Non-HDL Cholesterol, Guideline Targets, and Population Percentiles for Secondary Prevention in a Clinical Sample of 1.3 Million Adults The Very Large Database of Lipids (VLDL-2 Study)

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Non-HDL Cholesterol, Guideline Targets, and Population Percentiles for Secondary Prevention in a Clinical Sample of 1.3 Million Adults The Very Large Database of Lipids (VLDL-2 Study)

Brief Title: Non-HDL-C & LDL-C percentile discordance

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Word count: 2243
Abstract

Objectives: To examine patient-level discordance between population percentiles of non-HDL cholesterol (non-HDL-C) and LDL cholesterol (LDL-C).

Background: Non-HDL-C is an alternative to LDL-C for risk stratification and lipid-lowering therapy. The justification for the present guideline-based non-HDL-C cutpoints of 30 mg/dL higher than LDL-C cutpoints remains largely untested.

Methods: We assigned population percentiles to non-HDL-C and Friedewald-estimated LDL-C values of 1,310,440 U.S. adults with triglycerides < 400 mg/dL who underwent lipid testing by vertical spin density gradient ultracentrifugation (Atherotech, Birmingham, Alabama) from 2009 to 2011.

Results: LDL-C cutpoints of 70, 100, 130, 160, and 190 mg/dL were in the same population percentiles as non-HDL-C values of 93, 125, 157, 190, and 223 mg/dL, respectively. Non-HDL-C reclassified a significant proportion of patients within a higher treatment category compared with Friedewald LDL-C, especially at LDL-C levels in the treatment range of high-risk patients and at triglyceride levels ≥ 150 mg/dL. Of patients with LDL-C < 70 mg/dL, 15% had a non-HDL-C ≥ 100 mg/dL (guideline-based cutpoint) and 25% had a non-HDL-C ≥ 93 mg/dL (percentile-based cutpoint); 22% and 50% respectively if triglycerides concurrently 150-199 mg/dL.

Conclusions: There is significant patient-level discordance between non-HDL-C and LDL-C percentiles at lower LDL-C and higher triglycerides; a finding with implications for treatment of high-risk patients. Current non-HDL-C cutpoints for high-risk patients may need to be lowered to match percentiles of LDL-C cutpoints. Relatively small absolute reductions in non-HDL-C cutpoints result in substantial reclassification of patients to higher treatment categories with potential implications for risk assessment and treatment.

Clinical trial info: VLDL-2; NCT01698489

Keywords: Non-HDL Cholesterol; LDL Cholesterol; discordance; percentiles; lipids; secondary prevention

Abbreviations
Cardiovascular Disease = CVD
Low-Density Lipoprotein Cholesterol = LDL-C
Non-High-Density Lipoprotein Cholesterol = Non-HDL-C
High-Density Lipoprotein Cholesterol = HDL-C
Very-Low-Density Lipoprotein Cholesterol = VLDL-C
Intermediate-Density Lipoprotein Cholesterol = IDL-C
Apolipoprotein B = ApoB
Vertical Auto Profile = VAP
National Health and Nutrition Examination Survey = NHANES
The Very Large Database of Lipids = VLDL
Introduction

Cardiovascular disease (CVD) is the leading cause of death in the developed world, accounting for 33% of deaths in the United States and 47% of deaths in Europe (1, 2). For the past 25 years, low-density lipoprotein cholesterol (LDL-C) has been the primary lipid parameter for risk stratification and goal-directed therapy. However, an epidemic of obesity and metabolic syndrome has evolved over the past few decades, mostly due to changes in diet and lifestyle. The current prevalence of metabolic syndrome is approximately 1 out of 3 U.S. adults (1). This became associated with an increasing prevalence of elevated triglyceride-rich remnant lipoproteins, characteristic of insulin resistance. These include very-low density lipoproteins (VLDL) and their remnants, intermediate-density lipoproteins (IDL), and chylomicron remnant particles whose contribution to atherogenic risk is accounted for by non-high density lipoprotein cholesterol (non-HDL-C) not LDL-C.

Current guidelines recommend using non-HDL-C as a secondary treatment target in patients with triglycerides $\geq 200$ mg/dL (3-5), setting non-HDL-C goals 30 mg/dL higher than respective LDL-C goals. However, some reports have suggested using non-HDL-C goals at the same population percentiles as the respective LDL-C goals (6, 7).

