Comparison of a Novel Method vs the Friedewald Equation for Estimating Low-Density Lipoprotein Cholesterol Levels From the Standard Lipid Profile

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Abstract

IMPORTANCE—In clinical and research settings worldwide, low-density lipoprotein cholesterol (LDL-C) is typically estimated using the Friedewald equation. This equation assumes a fixed factor of 5 for the ratio of triglycerides to very low-density lipoprotein cholesterol (TG:VLDL-C); however, the actual TG:VLDL-C ratio varies significantly across the range of triglyceride and cholesterol levels.

OBJECTIVE—To derive and validate a more accurate method for LDL-C estimation from the standard lipid profile using an adjustable factor for the TG:VLDL-C ratio.

DESIGN, SETTING, AND PARTICIPANTS—We used a convenience sample of consecutive clinical lipid profiles obtained from 2009 through 2011 from 1 350 908 children, adolescents, and adults in the United States. Cholesterol concentrations were directly measured after vertical spin density-gradient ultracentrifugation, and triglycerides were directly measured. Lipid distributions

closely matched the population-based National Health and Nutrition Examination Survey (NHANES). Samples were randomly assigned to derivation (n = 900 605) and validation (n = 450 303) data sets.

MAIN OUTCOMES AND MEASURES—Individual patient-level concordance in clinical practice guideline LDL-C risk classification using estimated vs directly measured LDL-C (LDL-C_D).

RESULTS—In the derivation data set, the median TG:VLDL-C was 5.2 (IQR, 4.5–6.0). The triglyceride and non–high-density lipoprotein cholesterol (HDL-C) levels explained 65% of the variance in the TG:VLDL-C ratio. Based on strata of triglyceride and non–HDL-C values, a 180-cell table of median TG:VLDL-C values was derived and applied in the validation data set to estimate the novel LDL-C (LDL-C_N). For patients with triglycerides lower than 400 mg/dL, overall concordance in guideline risk classification with LDL-C_D was 91.7% (95% CI, 91.6%–91.8%) for LDL-C_N vs 85.4% (95% CI, 85.3%–85.5%) for Friedewald LDL-C (LDL-C_F) ($P <$ .001). The greatest improvement in concordance occurred in classifying LDL-C lower than 70 mg/dL, especially in patients with high triglyceride levels. In patients with an estimated LDL-C lower than 70 mg/dL, LDL-C_D was also lower than 70 mg/dL in 94.3% (95% CI, 93.9%–94.7%) for LDL-C_N vs 79.9% (95% CI, 79.3%–80.4%) for LDL-C_F in samples with triglyceride levels of 100 to 149 mg/dL; 92.4% (95% CI, 91.7%–93.1%) for LDL-C_N vs 61.3% (95% CI, 60.3%–62.3%) for LDL-C_F in samples with triglyceride levels of 150 to 199 mg/dL; and 84.0% (95% CI, 82.9%–85.1%) for LDL-C_N vs 40.3% (95% CI, 39.4%–41.3%) for LDL-C_F in samples with triglyceride levels of 200 to 399 mg/dL ($P <$ .001 for each comparison).

CONCLUSIONS AND RELEVANCE—A novel method to estimate LDL-C using an adjustable factor for the TG:VLDL-C ratio provided more accurate guideline risk classification than the Friedewald equation. These findings require external validation, as well as assessment of their clinical importance. The implementation of these findings into clinical practice would be straightforward and at virtually no cost.

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Low-density lipoprotein cholesterol (LDL-C) is of longstanding clinical and research interest and the primary target in national and international clinical practice guidelines.[1–10] Conventionally, LDL-C is estimated by the Friedewald equation, obviating need for an ultracentrifuge.[1] This equation is based on an analysis of 448 patients from 1972 and estimates LDL-C as (total cholesterol) – (high-density lipoprotein cholesterol [HDL-C]) – (triglycerides/5) in mg/dL.[1] The final term assumes a fixed ratio of triglyceride levels to very low-density lipoprotein cholesterol (TG:VLDL-C) of 5:1.

Applying a factor of 5 to every individual patient is problematic given variance in the TG:VLDL-C ratio across the range of triglyceride and non–HDL-C levels. Indeed, Friedewald and colleagues[1] noted that simply dividing triglyceride values by 5 does not give an accurate estimate of VLDL-C. Providing further evidence of variance, the mean TG:VLDL-C ratio ranged from 5.2 to 8.9 across clinics in the Lipid Research Clinics Prevalence Study.[2] DeLong and colleagues[2] proposed a fixed factor of 6, effectively resetting the population mean, although not addressing interindividual variance in the TG:VLDL-C ratio.

In the eras in which the Friedewald equation[1] and De-Long modification[2] were proposed, an LDL-C lower than 70 mg/dL was not yet established as an ideal secondary prevention target for treatment of high-risk patients.[5,7] In fact, an LDL-C level in this range was at the low end or outside of the distribution of the original training data set used in deriving the Friedewald equation.[1] At higher LDL-C concentrations, error in VLDL-C estimation was relatively small with respect to non–HDL-C and actual LDL-C levels. Hence, it was believed that the VLDL-C estimation using a fixed factor was sufficiently accurate, and this approach simplified computation.

