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CME

Friedewald-Estimated Versus Directly Measured Low-Density Lipoprotein Cholesterol and Treatment Implications

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Friedewald-Estimated Versus Directly Measured Low-Density Lipoprotein Cholesterol and Treatment Implications

Objectives The aim of this study was to compare Friedewald-estimated and directly measured low-density lipoprotein cholesterol (LDL-C) values.

Background LDL-C is routinely estimated by the Friedewald equation to guide treatment; however, compatibility with direct measurement has received relatively little scrutiny, especially at levels <70 mg/dl now targeted in high-risk patients.

Methods We examined 1,340,614 U.S. adults who underwent lipid profiling by vertical spin density gradient ultracentrifugation (Atherotech, Birmingham, Alabama) from 2009 to 2011. Following standard practice, Friedewald LDL-C was not estimated if triglyceride levels were ≥400 mg/dl (n = 30,174), yielding 1,310,440 total patients and 191,333 patients with Friedewald LDL-C <70 mg/dl.

Results Patients were 59 ± 15 years of age and 52% were women. Lipid distributions closely matched those in the National Health and Nutrition Examination Survey. A greater difference in the Friedewald-estimated versus directly measured LDL-C occurred at lower LDL-C and higher triglyceride levels. If the Friedewald-estimated LDL-C was <70 mg/dl, the median directly measured LDL-C was 9.0 mg/dl higher (5th to 95th percentiles, 1.8 to 15.4 mg/dl) when triglyceride levels were 150 to 199 mg/dl and 18.4 mg/dl higher (5th to 95th percentiles, 6.6 to 36.0 mg/dl) when triglyceride levels were 200 to 399 mg/dl. Of patients with a Friedewald-estimated LDL-C <70 mg/dl, 23% had a directly measured LDL-C ≥70 mg/dl (39% if triglyceride levels were concurrently 150 to 199 mg/dl; 59% if triglyceride levels were concurrently 200 to 399 mg/dl).

Conclusions The Friedewald equation tends to underestimate LDL-C most when accuracy is most crucial. Especially if triglyceride levels are ≥150 mg/dl, Friedewald estimation commonly classifies LDL-C as <70 mg/dl despite directly measured levels ≥70 mg/dl, and therefore additional evaluation is warranted in high-risk patients. (J Am Coll Cardiol 2013;62:732–9) © 2013 by the American College of Cardiology Foundation

Low-density lipoprotein cholesterol (LDL-C), as estimated by the Friedewald equation in routine patient care, is a central focus of clinical practice guidelines throughout the world, including in the United States (1–3), Europe (4), and Canada (5). The Friedewald equation estimates LDL-C as total cholesterol minus high-density lipoprotein cholesterol (HDL-C) minus triglycerides/5 in milligrams per deciliter (6). The equation was introduced into clinical practice in 1972 because of the additional time and financial costs associated with ultracentrifugation to directly measure LDL-C (6).

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Friedewald et al. (6) recognized in their original paper that "simple division of the plasma triglyceride by five does not give a very accurate estimate of very low-density lipoprotein cholesterol." A central idea in the development of the Friedewald equation was that inaccuracy in very low density lipoprotein cholesterol (VLDL-C) could be tolerated because the VLDL-C concentration was small relative to LDL-C (6). However, this issue must be reevaluated in the contemporary treatment era wherein much lower LDL-C levels are sought (1–5) and hypertriglyceridemia is a greater problem due to epidemics of obesity, insulin resistance, and diabetes mellitus (7). Although previous reports suggest underestimation of LDL-C by the Friedewald equation at low LDL-C levels (8–10) and high triglyceride levels (10,11), the equation has remained in routine use with remarkably little scrutiny.

Therefore, in the largest study of its kind to date (2,925 times larger than the original Friedewald dataset), we examined Friedewald estimation of LDL-C relative to direct measurement by vertical spin density gradient ultracentrifugation. We investigated the potential importance of differences between the 2 methods in clinical decision making by comparing treatment classification according to worldwide clinical practice guidelines.

