Research Article

# Why Non-HDL Cholesterol is Preferred over Apolipoprotein B-100 (Apo B)

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**Importance**

**Most studies have found that apo B-100 is a superior marker for Coronary risk (ASCVD) than non-HDL cholesterol (C). Usually, studies use multivariant analysis to compare indexes with single-point odds or risk ratios. In multivariant analysis when variables are highly correlated, they are difficult to interpret and the lesser may be excluded. As a result, effect sizes cannot be well compared. Receiver operator characteristic (ROC) curves provide a visual portrait of the accuracy and the diagnostic sensitivity and specificity at each decision level so that relative discrimination of each variable can be well compared. Since non-HDLC has distinct economic value, it is important to compare clinical value in an appropriate format.**

**Objective**

**To compare outcomes from ROC analysis with routine one-point logistic regression.**

**Design, Setting, and Participants**

**Lipoprotein variables alone and after correction for non-lipoprotein risk factors were compared from patients with and without significant ASCVD undergoing coronary angiography.**

**Main Outcome measures**

**The variables were assessed by standard logistic regression alone and by ROC curve analysis.**

**Results**

**Although non-HDLC and apo B were stronger markers than LDLC, when examined by logistic regression, as a result of very strong collinearity, non-HDLC appeared weaker than LDLC in the presence of apo B, based on p-values. This was true when analyzed with and without non-lipid risk factors. When analyzed by ROC analysis, apo B and non-HDLC showed stronger C-statistics than LDLC and total C. At an appropriate apolipoprotein/lipid, decision level apo B showed about 6.1% greater specificity than non-HDLC. But, after adjustment for non-lipid risk factors, the c-statistics**

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**for apo B and non-HDLC were 0.64 and 0.63, respectively and there was little difference in specificity at a standard selected decision value.**

**Conclusion and Relevance**

**Except for persons with acquired or genetically determined hypercholesterolemia, the ten-year risk is calculated from an algorithm that includes non-lipid risk factors similar to those examined here. Based on this data, when assessed by the AHA/ACC ten-year screening algorithm, it is likely that non-HDLC would provide greater economic value than would apo B with similar clinical efficacy. Non-HDLC should be utilized as the preferred lipid marker.**

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# Introduction

It was recently suggested that apoB-100 (apo B) should be the primary marker to assess the cardiovascular risk[1]. This suggestion followed from a paper showing in head to head comparison that apo B was a better marker for risk than LDLC.[2] Presumedly, this means adding apo B to the standard lipid panel. The purpose of this Report is to question whether or not such a revision would be clinically and economically reasonable since much information can be obtained from the current panel including an estimate of risk that agrees well with the measurement of apo B. The routine lipid panel consists of Total cholesterol, calculated or measured LDLC, triglyceride and HDLC. Historically, LDLC has been the targeted risk marker, both because elevated LDLC imparts increased risk and because lower LDLC is the treatment goal. It is proven that elevated LDLC causes coronary disease, and that lowering LDLC reduces risk[3]. But many studies, including our own, have shown that apo B is a better marker of coronary risk than LDLC.[4][5][6] A major reason for this peculiarity is that as the world has grown fatter, the most common dyslipidemia has become the atherogenic phenotype which tends to be over-expressed in overweight persons[7][8][9][10].

This phenotype most often is expressed as slightly to moderately elevated triglyceride, slightly to moderately decreased HDLC and so-called discordant LDL where, although there are more LDL particles, each particle contains less cholesterol so that the particles are small and dense (sdLDL). As a result, although there may be more particles, the measured serum cholesterol is often within recommended limits. Nevertheless, sdLDLs are clearly linked to arteriosclerotic coronary vascular

disease ·(ASCVD),[11] presumedly, because the small particles can more easily penetrate the arterial wall facilitating the arteriosclerotic process. Moreover, excess fat tissue is toxic and leads to insulin resistance and vessel wall inflammation[9][12][13] which further facilitate ASCVD. The advantage of assessing risk using apo B is that each LDL particle contains one molecule of apo B and persons with sdLDLC have more particles with less cholesterol so that high-risk persons are more consistently identified.