Leveraging improvements in computing and data availability, we aimed to derive and validate a novel method for estimation of LDL-C from the standard lipid profile using an adjustable factor for the TG:VLDL-C ratio.

Methods

Study Population and Lipid Testing

The Johns Hopkins institutional review board declared our study exempt. We examined a convenience sample of consecutive lipid profiles from the Very Large Database of Lipids (VLDL).[11] Samples were obtained for clinical indications by Atherotech Diagnostics Laboratory (Birmingham, AL) from 2009 through 2011 from persons living in the United States. To enhance generalizability, we included children (aged <11 years), adolescents (aged 11 to <18 years), and adults (aged 18 years) in our primary analyses. We also included both sexes and did not exclude any patient based on his/her lipid profile. We subsequently explored the contribution of age, sex, and lipid profile characteristics to variance in TG:VLDL-C and also evaluated the performance of the novel method for LDL-C estimation within subgroups.

Deidentified data were transferred to the investigators. As previously reported,[11,12] lipid distributions in the study sample closely matched those from a population-based survey, the National Health and Nutrition Examination Survey (NHANES) 2007–2008.[13] Our study (VLDL-1B) is the second phase of the VLDL-1 study,[11,12] based on a registered data set[14] and peer-reviewed statistical analysis plan.[15]

Cholesterol concentrations were directly measured by the Vertical Auto Profile (VAP; Atherotech), an inverted rate zonal, single-vertical spin, density-gradient ultracentrifugation technique that separates lipoprotein subfractions and then measures the cholesterol content, including LDL-C, VLDL-C, and HDL-C.[16] Triglycerides were directly measured using the ARCHITECT C-8000 system (Abbott).

Analytical performances of direct measures met guideline-established benchmarks.[17] For the vertical spin density-gradient ultracentrifugation, accuracy was monitored by yearly random split-sample comparison with β quantification at Washington University's Core Laboratory for Clinical Studies (St Louis, Missouri), and triglyceride measurements were compared with those obtained at the University of Alabama School of Medicine laboratory (Birmingham). From 2009 through 2011, the following correlation coefficients were typically obtained: total cholesterol, 0.99; HDL-C, 0.99; LDL-C, 0.98; VLDL-C, 0.98;

triglycerides, 0.99. Between-day intra-assay coefficients of variation were lower than 3.0% for each of these lipid parameters.

Derivation

Two-thirds of patients were randomly assigned to a derivation data set. We first explored the distribution of TG: VLDL-C, anticipating, based on prior literature,[1,2] interindividual variance. After confirming interindividual variance, we performed multiple linear regression analysis examining the extent to which TG:VLDL-C was explained by information in the standard lipid profile, age, and sex. Results from this analysis guided the choice of parameters for stratification to determine strata-specific median TG:VLDL-C ratios.

Validation

One-third of patients in the study sample were randomly assigned to a validation data set. Patients were grouped by those fulfilling the Friedewald equation criterion of triglycerides lower than 400 mg/dL (to convert to millimoles per liter, multiply by 0.0113) and those with triglycerides of 400 or higher.

Friedewald LDL-C ($LDL-C_F$) was estimated as (non–HDL-C) – (triglycerides/5) in mg/dL.[1] Novel LDL-C ($LDL-C_N$) estimates were derived as (non–HDL-C) – (triglycerides/ adjustable factor mg/dL), where the adjustable factor was determined as the strata-specific median TG:VLDL-C ratio. Numerical subscripts (eg, $LDL-C_{180}$ for 180-cell stratification) were used to identify variants of $LDL-C_N$. Alternative LDL-C estimates were also calculated based on previously proposed formulas.[2,18–23] The reference standard direct LDL-C ($LDL-C_D$) was subtracted from each LDL-C estimate to determine the absolute difference in their values in milligrams per deciliter.

Direct and estimated LDL-C values were classified according to clinical practice guidelines in the United States (<70, 70–99, 100–129, 130–159, 160–189, and 190 mg/dL; to convert to millimole per liter, multiply by 0.0259) and Europe (<70, 70–99, 100–154, 155–189, and 190 mg/dL).[3–5,7,8] Concordance in classification between LDL-C estimates and $LDL-C_D$ was examined in the whole study population and subgroups. The initial classification was defined by the estimated parameter because this is the parameter routinely available in clinical practice. Odds ratios (ORs) for discordance in subgroups were calculated using logistic regression. Based on prior literature,[24–30] definitions of Fredrickson-Levy phenotypes are provided in eTable 4 in the Supplement.

Statistical analyses were performed in Stata (StataCorp), version 11.0, and logarithmically scaled pseudocolor encoded data density plots were generated in R (http://r-project.org), version 2.14.1. We considered a 2-tailed *P* of less than .05 statistically significant.