Methods

Study population. We examined consecutive lipid profiles from a clinical sample of 1,340,614 U.S. adults (18 years of age and older) who underwent vertical spin density gradient ultracentrifugation of cholesterol by the Vertical Auto

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Abbreviations and Acronyms

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

NHANES = National Health and Nutrition Examination Survey

VAP = Vertical Auto Profile

VLDL-C = very low density lipoprotein cholesterol

Profile (VAP, Atherotech Diagnostics Lab, Birmingham, Alabama) from 2009 to 2011. Consecutive denotes that the first available lipid profile for each patient was examined. The present report focuses on Friedewald-estimated versus directly measured LDL-C; therefore, we excluded patients with triglyceride levels ≥400 mg/dl (n = 30,174; 2.3% of sample) due to known limitations of Friedewald estimation in such individuals (6). This yielded a study sample of 1,310,440 patients for analysis. We determined a priori based on the characteristics of the Friedewald equation and previous literature that our analysis would focus on patients with Friedewald-estimated LDL-C levels of 70 to 99 mg/dl (n = 376,323) and particularly those with levels <70 mg/dl (n = 191,333), as targeted in high-risk patients (1–5).

Lipid measurements. Inverted rate zonal, single vertical spin, density gradient ultracentrifugation by the VAP technique allowed direct measurement of LDL-C, VLDL-C, intermediate-density lipoprotein cholesterol, lipoprotein(a) cholesterol, and HDL-C (12). VAP accuracy was examined by yearly (2007 to 2012) random split sample comparison (n = 330; LDL-C range, 25 to 239 mg/dl; 107 ± 37 mg/dl) with beta quantification at Washington University's Core Laboratory for Clinical Studies (St. Louis, Missouri), a reference laboratory for lipoprotein analysis (r = 0.973, bias = 1.1%). Triglycerides were directly measured using the Abbott ARCHITECT C-8000 system (Abbott Laboratories, Abbott Park, Illinois) and were compared with the University of Alabama School of Medicine (Birmingham, Alabama) laboratory (n = 40, r = 0.997, bias = −0.05%). Overall, the analytical performance of lipid measurements met guideline-established benchmarks and are further detailed in the Online Appendix (13).

Data management. Raw individual patient data were electronically downloaded at Atherotech Diagnostics Laboratory, cleaned of duplicates, then de-identified and transferred in aggregate to the senior investigator of this study. The master database, named the Very Large Database of Lipids, is housed at The Johns Hopkins Hospital in Baltimore, Maryland. This is the Very Large Database of Lipids (VLDL). The Johns Hopkins Institutional Review Board declared the study exempt. The study is registered on clinicaltrials.gov (NCT01698489).

Statistical methods. We sought to assess whether lipids in our sample were representative of the general adult population. To test this, we generated kernel density