Although newer equations for calculating LDLC are largely empirical,[14] LDLC by the classic Friedwald equation subtracts HDLC and a theoretical measure of VLDLC from total C. Theoretically, these estimates compare well with the tedious beta-quantification reference method that was used to measure LDLC in earlier clinical studies,[15][16] where the VLDL are removed by ultracentrifugation and the HDL by precipitation so that cholesterol in particles considered very atherogenic particles [LDL, IDL, some VLDL remnants[17] and Lp(a)] are left in the remaining solution to be measured along with LDLC. Among other problems,[18] directly measured LDLC does not measure IDL, Lp(a) or remnants and is apt to be a poorer marker of ASCVD risk. Measurement of LDLC overlooks the risk associated with discordant, sd-LDL particles containing less cholesterol and may not measure atherogenic cholesterol in some VLDL.

Non-HDLC represents all of the Cholesterol in the beta-lipoprotein fractions. We showed that non-HDLC correlated better with apo B than did calculated LDLC: r = 0.96 for non-HDLC vs. apo B and r = 0.85 for LDLC vs, apo B.[5] It is estimated that VLDLC accounts for one-half of the risk of myocardial infarction associated with beta-lipoproteins.[19] It is likely that non-HDLC measures more atherogenic particles in VLDL than apo B or LDLC do, but both LDLC and non-HDLC suffer from an inability to identify risk in discordant sdLDL. Clinical studies have shown that non-HDLC levels seemed more closely associated with coronary atheroma progression than LDLC,[20] and apo B and non-HDLC had comparable outcomes in the multivariate-adjusted hazard ratios,[21] non-attaining non-HDL-C goal was associated with a higher risk of long-term MACE whereas the non-attaining LDL-C goal was not associated with the increased risk of long-term MACE,[22] that non-HDL cholesterol may be particularly useful in treating patients with diabetes[23] and among statin-treated patients, on-treatment levels of non-HDL-C showed a greater association with future ASCVD risk than apoB.[24] In fact, a Mendelian randomization analysis suggested that the risk of ASCVD is more

associated with non-HDL-C than apo B particle concentration,[25] although pitfalls of this type of analysis were well delineated.[26]

Thus, it appears apo B and non-HDLC are highly correlated in risk assessment. Usually, studies use OR or RR derived from multivariant analysis to compare indexes. A problem with these techniques is that in multivariant regression, with a single-point estimate, it is difficult to interpret the model if two variables are highly correlated, the lesser will appear inferior, and in stepwise regression be excluded from the final model. Moreover, the effect sizes cannot be well compared. Receiver operator characteristic (ROC) curves provide a visual portrait of the accuracy of each variable along with the diagnostic sensitivity and specificity at each decision point so that the discrimination of each variable can be well compared.

In this report, apo B, LDLC, and non-HDLC are compared both by the usual logistic regression and by ROC analysis. The data from standard logistic regression shows the ambiguity in comparing discrimination for the variables while the data from ROC analysis indicates that LDLC and total C are clearly inferior to apo B and non-HDLC and that, although nonHDLC appears poorer than apo B at a standard decision point, this difference is diminished to a clinically insignificant level in the presence of other standard non-lipid risk factors.

## Materials and Methods

### *Subjects, Blood Sample Collection, and Angiography*

Treatment of the patients, samples, and angiography are the same as previously described[5] [27] Briefly, there were 140 Normal and 242 ASCD patients, all men, 40 to 70 years old, entering the Veterans Administration Hospital for clinically indicated angiographic studies. Samples were obtained from consecutively examined patients, except for the following exclusion criteria: patients taking known lipid-altering (lowering) medications or heparin, people with diabetes, people with chronic kidney disease, and people experiencing a myocardial infarction within 3 months. The study was approved by the Veteran Administration Medical Center and the University of Louisville Committees on the protection of human rights. Cholesterol assays were performed by standard methods with automated analyzers. on fresh serum samples. Aliquots were frozen at −70°C for apo B measurements. Apo B was measured by automated rate immunonephelometry using kits with the Array (Beckman Instruments, Brea, CA). Angiography was performed by the standard radial artery approach. Subjects

with >70% stenosis in at least 1 major vessel were defined as ASCVD and those with <20% stenosis as normal. Non-HDLC was calculated and LDLC was calculated using the Friedwald equation. Six patients did not have apo B performed