Results

Study Samples

Of 1 350 908 samples, there were 2129 children, 8165 adolescents, and 1 340 614 adults. Table 1 shows age, sex, and lipid characteristics of the derivation (n = 900 605) and validation (n = 450 303) data sets. Triglycerides were lower than 400 mg/dL in 440 179

samples in the validation data set. Patients were generally middle-aged and evenly distributed by sex, with lipid distributions similar to that seen in NHANES.

Estimation Method Derivation and Development

Figure 1 illustrates the distribution of TG:VLDL-C ratios in relation to triglyceride and non–HDL-C concentrations. The median ratio of TG:VLDL-C was 5.2 (interquartile range [IQR], 4.5–6.0). Approximately one-third of the samples had a TG: VLDL-C ratio of 4.5 to 5.5, and approximately two-thirds had a ratio from 4.0 to 6.0. The 5th to 95th percentile was 3.7 to 7.8; 1st to 99th percentile, 3.1 to 9.9; and the full range, 0.4 to 145.

The distribution of the TG:VLDL-C ratio was not normal (skewness, 7.1; kurtosis, 295.8). After log transformation, the TG:VLDL-C ratio was more normally distributed (skewness, 0.5; kurtosis, 5.6). In regression, the fraction of variance in the log-transformed TG:VLDL-C ratio explained by log-transformed triglycerides was 0.56 ($P < .001$), 0.65 ($P < .001$) after adding non–HDL-C to the model, and 0.66 ($P < .001$) if the total cholesterol and HDL-C were added as individual components. Adding age and sex to this model did not materially improve the fraction of variance explained (<0.01 improvement). There was also no material improvement by using ratio variables (total cholesterol to HDL-C, triglycerides to HDL-C, triglycerides to total cholesterol) or using higher degree fractional polynomial regressions rather than linear regression.

For stratification, we used triglycerides and non–HDL-C because of their performance in explaining variance in the TG: VLDL-C ratio compared with other combinations of parameters and because they capture information on the 3 core elements from the standard lipid profile. Varying the number of triglycerides and non–HDL-C strata based on quantiles or accepted cut points, we generated 2-dimensional tables of median TG:VLDL-C ratios using 10, 20, 30, 60, 90, 120, 150, 180, 200, 300, 360, 400, 720, 800, 1000, and 2000 cells. The 180-cell table is shown in Figure 2. We focused on the 180-cell results because there was a less than 0.1% overall increase in concordance estimates for guideline classification using larger tables. Cell counts and IQRs for the 180-cell table are provided in eTables 1A and 1B in the Supplement. The 10-cell, 360-cell, and 2000-cell tables of median TG:VLDL-C ratios are provided in eTables 2A, 2B, and 2C in the Supplement.

Validation and Concordance in Guideline Classification

Strata-specific median TG:VLDL-C ratios from the derivation data set were applied in the validation data set to generate LDL-C_N estimates, including those using a 10-cell (LDL-C_{10}), 180-cell (LDL-C_{180}), or 360-cell (LDL-C_{360}) table. Compared with LDL-C_F, these LDL-C_N estimates more closely approximated LDL-C_D in patients with triglyceride levels lower than 400 mg/dL ($P < .001$ for each comparison). The median for (LDL-C_F) – (LDL-C_D) was 0.6mg/dL (5th–95th percentile, −15.4 to 5.0mg/dL), root-mean-squared error, 6.6. Examining LDL-C_N – LDL-C_D, the median was 0.0 mg/dL (5th–95th percentile, −6.0 to 6.6 mg/dL) for LDL-C_{10}, root-mean- squared error, 4.4; 0.0mg/dL (5th–95th percentile, −5.0 to 6.4 mg/dL) for LDL-C_{180}, root-mean-squared error, 4.1; and 0.0 mg/dL (5th–95th percentile, −5.0 to 6.3 mg/dL) for LDL-C_{360}, root-mean-squared error, 4.1.

Overall concordance in guideline classification by LDL-C estimates and LDL-C_D if triglyceride levels were lower than 400 mg/dL was 85.4% [95% CI, 85.3%–85.5%] for LDL-C_F; 90.5% [95% CI, 90.4%–90.6%] for LDL-C_{10}; 91.7% [95% CI, 91.6%–91.8%] for LDL-C_{180}, and 91.7% [95% CI, 91.6%–91.8%] for LDL-C_{360}. By individual guideline LDL-C classes, concordances are shown in Table 2. The greatest improvement in concordance with LDL-C_N estimates compared with LDL-C_F was observed in classifying LDL-C lower than 70 mg/dL.