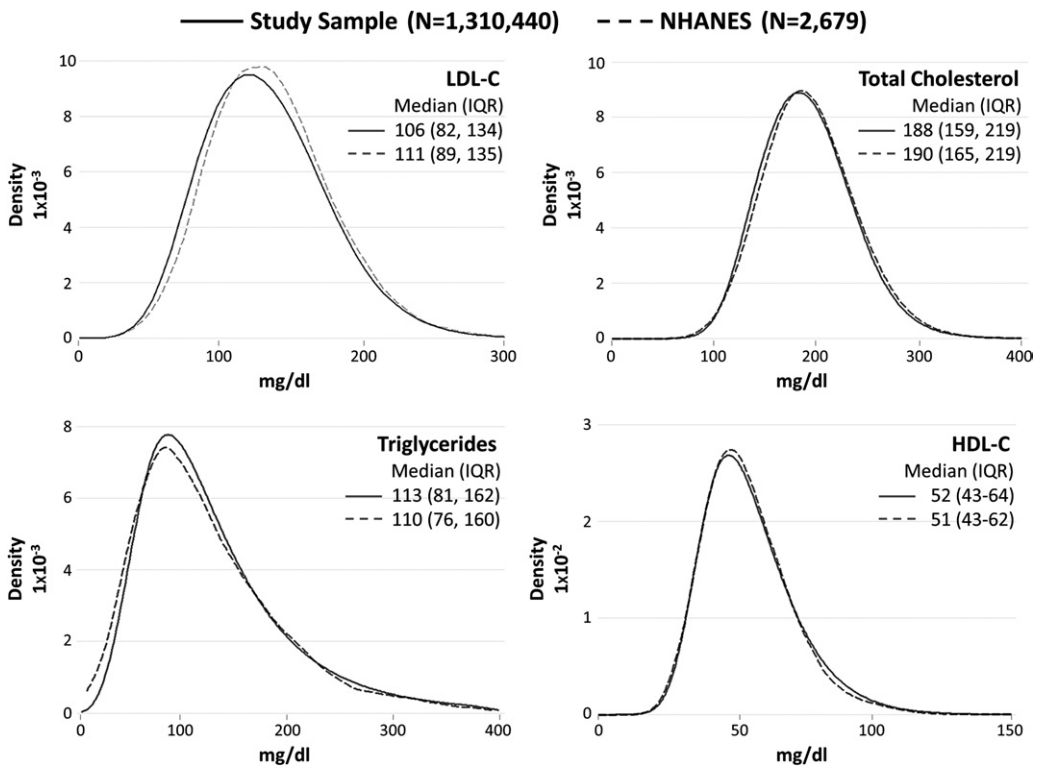


Figure 1 Lipid Distributions in Study Sample and NHANES

Kernel density plots of lipid parameters in study sample (Very Large Database of Lipids, 2009 to 2011) and the National Health and Nutrition Examination Survey (NHANES) 2007 to 2008. HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol.

plots to compare lipid parameter distributions between our database and recent lipid data from the National Health and Nutrition Examination Survey (NHANES) 2007 to 2008 (14). We examined NHANES subjects who were 18 years of age and older with triglyceride levels <400 mg/dl (n = 2,679).

Friedewald LDL-C was estimated as total cholesterol minus HDL-C minus triglycerides/5 in milligrams per deciliter. Direct LDL-C was subtracted from Friedewald-estimated LDL-C to determine the absolute difference in their values in milligrams per deciliter. The definition of LDL-C by the Friedewald equation and by direct measurement was the same, non–HDL-C minus VLDL-C, representing the sum of cholesterol carried by biochemically defined LDL (real LDL, LDLr), intermediate-density lipoprotein, and lipoprotein(a) subfractions (for additional discussion, see the Online Appendix, LDL-C definitions).

Direct and Friedewald-estimated LDL-C values were classified as <70 mg/dl or 70 to 99 mg/dl as emphasized for high-risk patients in worldwide clinical practice guidelines (1–5) with the same 30-mg/dl increment used to define higher groups up to ≥190 mg/dl. Reclassification was defined as present when direct LDL-C classified a patient within a higher (upward) or lower (downward) treatment group compared with Friedewald-estimated LDL-C.

Statistical analyses of numerical data and kernel density plots were performed in Stata version 11.0 (StataCorp LP, College Station, Texas), bar charts were created in Microsoft Excel 2010 (Microsoft, Redmond, Washington), and logarithmically scaled pseudocolor-encoded data density plots were generated in R Version 2.14.1 (Foundation for Statistical Computing, Vienna, Austria).