In this report, we examine patient-level discordance between non-HDL-C and LDL-C percentiles at different LDL-C and triglyceride strata and implications for risk assessment and treatment.

Methods

Study Population

We examined consecutive lipid profiles from 1,310,440 U.S. adults $\geq 18$ years of age with triglycerides $< 400$ mg/dL who underwent direct ultracentrifugation of cholesterol by the
Vertical Auto Profile (VAP; Atherotech Diagnostics Lab, Birmingham, AL) from 2009 to 2011 (8, 9). ‘Consecutive’ denotes that we only included the first available lipid profile for each patient. Consistent with routine clinical practice, LDL-C was estimated by the Friedewald formula, thus excluding patients with triglycerides $\geq 400$ mg/dL (9, 10).

**VAP Lipid Measurement**

The VAP is an inverted rate zonal, single vertical spin, density-gradient ultracentrifugation technique that directly measures cholesterol concentrations of the five lipoprotein classes [LDL-C, VLDL-C, IDL-C, HDL-C, lipoprotein(a)] and their subclasses. Triglycerides were directly measured using the Abbott ARCHITECT C8000 system (Abbott Park, IL) (8, 9). The accuracy of VAP lipid parameters were cross-validated with reference standards as previously described (9).

**Data Management**

Raw individual patient data were extracted at Atherotech, cleaned of duplicate samples, then de-identified and transferred to the senior investigator. The master database, the Very Large Database of Lipids (VLDL), is maintained at The Johns Hopkins Hospital (Baltimore, MD) and registered on clinicaltrials.gov (NCT01698489). The Johns Hopkins Institutional Review Board declared the study exempt.

**Statistical Analysis**

Friedewald-estimated LDL-C was calculated as [total cholesterol – HDL-C – triglycerides/5]. Non-HDL-C was calculated as [total cholesterol – HDL-C]. We assigned population percentiles to LDL-C and non-HDL-C, then determined the percentiles corresponding to LDL-C cutoff points in current guidelines (70, 100, 130, 160, and 190 mg/dL) (3-5).

Reclassification was defined as present when non-HDL-C reclassified a patient within a
higher (upward) or lower (downward) treatment category compared with Friedewald LDL-C. The analysis was performed using guideline-based non-HDL-C cutpoints, defined as 30 mg/dL higher than LDL-C cutpoints, and percentile-based cutpoints, defined as those at equivalent percentiles to LDL-C cutpoints. We focused on upward reclassification since current guidelines recommend using non-HDL-C only as a secondary treatment target after the LDL-C target is reached; thus, downward reclassification becomes irrelevant.

Statistical analyses and logarithmically scaled pseudocolor density plots were generated in R Version 2.15.1 (Vienna, Austria) and Stata Version 11.0 (College Station, TX).

Results

Population Characteristics

Patients were 59±15 years old (mean±SD), 52% were women, and lipid parameter distributions were nearly super-imposable with recent lipid data from the National Health and Nutrition Examination Survey (NHANES) 2007-2008 (11), as previously described by our group (9) (Appendix Figure 1).

Population Percentiles

LDL-C cutpoints of 70, 100, 130, 160, and 190 mg/dL were at the same population percentiles as non-HDL-C values of 93, 125, 157, 190, and 223 mg/dL, respectively (Table 1).

Non-HDL-C and LDL-C Percentile Discordance

We visually assessed discordance between LDL-C and non-HDL-C percentiles and found greater discordance at lower LDL-C and higher triglycerides (Figure 1). Similarly, the absolute difference between non-HDL-C and LDL-C percentiles was more pronounced with greater in-group variation at lower LDL-C and higher triglycerides (Appendix Figure 2).

Treatment Category Reclassification by Non-HDL-C
When using conventional non-HDL-C cutpoints, non-HDL-C reclassified 10.5\% (n=137,744) of the study population upward and 22.3\% (n=291,499) downward. Using percentile-based cutpoints reclassified 14.2\% (n=186,106) upward and 13.7\% (n=178,860) downward (Figure 2).