This was particularly the case in samples with high triglyceride levels (Figure 3; *P* < .001 for those with triglyceride levels of 100 mg/dL or lower vs higher than 100 mg/dL). For example, of patients with estimated LDL-C levels lower than 70 mg/dL, LDL-C_D was also lower than 70 mg/dL for 94.3% (95% CI, 93.9%–94.7%) of LDL-C_N samples vs 79.9% (95% CI, 79.3%–80.4%) of LDL-C_F samples with triglyceride levels of 100 to 149 mg/dL; 92.4% (95% CI, 91.7%–93.1%) of LDL-C_N samples vs 61.3% (95% CI, 60.3%–62.3%) of LDL-C_F samples with triglyceride levels of 150 to 199 mg/dL; and 84.0% (95% CI, 82.9%– 85.1%) of LDL-C_N samples vs 40.3% (95% CI, 39.4%–41.3%) of LDL-C_F samples with triglyceride levels of 200 to 399 mg/dL.

In classifying LDL-C lower than 70 mg/dL, LDL-C_{180} and LDL-C_{360} were within 0.5% of each other in each triglyceride category (Figure 2), and overall concordance with LDL-C_D in classifying LDL-C levels lower than 70 mg/dL was 94.0% (95% CI, 93.8%–94.2%) for LDL-C_{180} and 94.1% (95% CI, 93.9%–94.3%) for LDL-C_{360}. Confidence intervals for concordance were also overlapping with LDL-C estimates using more than 360 cells, up to 2000 cells (94.3% [95% CI, 94.1%–94.5%]).

Adjusting for non–HDL-C and log-transformed triglyceride levels, there was an inverse association of age with discordance in guideline classification between LDL-C_{180} and LDL-C_D with an OR close to 1 (OR per 10-year increase in age, 0.98 [95% CI, 0.97–0.99], *P* < . 001), and there was no association of sex with discordance (men vs women, *P* = .91). In contrast, adjusting for non–HDL-C, those with triglyceride levels of 400 mg/dL or higher vs lower than 400 mg/dL had higher odds of discordance (OR, 4.73 [95% CI, 4.53–4.94]; *P* < . 001).

Adjusting for non–HDL-C and log-transformed triglycerides, greater discordance was strongly associated with the type III phenotype, characterized by excess of remnants and higher cholesterol content of VLDL (OR, 49.9 [95% CI, 38.1–65.3], *P* < .001). More modest associations with greater discordance were present for the type IIa (OR, 1.05 [95% CI, 1.00– 1.10], *P* = .049) and type IV phenotype (OR, 1.64 [95% CI, 1.58–1.71], *P* < .001). However, the type IIb phenotype was associated with less discordance (OR, 0.71 [95% CI, 0.66–0.77], *P* < .001).

eTable 3 in the Supplement shows concordance in patients with triglyceride levels of 400 mg/dL or higher; concordance with LDL-C_D improved using LDL-C_{180} relative to LDL-C_F at lower LDL-C levels, although concordance remained modest. eTable 4 in the Supplement shows concordance in the setting of Fredrickson-Levy phenotypes; compatible with the

above results and the report of Friedewald et al,[1] the largest discordance occurred for LDL-C_{180} and LDL-C_F in those with type 3 phenotype.

Although multiple groups have previously proposed alternative methods for LDL-C estimation, these have not supplanted LDL-C_F in routine practice.[2, 18–23] To our knowledge, none have used a stratification approach as done in our study and none perform as well in classifying LDL-C based on clinical practice guidelines (see eTable 5 in the Supplement).

Discussion

We present the development and validation of a novel method for estimating LDL-C from the standard lipid profile. Rather than assuming a fixed factor of 5, it applies an adjustable factor for the TG:VLDL-C ratio based on triglyceride and non–HDL-C concentrations. The 180-cell approach could be coded into an online calculator, smartphone application, or automated laboratory reporting system. Compared with Friedewald estimation, classifications based on US and European clinical practice guidelines using LDL-C estimates by the novel method are more concordant with those by LDL-C_D. The greatest advantage occurs in classification of LDL-C concentrations lower than 70 mg/dL, especially in patients with elevated triglyceride concentrations. In addition to the novel analytic approach, a major strength of this study is its size, 3015 times larger than the original Friedewald database.

The Friedewald Equation and Other Previous Methods for LDL-C Estimation

Considering interindividual variance in the TG:VLDL-C ratio and that the Friedewald equation was developed in only 448 patients with familial hyperlipoproteinemia or their relatives,[1] it is remarkable how well the equation has withstood the test of time. Nevertheless, Friedewald et al[1] recognized that inaccuracies in VLDL-C estimation could become more important at lower cholesterol concentrations and higher triglyceride concentrations, because VLDL-C constitutes a greater portion of the equation and errors in its estimate introduce larger relative errors in the resulting LDL-C estimate.[15] It is under these circumstances that our proposed method produces the greatest improvement and in which an accurate LDL-C estimate is most crucial—in the range required for secondary prevention treatment of high-risk patients with hypertriglyceridemia.