Results

Study sample. Patients were 59 ± 15 years of age and evenly distributed by sex (52% women). Distributions of total cholesterol, HDL-C, triglycerides, and Friedewald-estimated LDL-C in our study sample closely matched those in the NHANES (Fig. 1). The median directly measured LDL-C was 109 mg/dl (interquartile range: 85 to 135 mg/dl; 112 ± 38 mg/dl; full range: 2 to 1077 mg/dl). In a random subsample with additional clinical laboratory data (n = 3,107), the median hemoglobin A_{1c} was 5.7% (interquartile range: 5.5% to 6.1%), median high-sensitivity C-reactive protein level was 1.8 mg/l (interquartile range: 0.8 to 4.4 mg/l), and median estimated glomerular filtration rate was 67.4 ml/min/1.73 m^2 (interquartile range: 49.3 to 84.1 ml/min/1.73 m^2) (for additional details, see Online Table 1).

Impact of low LDL-C and high triglyceride levels on Friedewald-estimated versus directly measured LDL-C. At low Friedewald-estimated LDL-C levels, particularly those <100 mg/dl, Friedewald-estimated LDL-C was typically lower than directly measured LDL-C (Figs. 2A and 2B). A greater absolute difference in Friedewald-estimated versus directly measured LDL-C occurred at higher triglyceride concentrations (Online Fig. 1). Differences between Friedewald-estimated and directly measured LDL-C were compatible with differences in the estimation of VLDL-C as triglycerides/5 by the Friedewald equation compared with direct VLDL-C measurement (Online Fig. 2).

Comparing Friedewald-estimated and directly measured LDL-C in patients with Friedewald-estimated LDL-C levels in the 2 lowest groups, those with higher triglyceride levels had greater median differences and within-group variance (Fig. 3A). If Friedewald-estimated LDL-C was <70 mg/dl, the median directly measured LDL-C was 9.0 mg/dl higher (5th to 95th percentiles,

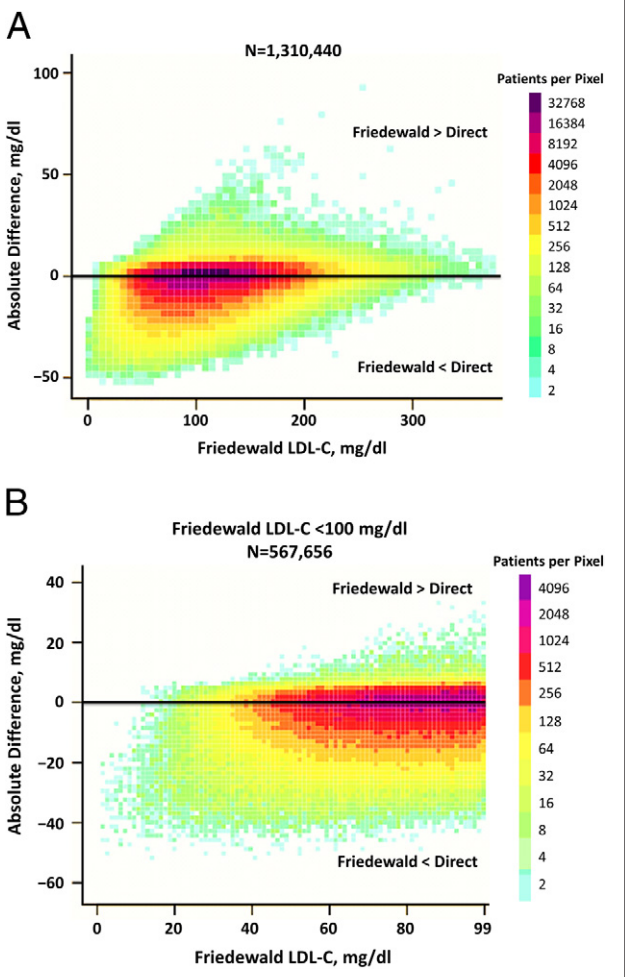


Figure 2 **Impact of LDL-C Level on Absolute Difference in Friedewald-Estimated and Directly Measured LDL-C**

Absolute difference (Friedewald − direct LDL-C) across Friedewald-estimated LDL-C levels in the full study sample of 1,310,440 adults **(A)** and 567,656 adults with Friedewald-estimated LDL-C <100 mg/dl **(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. Color pixels below the **dark horizontal line** represent cases in which Friedewald-estimated LDL-C is lower than directly measured LDL-C and vice versa for color pixels above the line. LDL-C = low-density lipoprotein cholesterol.