### *Statistics*

In this study, there were 382 patients with 6 not assayed for apo B, but all were included in the calculations. ROC curves were calculated using the program Rockit (available from Metz ROC Software, Department of Radiology, University of Chicago): This program uses the maximum-likelihood-estimation technique for estimating the curve shape. Logistic regression was performed with JMP 10 (SAS Institute, Cary, NC). The output from logistic regression equations for lipoprotein variables and risk factors were used to develop the ROC curves corrected for non-lipid risk factors of hypertension (HT), familial history (FH), smoking (S) and body mass index (BMI). For the ROC curves adjusted for these standard risk factors, the following equations were used[27] Disease (yes or no) = 0.093age– 0.04HT + 0.12FH + 0.27S – 0.021BMI + 0.0017apo B – 7.6; 0.092age – 0.083HT + 0.24FH + 0.16S – 0.021BMI + 0.0012non-HDLC – 7.40; and 0.090age – 0.11HT + 0.13FH +0.24S – 0.009BMI + 0.001LDLC.

### *Results with Interpretation*

Table 1 displays the results of routine logistic regression. Based on p values for each analyte assayed alone. It is apparent in the upper grouping that apo B is the strongest risk factor and LDLC the weakest. It also seems that both apo B (p = <0.0002) and non-HDLC (p = 0.0012) are stronger predictors than LDLC (p = 0.0109) by about 10-fold. When the variables are combined, it is difficult to interpret a model when there is a very high collinearity of variables. Thus, when the assays are run in combination, middle group, and apo B is included, it is the only analyte that shows a significant predictive value (p<0.05). In fact, based on p-values, it appears that the very high collinearity between apo B and non-HDLC causes the non-HDLC (p= 0.3938) to become a poorer predictor than LDLC (p = 0.2201), middle group, when it is clear non-HDLC is a more powerful predictor (Table 1, Top group and middle group where HDLC and LDLC are compared). The same trends are seen in the lower grouping after correction for non-lipid risk factors.

| Apo B | NonHDLC | LDLC | n |
|---|---|---|---|
| <0.0002 | | | 376 |
| | 0.0012 | | 382 |
| | | 0.0109 | 382 |
| 0.0022 | | 0.3622 | 376 |
| | 0.0180 | 0.2148 | 382 |
| 0.0239 | 0.8102 | | 376 |
| 0.0283 | 0.3938 | 0.2201 | 376 |
| Adjusted for age, smoking, family history, hypertension and for body mass index. | | | |
| 0.0011 | | 0.5532 | 382 |
| | 0.0055 | 0.2282 | 382 |
| 0.0383 | 0.7119 | | 376 |
| 0.0277 | 0.2381 | 0.1943 | 376 |
| n = number of patients. | | | |

**Table 1.** p-value Comparison of Lipoprotein Parameters from Logistic Regression

Aside from bias from very high correlation between non-HDLC and apo B, logistic regression with a single point interpretation does not allow a good comparison of the relative discrimination of each variable so one cannot tell how much better one variable differentiates risk as compared to the next. One way to examine the relative effect of each is to develop ROC curves.

Figure 1 and Figure 2 show ROC curves depicting the data. These Figures were previously published[27] and are reproduced with slight modifications with permission.