Regarding previous methods, Delong et al[2] proposed a fixed factor of 6 rather than 5; however, the overall median TG: VLDL-C ratio in our sample is closer to the original Friedewald factor of 5. Moreover, any fixed factor will not account for variance in the TG:VLDL-C ratio. This issue applies to the majority of other previous methods,[18–22] including that of Chen and colleagues,[20] which sets LDL-C equal to 90% of non–HDL-C plus 10% of triglycerides, and de Cordova and de Cordova,[22] which takes 75% of non–HDL-C. In contrast, the equation of Rao and colleagues[23] applies an adjustable factor that considers triglycerides but not cholesterol concentrations.

Implications for Patient Care

Measurement of LDL-C is of wide interest and deeply ingrained in practice. Guidelines around the globe focus on the LDL-C cut points, including guidelines from the National

Heart, Lung, and Blood Institute,[3–5] Canadian Cardiovascular Society,[6] European Society of Cardiology and European Atherosclerosis Society,[7] and the American Heart Association and American College of Cardiology.[8] Some of these guidelines[6,7] assign the highest level of evidence (class 1A) to LDL-C treatment goals. Low-density lipoprotein cholesterol has been a focus in the inclusion criteria of numerous clinical trials, serially quantified during trials, and used as a target for drug titration in some trials.[9,10] The Cholesterol Treatment Trialists summarize the totality of evidence for statin therapy as the risk reduction indexed to a 39 mg/dL lowering of LDL-C.[9,10]

Without resorting to direct assays, estimation using an adjustable factor for estimation of VLDL-C seems to provide the most accurate quantification of LDL-C from patient to patient. Nevertheless, one-third of variance in the TG:VLDL-C ratio is not explained by the standard lipid profile and remains a point of caution. This unexplained variance in the TG:VLDL-C ratio represents an intrinsic error in VLDL-C estimation and is most problematic when the clinical question is if a high-risk patient with hypertriglyceridemia has attained a LDL-C level lower than 70 mg/dL. Our method is notably limited in the setting of severe hypertriglyceridemia and type III Fredrickson-Levy dyslipidemia. However, these conditions do not define the full extent of circumstances in which patients may deviate considerably from average. Although relatively uncommon in clinical practice, type III dyslipidemia serum lipid phenotype cannot be reliably identified using the standard lipid panel alone.

Another cholesterol-based parameter, non–HDL-C, is not dependent on VLDL-C estimation and has multiple other favorable characteristics, which have been reviewed elsewhere.[31] Most notably, non–HDL-C includes cholesterol carried by all atherogenic apolipoprotein B–containing lipoproteins, not only that carried by LDL. Nevertheless, as one expert panel stated, "many years of public and professional education geared toward measurement of LDL cholesterol has resulted in its successful integration into the fabric of CVD [cardiovascular disease] prevention and treatment, and it would be a mistake to discontinue its use."[31]

Ultimately, LDL-C and non–HDL-C may be best viewed in tandem. At low triglyceride levels, as VLDL-C approaches 0, LDL-C_F approaches non–HDL-C. At triglyceride levels of 200 mg/dL or higher, guidelines recommend non–HDL-C as a treatment goal.[3–5,8] Still, inherent limitations in LDL-C estimation are not a binary situation confined to patients with triglyceride levels either of 200 mg/dL or higher, supporting broader consideration of non–HDL-C in practice.

Study Limitations

The method requires validation in an independent population and using other laboratory techniques. Although lipid distributions in our sample closely matched a nationally representative population-based survey, patients who have their cholesterol concentrations measured by vertical spin, density-gradient ultracentrifugation may still be a special population. Factors such as race/ethnicity, obesity, diabetes, and insulin resistance, which may affect variance in the TG:VLDL-C ratio, were not available for analysis. It is unknown to what extent patients in our study sample were treated with lipid-modifying drug therapies,

although LDL-C$_F$ is used ubiquitously in clinical practice for patients regardless of coincident drug therapy. Fasting status was not known in this study. Nonfasting lipid analysis is a common and accepted practice,[32–34] and variance in TG:VLDL-C also exists in completely fasting samples.[2]

This study examines 1-time measurements. Therefore, this study does not address the problem of intraindividual variation in lipid levels, which is a major limitation in assessing the value of this study. It remains possible that intra-individual variation may exceed the improvement in classification provided by the new method so that there may not be a significant clinical improvement in classification. Due largely to biological variation, as well as analytical variation, there may be a 5% to 10% coefficient of variation when repeating lipid levels on the same individuals.[35] Moreover, guidelines also support serial measurements to calculate a relative change with intervention (eg, goal of 50% lowering in LDL-C for high-risk patients).[6,7] This study does not examine the effect of the new method on serial assessment of relative changes in LDL-C. Rather than relying on measurements at a single time point, a strategy that deserves further study is bringing the patient who returns in a few months for repeat risk factor measurements, including lipids, to further refine risk assessment and treatment decisions.[36]

Conclusion

In a very large sample of lipid profiles, we derived and validated a novel method to estimate LDL-C. If externally validated, when LDL-C must be known for clinical or research purposes and when direct measurement is not available or too costly, there may be an advantage to automated LDL-C estimation using a 180-cell array of TG:VLDL-C factors determined by triglyceride and non–HDL-C levels. This estimation method provided higher-fidelity estimates than the Friedewald equation or other methods, particularly when classifying LDL-C levels lower than 70 mg/dL in the presence of high triglyceride levels.