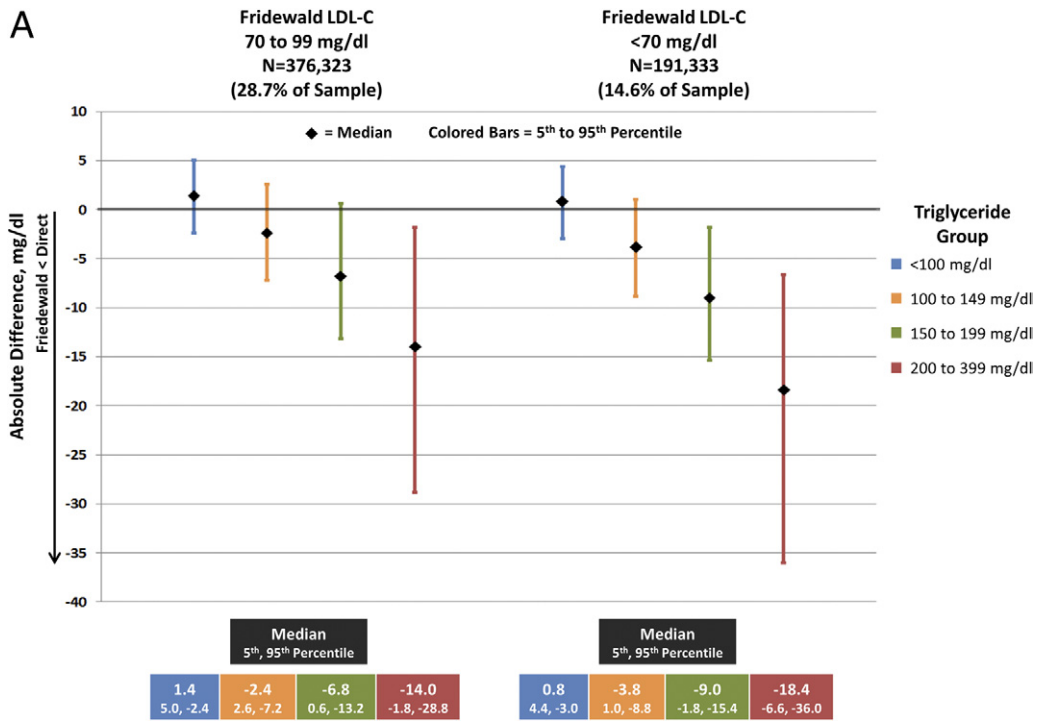


Figure 3 **Absolute Difference in Friedewald-Estimated and Directly Measured LDL-C by Triglyceride Strata at LDL-C Levels in the Treatment Range for High-Risk Patients and Treatment Group Reclassification**

(A) Absolute difference (Friedewald − direct LDL-C) in Friedewald-estimated LDL-C groups of 70 to 99 mg/dl and <70 mg/dl with substratification into 4 triglyceride groups (each assigned a color, as depicted). Proportion reclassified by direct LDL-C if Friedewald–estimated LDL-C was 70 to 99 mg/dl **(B)** or <70 mg/dl **(C)**. LDL-C = low-density lipoprotein cholesterol **(B)** or 70 mg/dl **(C)**. LDL-C low-density lipoprotein cholesterol. *Continued on the next page.*

1.8 to 15.4 mg/dl) when triglyceride levels were 150 to 199 mg/dl and 18.4 mg/dl higher (5th to 95th percentiles, 6.6 to 36.0 mg/dl) when triglyceride levels were 200 to 399 mg/dl.