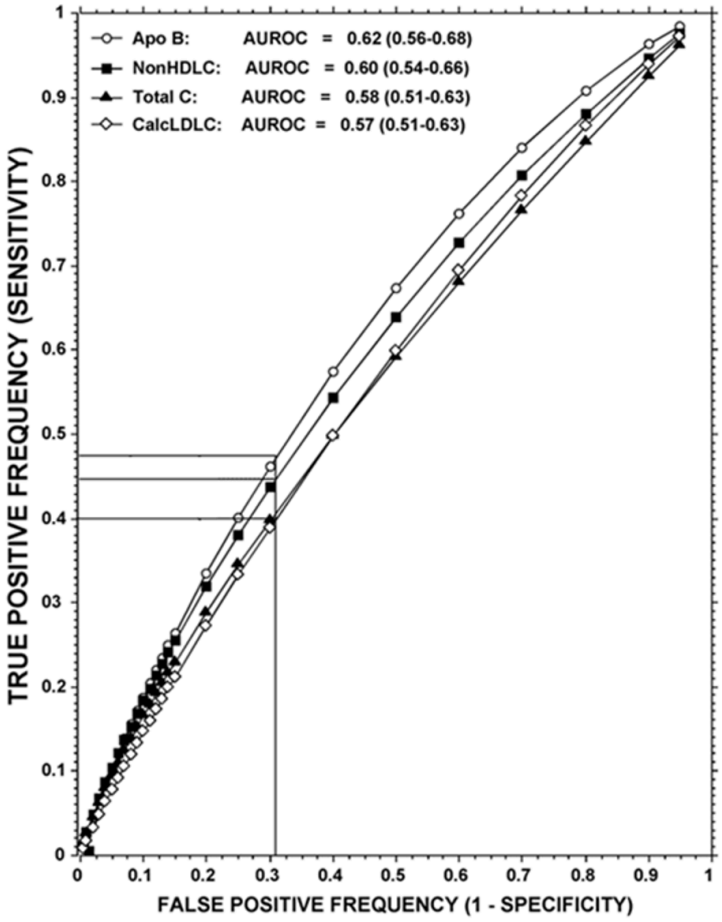


**Figure 1.** ROC Curves for apo B, non-HDLC, LDLC, and total C. Each analyte is displayed alone with no corrections. The vertical line at about 0.305 represents a common decision point, at about 130 mg/dL for LDLC, 160 mg/dL for non-HDLC and about 1.2 g/L for apo B. The horizontal lines correspond to sensitivities coincident with the selected decision level. AUROC, area under ROC or c-statistic.

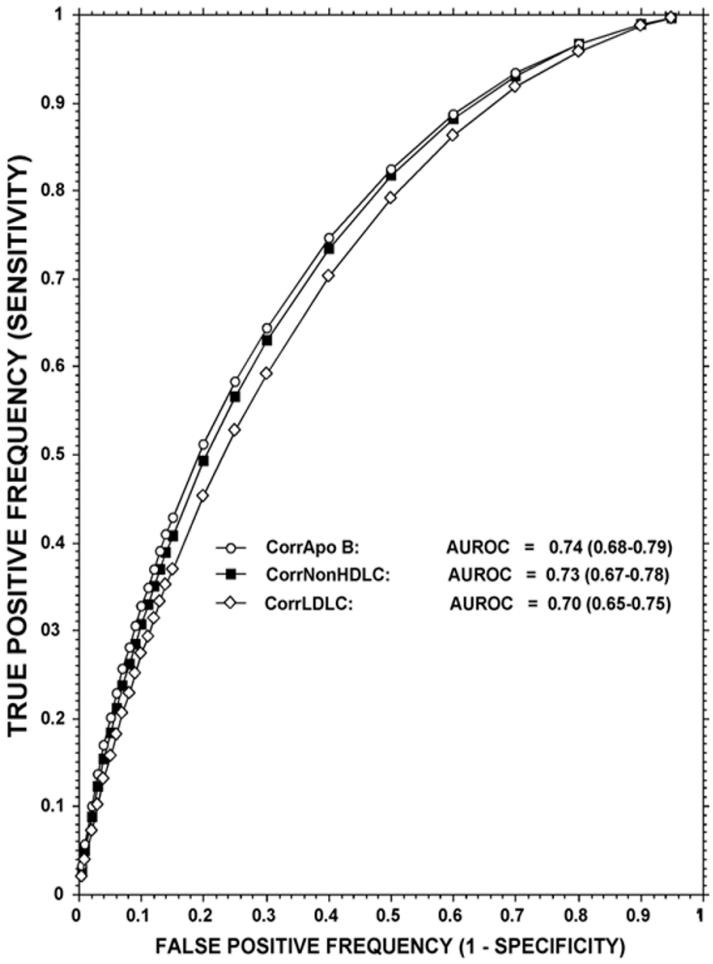


**Figure 2.** ROC Curves for apo B, non-HDLC, LDLC after correction (Corr) for non-lipid risk factors. The equation outputs for developing the curves are given in the text. The risk factors were: age, smoking, family history, hypertension and body mass index. AUROC, area under ROC or c-statistic.