Upward reclassification occurred more frequently at lower LDL-C and higher triglycerides (for additional discussion, see the Appendix, Reclassification analysis). Of patients with LDL-C < 70 mg/dL, 15\% had a non-HDL-C ≥ 100 mg/dL (the guideline-based cutpoint), while 25\% had a non-HDL-C ≥ 93 mg/dL (the percentile-based cutpoint); 22\% and 50\% respectively if triglycerides concurrently 150-199 mg/dL (Figure 3A). Similarly, of patients with LDL-C 70-99 mg/dL, 12\% had a non-HDL-C ≥ 130 mg/dL while 17\% had a non-HDL-C ≥ 125 mg/dL; 17\% and 35\% respectively if triglycerides concurrently 150-199 mg/dL (Figure 3B).

Discussion

Our study highlights the magnitude of patient-level discordance between LDL-C and non-HDL-C percentiles. They are most discordant when accuracy is most crucial, at low LDL-C and high triglycerides. Therefore, conventional non-HDL-C cutpoints for high-risk patients may need to be lowered to match percentiles of LDL-C cutpoints.

Non-HDL-C: A Better Marker of CVD risk assessment and treatment

The National Cholesterol Education Program Adult Treatment Panel III guidelines state that “In most persons with triglycerides < 200 mg/dL, adding VLDL-C to LDL-C would be expected to provide little additional power to predict CVD” (3); a disputable statement in lieu of the increasing prevalence of obesity and metabolic syndrome. Non-HDL-C represents the aggregate cholesterol content of apolipoprotein B (apoB) containing atherogenic lipoproteins including LDL, VLDL, IDL, remnants and lipoprotein(a); in principle a broader, more inclusive
measure of atherogenic risk. Recent evidence suggests that non-HDL-C is superior for risk prediction and might be a more effective target for lipid lowering therapy particularly in high-risk patients (12-15). A meta-analysis of 233,455 patients showed that non-HDL-C is a more potent marker of CVD risk than LDL-C (16). Calculating the number of clinical events prevented by a high-risk treatment regimen of those > 70th percentile of the US adult population, Sniderman et al. suggested that a non-HDL-C based strategy may prevent 300,000 more events than an LDL-C strategy over a 10-year period.

In addition, non-HDL-C measurement comes at no additional cost or inconvenience since it is easily calculated from the standard lipid profile without requirement for prior fasting. Moreover, the adoption of non-HDL-C across all levels of triglycerides would substantially simplify implementation of clinical guidelines.

**Potential Implications for Guideline Development**

Guideline-based non-HDL-C cutpoints are based on the assumption that a normal VLDL-C exists when triglycerides are < 150 mg/dL; which is < 30 mg/dL as estimated by the Friedewald formula (3). More recent evidence suggests that a biologically optimal fasting triglyceride level is < 100 mg/dL (17); thus, a normal VLDL-C is likely closer to 20 mg/dL, also suggesting that non-HDL-C cutpoints should be 20 mg/dL higher than LDL-C cutpoints.

Studying patients with acute coronary syndromes, Ballantyne et al. suggested that the current non-HDL-C goal should be lowered by 8 to 10 mg/dL in order to match LDL-C and apoB treatment goals in the very-high-risk category (18). Other reports have recommended lowering non-HDL-C cutpoints to match percentiles of LDL-C cutpoints (6, 7). In our study, the non-HDL-C values with percentile equivalence to LDL-C cutpoints of 100 and 70 mg/dL were 125 and 93 mg/dL, respectively. Therefore, non-HDL-C cutpoints may need to be lowered by 5
mg/dL and 7 mg/dL for the high-risk and very-high-risk categories, respectively. This leads to substantial upward reclassification of patients particularly at concurrent high triglycerides. For example, of patients with LDL-C < 70 mg/dL and concurrent triglycerides 150-199 mg/dL, more than twice as many patients were reclassified upward when the non-HDL-C cutpoint was lowered from 100 mg/dL to 93 mg/dL (Figure 3A).

Our study also showed that the current guidelines triglyceride threshold of ≥ 200 mg/dL for using non-HDL-C as a secondary treatment target may need to be lowered given that considerable upward reclassification occurs also at triglycerides 150-199 mg/dL (Figure 2).