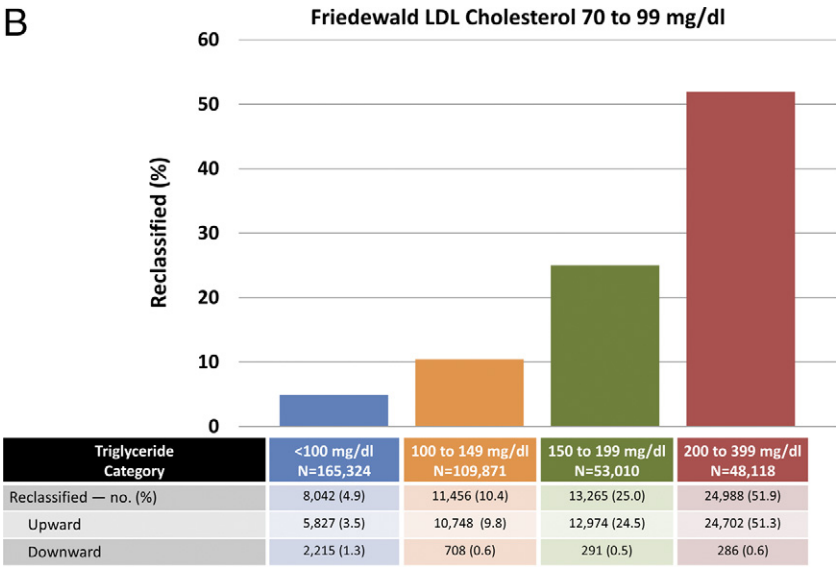
Treatment group reclassification by directly measured LDL-C. Overall, 191,563 patients (14.6%) were reclassified by directly measured LDL-C, which was largely due to upward reclassification into a higher LDL-C treatment group (n = 147,759; 11.3%). Treatment group reclassification primarily occurred in patients in lower LDL-C and higher triglyceride level groups (Table 1).

Reclassification was more frequent in patients with low LDL-C and concurrently high triglyceride levels (Figs. 3B and 3C). Of patients with Friedewald-estimated LDL-C <70 mg/dl, 23% had a directly measured LDL-C ≥70 mg/dl (39% if triglyceride levels are concurrently 150 to 199 mg/dl; 59% if triglyceride levels are concurrently 200 to 399 mg/dl).