These findings require external validation, as well as assessment of their clinical importance. The novel method could be easily implemented in most laboratory reporting systems at virtually no cost.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Glossary

HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
TG	triglycerides
VLDL-C	very low-density lipoprotein cholesterol

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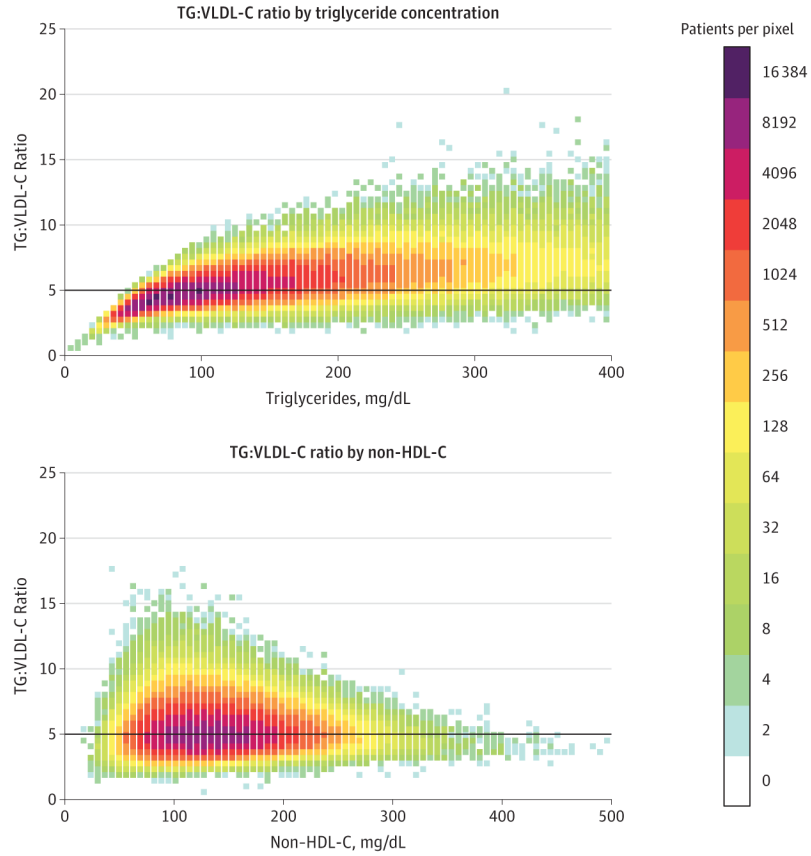
Figure 1. Ratio of Triglycerides to Very Low-Density Lipoprotein Cholesterol by Concentrations of Triglycerides and Non–High-Density Lipoprotein Cholesterol

Non–HDL-C indicates non–high-density lipoprotein cholesterol; TG:VLDL-C, the ratio of triglycerides to very low-density lipoprotein cholesterol. SI conversion factors: To convert non-HDL-C, multiply by 0.0259; triglycerides, multiply by 0.0113. Figure generated from derivation data set (n = 900 605). Dark horizontal lines represent a TG:VLDL-C ratio of 5, the constant factor used in the Friedewald equation. If the true TG:VLDL-C ratio is greater than 5 (pixels above line), then the Friedewald formula will tend to underestimate low-density lipoprotein cholesterol; and vice versa, if the true TG:VLDL-C is less than 5 (pixels below line). The shades of color represent increasing densities of patients per pixel, from light blue to purple.

Triglyceride Levels, mg/dL[a]	Non-HDL-C, mg/dL					
	<100	100-129	130-159	160-189	190-219	≥220
7-49	3.5	3.4	3.3	3.3	3.2	3.1
50-56	4.0	3.9	3.7	3.6	3.6	3.4
57-61	4.3	4.1	4.0	3.9	3.8	3.6
62-66	4.5	4.3	4.1	4.0	3.9	3.9
67-71	4.7	4.4	4.3	4.2	4.1	3.9
72-75	4.8	4.6	4.4	4.2	4.2	4.1
76-79	4.9	4.6	4.5	4.3	4.3	4.2
80-83	5.0	4.8	4.6	4.4	4.3	4.2
84-87	5.1	4.8	4.6	4.5	4.4	4.3
88-92	5.2	4.9	4.7	4.6	4.4	4.3
93-96	5.3	5.0	4.8	4.7	4.5	4.4
97-100	5.4	5.1	4.8	4.7	4.5	4.3
101-105	5.5	5.2	5.0	4.7	4.6	4.5
106-110	5.6	5.3	5.0	4.8	4.6	4.5
111-115	5.7	5.4	5.1	4.9	4.7	4.5
116-120	5.8	5.5	5.2	5.0	4.8	4.6
121-126	6.0	5.5	5.3	5.0	4.8	4.6
127-132	6.1	5.7	5.3	5.1	4.9	4.7
133-138	6.2	5.8	5.4	5.2	5.0	4.7
139-146	6.3	5.9	5.6	5.3	5.0	4.8
147-154	6.5	6.0	5.7	5.4	5.1	4.8
155-163	6.7	6.2	5.8	5.4	5.2	4.9
164-173	6.8	6.3	5.9	5.5	5.3	5.0
174-185	7.0	6.5	6.0	5.7	5.4	5.1
186-201	7.3	6.7	6.2	5.8	5.5	5.2
202-220	7.6	6.9	6.4	6.0	5.6	5.3
221-247	8.0	7.2	6.6	6.2	5.9	5.4
248-292	8.5	7.6	7.0	6.5	6.1	5.6
293-399	9.5	8.3	7.5	7.0	6.5	5.9
400-13975	11.9	10.0	8.8	8.1	7.5	6.7

