLA report was written. Accordingly, more information is available now than when their report was written. Nevertheless, most of the studies cited in this analysis were available for review of the panel. Moreover, recommendations that are shown to be inadequate need to be identified when this is demonstrated, not maintained in force until the next scheduled meeting of a panel. Third, we have focused on one issue: the comparison of LDL-C, non-HDL-C, and apoB as markers of cardiovascular risk, whereas the panel had to deal with many. However, the choice by the NLA of non-HDL-C as their primary index of the atherogenic apoB lipoproteins was one of the most significant they made and therefore the presumption must be that it was made after due deliberation. Accordingly, a detailed examination of their decisions and the reasoning they offered to support them is appropriate and fair.

Conclusion

Guideline recommendations have consequences. The failure of guidelines to recommend apoB for routine clinical care is the reason that apoB is not widely used in clinical care and while guidelines influence physicians, they influence payers even more. Reimbursement decisions relate to guideline decisions. The evidence and the analyses of the evidence in this review indicate that the recommendations of the NLA report regarding non-HDL-C and apoB should be reconsidered because not all the relevant evidence and interpretations of the evidence were considered. If there are counterarguments against the interpretations of the evidence that have been put forward that tip the balance back in favor of the conclusions reached by the NLA, these should be marshalled and put forward.

The evidence on which our guidelines are based is always incomplete and our experimental methods to obtain the evidence are imperfect. Moreover, the evidence does not speak for itself. The evidence must be gathered, analyzed, interpreted, and extrapolated. For the guideline process to succeed, intellectual pluralism among the participants is essential and a reasoned, respectful, and open contest of ideas and evidence must occur.

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Dr Sniderman conceived the project and wrote the initial draft. This was individually reviewed and significantly revised

by Drs Thanassoulis, Toth and Furberg. Each new draft was generated based on these comments and recirculated. All authors contributed significantly to the structure and content of the final version. All authors have approved the final version.

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