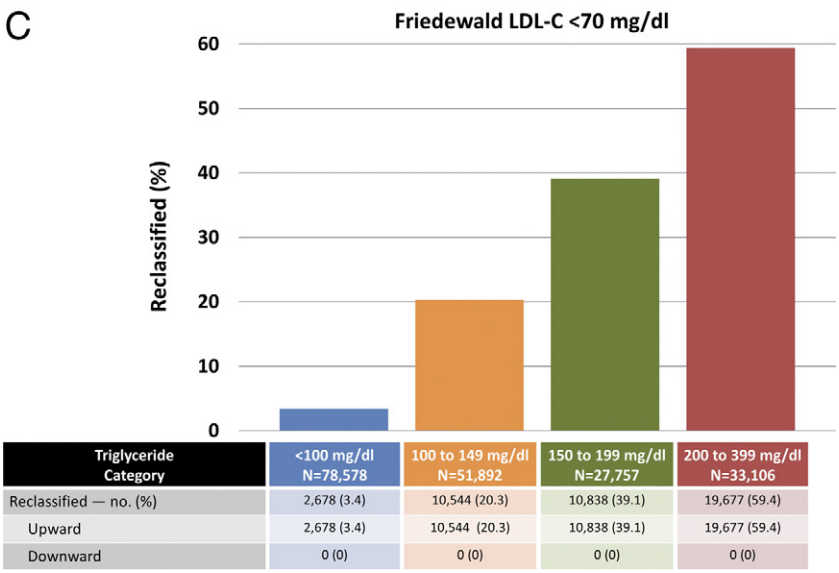
Discussion

The most important finding of our study is that the Friedewald equation tends to underestimate LDL-C most when accuracy is most crucial. Particularly in the presence of triglyceride levels ≥150 mg/dl, LDL-C underestimation is sufficient to generate considerable reclassification by direct LDL-C with respect to the high-risk treatment target of <70 mg/dl. Our study is by far the largest to date to examine the Friedewald estimation of LDL-C relative to direct measurement, 2,925 times larger than the original Friedewald dataset, with approximately 1 in every 180 U.S. adults represented. In this contemporary sample, we used a different laboratory methodology than that used in previous studies and had simultaneous access to direct LDL-C and VLDL-C data.

Friedewald equation: development and potential limitations. Now widely applied, the Friedewald equation was originally developed for use in patients with familial dyslipidemia or their relatives to distinguish Fredrickson-Levy dyslipidemias (6). The Friedewald equation performs remarkably well considering this context and its derivation in 448 subjects. However, as shown in our study and previous smaller studies (8–11) and as cautioned in the original Friedewald et al. paper (6), material differences between Friedewald-estimated and directly measured LDL-C may arise at lower LDL-C and higher triglyceride concentrations because VLDL-C estimation constitutes a relatively larger portion of the equation. Notably, the lowest LDL-C concentrations, where we observe



Triglyceride Category	<100 mg/dl N=165,324	100 to 149 mg/dl N=109,871	150 to 199 mg/dl N=53,010	200 to 399 mg/dl N=48,118
Reclassified — no. (%)	8,042 (4.9)	11,456 (10.4)	13,265 (25.0)	24,988 (51.9)
Upward	5,827 (3.5)	10,748 (9.8)	12,974 (24.5)	24,702 (51.3)
Downward	2,215 (1.3)	708 (0.6)	291 (0.5)	286 (0.6)



Triglyceride Category	<100 mg/dl N=78,578	100 to 149 mg/dl N=51,892	150 to 199 mg/dl N=27,757	200 to 399 mg/dl N=33,106
Reclassified — no. (%)	2,678 (3.4)	10,544 (20.3)	10,838 (39.1)	19,677 (59.4)
Upward	2,678 (3.4)	10,544 (20.3)	10,838 (39.1)	19,677 (59.4)
Downward	0 (0)	0 (0)	0 (0)	0 (0)

Figure 3 **Continued**

the greatest difference and variance in Friedewald-estimated versus directly measured LDL-C, fall at the low end or outside of the distribution in the original training dataset used in the 1972 Friedewald analysis.

The <400 mg/dl triglyceride criterion for the Friedewald equation is widely known, and indeed 2% of our sample was not eligible for LDL-C estimation for this reason. However, other potential limitations of the equation have received remarkably little scrutiny despite the equation's status as an important paradigm in medicine for >40 years. Modifications to the Friedewald equation have been proposed (15), but not widely adopted, and such approaches are limited by variance in the triglyceride-to-VLDL-C ratio.

Although we are not suggesting routine clinical measurement of LDL-C by direct assays, it bears mentioning that multiple direct assays beyond the VAP test are available. Nevertheless, non–HDL-C and apolipoprotein B are alternative approaches, with potential advantages over any measure of LDL-C, and these measures avoid confusion that arises in defining LDL-C (conventional definition used in this study and most clinical trials versus biochemically defined LDL-C; see Online Appendix, LDL-C Definitions) (2). Moreover, in clinical trial patients with Friedewald-estimated LDL-C levels in the high-risk treatment target of <70 mg/dl highlighted in our study, non–HDL-C and apolipoprotein B were stronger markers of residual risk than Friedewald-estimated LDL-C (16). Additional discussions of non–HDL-C and apolipoprotein B are available elsewhere (4,5,17).