In Figure 1, at a FPF of about 0.305 corresponding to diagnostic specificity of about 0.695, the diagnostic sensitivity for apo B is about 0.475 and for non-HDLC the diagnostic sensitivity is about 0.448, for a difference of about 0.027. The cut-off at a FPF of 0.305 was used because it corresponds to about 130 mg/dL for LDLC, 160 mg/dL for non-HDLC and about 1.2 g/L for apo B, above which each analyte is considered definitively elevated. Apo B is about 6.1% more sensitive than non-HDLC. At a FPR of about 0.305. LDLC shows a diagnostic sensitivity of about 0.4% at the same decision point. The ROC curve for total C is also shown and it is very similar to LDLC. At the defined decision level, the

difference between LDLC and apo B is about 18.75%. When the analytes are compared against one another for assessing risk it is clear that non-HDLC and apo B are more sensitive makers but apo B is more sensitive than non-HDLC, and 6.1% improvement in diagnostic sensitivity may have clinical value for risk assessment while LDLC and total C are inferior. But, as shown in Figure 2, after correction for non-lipid risk factors, the diagnostic sensitivity differences between analytes are attenuated.

Figure 2 shows that at a FPR of about 30.5%, the ROC curve containing apo B shows a c-statistic of 0.74 and that for non-HDLC 0.73 with a diagnostic sensitivity of about 0.655% for apo B, and a diagnostic sensitivity for non-HDLC of about 0.64%, about a 1.5% difference in diagnostic sensitivity, with LDLC at a sensitivity of about 0.605 moderating to a difference from apo B of about 7.6% less sensitive.

## Conclusion

The standard lipid screen is a powerful tool for identifying dyslipidemias, When the LDLC is greater than 160 mg/d, it suggests possible familial or acquired hypercholesterolemia, where the risk of ASCVD is several folds increased,[18] If the LDLC is near normal but the HDLC and triglyceride are moderately aberrant, there is reason to suspect the atherogenic phenotype that increases risk. If the calculated LDLC is elevated but the LDLC does not respond well to statin treatment, it is possible Lp(a) is the culprit, especially if there is a family history of ASCVD.

Ten-year screening risk is calculated from an algorithm published in the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk,[28] where screening for risk is not dependent on lipid values alone but on multiple non-lipid risk factors as well.[29] These include the non-lipid factors of blood pressure, smoking and age. BMI is not included but this risk factor has been well-treated in the guidelines.[29] Moreover, total C not LDLC is a part of the risk assessment but as shown in Figure 1, it seems to be a less sensitive marker than apo B or non-HDLC, about equivalent to LDLC.

It appears that if non-HDLC or apo B were added to the 10-year risk assessment it would increase efficacy. The data presented here (Figure 2) suggests that after correction for standard non-lipid risk factor, there is no clinically important difference in discrimination between apo B and non-HDLC. Since non-HDLC is derived from the standard lipid profile and requires no additional testing and because the word cholesterol is already familiar to practitioners and patients while apo B is less

known, it seems economically and culturally that this is the more desirable index. Moreover, although non-HDLC is calculated from total C – HDLC, calculated values can be robust, depending on the accuracy of the values from which it is calculated.[30] Total C and HDLC are chemical assays with good accuracy and precision where manufacturers have to meet stringent analytical performance criteria defined by the Cholesterol Reference Method Laboratory Network (CREMLN).[30]

The 2016/2017 AHA/ACC guideline identify LDLC and non-HDLC as equivalent targets,[29][31][32] but disappointingly the 2018 guidelines focused mainly on LDLC.[18][33] The AHA presidential advisory Committee has defined the updated metric for blood lipids to be non-HDL cholesterol as the preferred number to monitor.[34] It seems that non-HDLC should be the focus.

### *Limitations*

The major weakness of the data presented here is that the cohort is limited in number and the study is not randomized. Nevertheless, the findings that apo B and non-HDLC are more highly correlated than LDLC and that apo B is the preferred marker when assessed by logistic regression have been confirmed by many randomized studies.[6][32] Moreover, there are now many randomized studies from which the data presented here could be confirmed retrospectively.

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