Study Limitations

We have limited clinical and demographic data regarding the full risk factor profile of our population. Therefore, reclassification analyses are inferred on the basis of the lipid profile only and we cannot determine its impact on clinical outcomes.

The nearly super-imposable age, sex, and lipid distributions between the VLDL and NHANES samples suggest that our study comprises a reasonable population of patients engaged in atherosclerosis prevention and treatment, not a special population that underwent VAP testing. We do not know the percentage of patients taking a statin. Perhaps, some samples in our study were acquired in a non-fasting state, but this is not uncommon in routine practice.

Despite focusing on upward reclassification in accordance with current guidelines, there was considerable downward reclassification in patients with triglycerides < 150 mg/dL (Figure 2). The significance of downward reclassification remains unclear in the literature and current guidelines and whether these patients should be treated to LDL-C vs. non-HDL-C goal needs further scrutiny.

Conclusion
Our study of 1.3 million patients builds on prior evidence that significant patient-level discordance exists between percentiles of LDL-C and non-HDL-C, particularly when accuracy is most crucial, at lower LDL-C and higher triglycerides. Therefore, lowering conventional non-HDL-C cutpoints for high-risk patients to match percentiles of LDL-C cutpoints as well as wider adoption of non-HDL-C in clinical practice may potentially improve secondary prevention outcomes and residual risk assessment and treatment.
References


7. Sniderman AD, De Graaf J, Couture P. Low-density lipoprotein-lowering strategies. Curr


**Figure Legends**

**Figure 1:** Patient-level discordance between population percentiles of LDL-C and non-HDL-C.

The total population (A) and four different triglyceride categories (B). The density of data is expressed by different shades of color, which represent increasing densities of patients per pixel, from light blue to purple.

**Figure 2:** Treatment category reclassification by using guideline-based non-HDL-C cutpoints vs. percentile-based cutpoints for the total population.

Four triglyceride categories are analyzed and each assigned a color, as depicted.

**Figure 3:** Treatment category reclassification by using guideline-based non-HDL-C cutpoints vs. percentile-based cutpoints at secondary prevention LDL-C range. LDL-C < 70 mg/dL (A), and LDL-C 70-99 mg/dL (B).
Study Sample (N=1,310,440) - - - NHANES (N=2,679)

**LDL-C**
- Median (IQR): 106 (82, 134)
- 111 (89, 135)

**Total Cholesterol**
- Median (IQR): 188 (159, 219)
- 190 (165, 219)

**Triglycerides**
- Median (IQR): 113 (81, 162)
- 110 (76, 160)

**Non-HDL-C**
- Median (IQR): 132 (106, 161)
- 135 (110, 164)
Patient-level percentile discordance between non-HDL-C and LDL-C

A) Total population, N = 1,310,440

B) By triglyceride categories

Triglycerides <100 mg/dL
N = 520,880

Triglycerides 100-149 mg/dL
N = 398,174

Triglycerides 150-199 mg/dL
N = 204,145

Triglycerides 200-399 mg/dL
N = 187,241
Reclassification analysis by triglyceride categories

N = 1,310,440

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<th>Population Percentile-based reclassification</th>
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<td>&lt;100 mg/dL</td>
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<td>100 - 149 mg/dL</td>
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<td>150 - 199 mg/dL</td>
<td>28,130 (13.8)</td>
<td>50,863 (24.9)</td>
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<td>200 - 399 mg/dL</td>
<td>109,614 (58.5)</td>
<td>123,262 (65.8)</td>
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Reclassification, N (%)

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<td>137,744 (10.5)</td>
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<td>Downward reclassification</td>
<td>229,084 (44)</td>
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Upward reclassification analysis for LDL-C < 70 mg/dL
N = 191,333

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<td>Non-HDL-C ≥ 93 mg/dL – no. (%) N = 46,840 (24.5%)</td>
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<td>6,123 (11.8)</td>
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<td>26,783 (80.9)</td>
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Upward reclassification analysis for LDL-C 70 - 99 mg/dL
N = 376,323

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<td>Non-HDL-C ≥ 125 mg/dL – no. (%) N = 62,817 (16.7%)</td>
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<td>18,514 (34.9)</td>
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