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Table 1 Reclassification by Directly Measured LDL-C in Strata of Friedewald-Estimated LDL-C and Triglyceride Levels

	Concordant (n = 1,118,877)	Reclassified (n = 191,563)
Friedewald-estimated LDL-C, mg/dl		
≥190	35,482/38,435 (92.3)	2,953/38,435 (7.7)
160–189	81,713/93,669 (87.2)	11,956/93,669 (12.8)
130–159	208,017/235,722 (88.2)	27,705/235,722 (11.8)
100–129	327,497/374,958 (87.3)	47,461/374,958 (12.7)
70–99	318,572/376,323 (84.7)	57,751/376,323 (15.3)
<70	147,596/191,333 (77.1)	43,737/191,333 (22.9)
Triglyceride levels, mg/dl		
<100	485,466/520,880 (93.2)	35,414/520,880 (6.8)
100–149	358,791/398,174 (90.1)	39,383/398,174 (9.9)
150–199	163,723/204,145 (80.2)	40,422/204,145 (19.8)
200–399	110,897/187,241 (59.2)	76,344/187,241 (40.8)

Values shown are n/N in group (%).
LDL-C = low-density lipoprotein cholesterol.

Potential treatment implications. Our results have potentially far-reaching implications for patient care. As many as 85% of U.S. adults reported having undergone lipid testing in a 2009 Centers for Disease Control and Prevention telephone survey (18). Indeed, worldwide guidelines recommend Friedewald-estimated LDL-C assessment every 3 to 5 years for screening and at least every 6 to 12 months for treatment monitoring (1–5). Guidelines in Europe (4) and Canada (5) assign the highest level of evidence (Class IA) to LDL-C treatment goals. Considering these treatment goals, we highlight that discordance in classification between Friedewald-estimated and directly measured LDL-C is more common at low LDL-C levels (e.g., when the clinical question is whether a patient has a LDL-C level <70 mg/dl).

Study limitations. Although patients undergoing VAP testing may be a special population, lipid distributions in our sample closely match those in a nationally representative sample. We do not have access to detailed clinical characteristics of patients in our sample or clinical outcomes; treatment groupings and potential implications are inferred on the basis of the lipid profile only. It is unknown whether patients in our sample were receiving statin therapy; in the NHANES adults analyzed, 5% were taking a statin. We found similar results in pediatric patients in whom statin therapy is less likely (Online Appendix, Pediatric Results). Moreover, Friedewald-estimated LDL-C is used in daily clinical practice for patients on and off statins.

Although some study samples may have been acquired in nonfasting states, this is compatible with clinical practice, and results similar to ours have been obtained in smaller, completely fasting samples (8,9). In addition, our study examines one-time LDL-C measurement. Although commonly used for clinical decision making, guidelines also support serial measurements to establish greater accuracy or assess the change in LDL-C with intervention (1–5). Finally, guideline cutpoints for LDL-C are based on population averages using mostly Friedewald-estimated data. Rather than challenging population-averaged cutpoints, this report illuminates the considerable discordance that may occur from 1 patient to the next in Friedewald-estimated versus directly measured LDL-C.

Conclusions

The Friedewald equation tends to underestimate LDL-C levels in the setting of high triglyceride levels, especially at low LDL-C levels, which could result in undertreatment of high-risk patients. Based on these results, high-risk patients should have additional evaluation, especially if triglyceride levels are ≥150 mg/dl. Underestimation in Friedewald-estimated LDL-C warrants consideration in contemporary patient care, as clinicians care for patients, as experts formulate clinical practice guidelines, and as investigators design future research studies.

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Key Words: Friedewald equation ■ low-density lipoprotein cholesterol ■ very low density lipoprotein cholesterol.

APPENDIX

For an expanded Methods section, and supplemental tables and figures, please see the online version of the article.

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