Figure 2. Median for the Ratio of Triglycerides to Very Low-Density Lipoprotein Cholesterol by Non–High-Density Lipoprotein Cholesterol and Triglyceride Strata (180-Cell)

HDL-C indicates high-density lipoprotein cholesterol. SI conversion factors: To convert HDL-C, multiply by 0.0259; triglycerides, multiply by 0.0113. Green, 4.5–5.5; yellow, 3.5–4.4, 5.6–6.5; red, <3.5, >6.5. Color banding is used to help visualize the pattern, but numerical results should be used for LDL-C estimation, rather than the boundaries or midpoints of the color ranges. Data are from the derivation data set (n = 900 605).
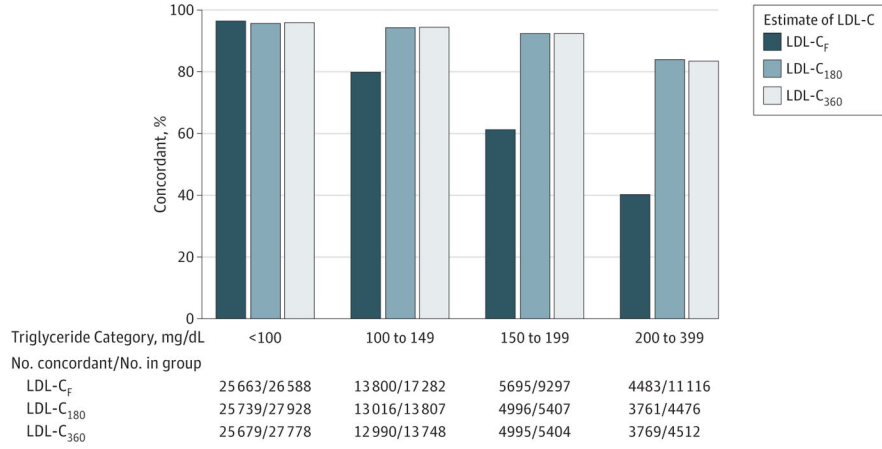
Figure 3. Concordance of Direct Measurement With Friedewald and Novel Estimates in Classifying LDL-C Lower Than 70 mg/dL by Triglyceride Strata

LDL-C indicates low-density lipoprotein cholesterol; F, Friedewald; 180, novel estimate by 180-cell method; and 360, novel estimate by 360-cell method. SI conversion factors: To convert LDL-C, multiply by 0.0259; triglycerides, multiply by 0.0113. Figure generated from validation data set.

Table 1

Characteristics of Derivation and Validation Data Sets

	Median (IQR)		
	Derivation (n = 900 605)	Validation (n = 450 303)	NHANES (n = 3035)
Age, No. (%), y	59 (49–69)	59 (49–69)	45 (27–63)
<11	1430 (0.2)	699 (0.2)	0 (0)
11–<18	5465 (0.6)	2700 (0.6)	356 (11.7)
18	893 710 (99.2)	446 904 (99.2)	2679 (88.3)
Sex, No. (%) [a]			
Men	430 148 (47.8)	215 120 (47.8)	1521 (50.1)
Women	465 276 (51.7)	232 539 (51.6)	1514 (49.9)
Cholesterol, mg/dL			
Total	188 (159–219)	188 (159–219)	185 (159–214)
HDL-C	52 (42–63)	52 (42–63)	51 (43–62)
Friedewald LDL-C[b]	106 (82–134)	106 (82–134)	108 (85–132)
Direct LDL-C	108 (84–135)	108 (84–135)	NA
Non–HDL-C	133 (106–162)	133 (106–163)	131 (105–160)
VLDL-C	22 (17–29)	22 (17–29)	NA
IDL-C	12 (8–16)	12 (8–16)	NA
Lp(a)-C	6 (4–10)	6 (4–10)	NA
Triglycerides, mg/dL	115 (82–166)	115 (82–167)	105 (72–154)
TC:HDL-C	3.5 (2.9–4.4)	3.5 (2.9–4.4)	3.5 (2.9–4.4)
TG:VLDL-C	5.2 (4.5–6.0)	5.2 (4.5–6.0)	NA
5th to 95th percentile, range	3.7–7.8	3.7–7.8	
1st to 99th percentile, range	3.1–9.9	3.1–9.9	

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IDL-C, intermediate-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Lp(a)-C, lipoprotein (a) cholesterol; NA, data not available; NHANES, National Health and Nutrition Examination Survey; TG:VLDL-C, ratio of triglycerides to very low-density lipoprotein cholesterol.

SI conversion factors: To convert HDL-C, LDL-C, and total cholesterol, multiply by 0.0259; triglycerides, multiply by 0.0113.

[a] There were 5181 patients (0.6%) missing sex data in the derivation sample and 2644 patients (0.6%) in the validation sample.

[b] After excluding samples with triglyceride levels of 400 mg/dL or higher, there were 880 403 samples in the derivation cohort and 440 179 samples in the validation cohort.

Table 2

Concordance in Guideline Classification by Friedewald *vs* Novel Estimates of Low-Density Lipoprotein Cholesterol (LDL-C) in Relation to Direct LDL-C if Triglycerides are Lower Than 400 mg/dL

LDL-C, mg/dL[a]	LDL-C$_F$		LDL-C$_{10}$		LDL-C$_{180}$		LDL-C$_{360}$	
	No. Concordant/ Total Group	% (95% CI)	No. Concordant/ Total Group	% (95% CI)	No. Concordant/ Total Group	% (95% CI)	No. Concordant/ Total Group	% (95% CI)
United States[a]								
190	11 891/12 854	92.5 (92.0–93.0)	12 683/14 346	88.4 (87.9–88.9)	12 067/12 912	93.5 (93.0–93.9)	12 084/12 942	93.4 (92.9–93.8)
160 to 189	27 322/31 232	87.5 (87.1–87.8)	29 076/33 072	87.9 (87.6–88.3)	29 449/33 371	88.3 (87.9–88.6)	29 402/33 284	88.3 (88.0–88.7)
130 to 159	69 670/78 974	88.2 (88.0–88.4)	73 471/80 368	91.4 (91.2–91.6)	75 838/83 885	90.4 (90.2–90.6)	76 082/84 306	90.3 (90.1–90.5)
100 to 129	109 881/126 094	87.1 (87.0–87.3)	119 277/132 437	90.1 (89.9–90.2)	120 515/131 804	91.4 (91.3–91.6)	120 526/131 704	91.5 (91.4–91.7)
70 to 99	107 307/126 742	84.7 (84.5–84.9)	114 826/125 533	91.5 (91.3–91.6)	117 320/126 670	92.6 (92.5–92.8)	117 258/126 491	92.7 (92.6–92.8)
<70	49 641/64 283	77.2 (76.9–77.5)	49 062/54 423	90.2 (89.9–90.4)	48 512/51 618	94.0 (93.8–94.2)	48 433/51 452	94.1 (93.9–94.3)
Europe[a]								
190	11 891/12 854	92.5 (92.0–93.0)	12 683/14 346	88.4 (87.9–88.9)	12 067/12 912	93.5 (93.0–93.9)	12 084/12 942	93.4 (92.9–93.8)
155 to 189	36 218/40 625	89.2 (88.8–89.5)	38 297/42 643	89.8 (89.5–90.1)	38 830/43 244	89.8 (89.5–90.1)	38 830/43 212	89.9 (89.6–90.1)
100 to 154	185 353/195 675	94.7 (94.6–94.8)	194 068/203 234	95.5 (95.4–95.6)	196 557/205 809	95.5 (95.4–95.6)	196 735/206 082	95.5 (95.4–95.6)
70 to 99	107 307/126 742	84.7 (84.5–84.9)	114 826/125 533	91.5 (91.3–91.6)	117 320/126 670	92.6 (92.5–92.8)	117 258/126 491	92.7 (92.6–92.8)
<70	49 641/64 283	77.2 (76.9–77.5)	49 062/54 423	90.2 (89.9–90.4)	48 512/51 618	94.0 (93.8–92.4)	48 433/51 452	94.1 (93.9–94.3)

Abbreviations: LDL-C, low-density lipoprotein cholesterol; LDL-C$_F$, Friedewald LDL-C; LDL-C$_{10}$, 10-cell method LDL-C; LDL-C$_{180}$, 180-cell method LDL-C; LDL-C$_{360}$, 360-cell method LDL-C.

SI conversion factors: To convert LDL-C, multiply by 0.0259.

[a] Data are from those with triglyceride levels lower than 400 mg/dL in the validation data set (n = 440 179). *P* value for difference in concordance rates between LDL-C$_F$ and each novel estimate is *P* < .001. Initial classification was defined by the estimated parameter; concordance was defined by agreement with direct LDL-C. United States indicates the National Cholesterol Education Program Adult Treatment Panel, American Heart Association and American College of Cardiology Foundation guidelines; Europe indicates the European Society of Cardiology and European Atherosclerosis Society guidelines.