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# Novel method versus the Friedewald method for estimating low-density lipoprotein cholesterol in determination of the eligibility for statin treatment for primary prevention in the United States

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**Abstract**

Although the Friedewald method has been used as the clinical standard to estimate low-density lipoprotein cholesterol (LDL-C) levels, a novel method with better accuracy was suggested and is now being adopted in real practice. We investigated the effect of this novel method on determining the eligibility for statin treatment for primary prevention in the United States.

In this cross-sectional study, we determined the discordance in the statin-eligible population for primary prevention according to the 2 different LDL-C estimating methods based on the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Using data from the National Health and Nutrition Examination Survey 2005–2014, we included 5302 nationally representative US adults aged between 40 and 75 years without history of atherosclerotic cardiovascular disease (ASCVD). Sampling weights were used in all statistical analyses to account for complex sampling design and nonresponse.

If the Friedewald method is replaced by the novel method for analysis of the fasting samples, 0.2% (95% confidence interval [CI], 0.0–0.8) and 0.4% (95% CI, 0.3–0.6) of the population would no longer be eligible or would become newly eligible for statin treatment, respectively. Among the individuals with a TG level ≥150 mg/dL and LDL-C level estimated using the Friedewald method <70 mg/dL, 11.6% (95% CI, 4.0–29.3) would become newly eligible for the statin treatment when using the novel method.

The use of the novel method for estimating LDL-C instead of the Friedewald method would be associated with a small net increase in statin eligible/needed US adults for primary prevention based on the 2013 ACC/AHA guidelines. Reassessment of individuals' statin eligibility using the novel method may be beneficial, particularly when their TG level is 150 mg/dL or higher and LDL-$C_F$ level is lower than 70 mg/dL.

**Abbreviations:** ACC = American College of Cardiology, AHA = American Heart Association, ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, IQR = interquartile range, LDL-C = low-density lipoprotein cholesterol, NCHS = National Center for Health Statistics, NHANES = National Health and Nutrition Examination Survey, TC = total cholesterol, TG = triglyceride, V-LDL = very-low-density lipoprotein cholesterol.

**Keywords:** low-density lipoprotein cholesterol, novel method, primary prevention, statin, the Friedewald method

## 1. Introduction

Low-density lipoprotein cholesterol (LDL-C) is a well-known biomarker and causal factor in the development of atherosclerotic cardiovascular disease (ASCVD).[1] Because lowering LDL-C levels has been considered a primary goal to prevent ASCVD,[2] a lipid profile is obtained frequently in both inpatient and outpatient settings. As the direct measurement of LDL-C levels from blood samples is time-consuming and expensive, an indirect method using the Friedewald equation (LDL-$C_F$) has been used as the clinical standard to estimate the LDL-C levels: total cholesterol [TC] – high-density lipoprotein cholesterol [HDL-C] – triglyceride [TG]/5 (in mg/dL).[3] This equation uses a fixed factor of 5 for the ratio of TG to very-low-density lipoprotein cholesterol (VLDL), but the actual ratio varies based on the TG and cholesterol levels.[4,5] As a result, the Friedewald method can underestimate the LDL-C level when the TG level was high, which resulted in misclassification and under-treatment of high-risk patients.[6] Given this limitation, Martin et al[5] suggested a novel method for estimating LDL-C using an adjustable factor for the TG:VLDL-C ratio determined by TG and non-HDL-C levels: TC – HDL-C – TG/adjustable factor. Because the novel method outperforms the Friedewald method with less misclassification of individuals according to the LDL-C levels,[5,7,8] it is now being adopted by several laboratories in the real practice, including QUEST Diagnostics; New Jersey, which is one of the largest diagnostic companies in the U.S.[9]

The clinical impact of replacing the Friedewald method by the novel method would be determined not only by the improved accuracy of the estimated LDL-C levels but also by any change in the treatment population per guideline.

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However, the latter is not known. Compared with the previous guideline of the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program,[10] the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines substantially modified the criteria for statin therapy by recommending statin to all secondary prevention populations, regardless of LDL-C levels and emphasizing more on the 10-year predicted risk of ASCVD than on the LDL-C levels for primary prevention.[11] These changes resulted in expansion of the statin-eligible population, particularly for primary prevention.[12] In this context, our study was intended to investigate the effect of using the novel method for estimating LDL-C levels, instead of the Friedewald method, on determination of the statin-eligible population for primary prevention based on the current guidelines. In detail, we examined the discordance in the statin-eligible population for primary prevention according to the 2 different methods for estimating LDL-C (the Friedewald method and the novel method) using data from National Health and Nutrition Examination Survey (NHANES) 2005–2014. As NHANES was designed to obtain the lipid profile in fasting samples, this study was also focused on the discordance in fasted individuals.

## 2. Methods

### 2.1. Subjects

NHANES is a cross-sectional nationwide survey representing the non-institutionalized civilian population in the United States, which includes an interview survey and physical and laboratory examinations. It is conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. Each year, a nationally representative sample of approximately 5000 people is selected from across the country using a stratified, multistage probability sample design. By using sample weights in statistical analysis, the results of NHANES represent the total noninstitutionalized civilian US population. Details of sample design were described elsewhere.[13,14] Between 2005 and 2014, the overall response rates for the completed examinations ranged from 68.5% to 77.5%. NHANES was approved by the NCHS Research Ethics Review Board, and all participants provided written informed consent before inclusion in the study.

In NHANES, a subsample of participants was selected and asked to fast for 8 or more hours for a blood test to estimate lipid profile.[15] This fasting subsample was selected at random with a specified sampling fraction in order to represent the national population.[16] With consideration of the probability of selection and nonresponse rate, special subsample weights were constructed for this population and provided in the data file.[16] There have been several studies similar to ours that used the fasting subsample population from NHANES and its subsample weights.[12,15,17] Among this population, initial candidates of our study included 6000 adults aged between 40 and 75 years without any history of ASCVD, which includes coronary heart disease, angina, myocardial infarction, and stroke. Participants with a missing lipid profile or blood pressure measurements or those whose TG levels were higher than 400 mg/dL were excluded (n = 692). Self-reported pregnant women or those who were confirmed by urine human chorionic gonadotropin test were further excluded (n = 6). After exclusions, 5302 participants remained eligible for participation in the present study (Fig. 1).

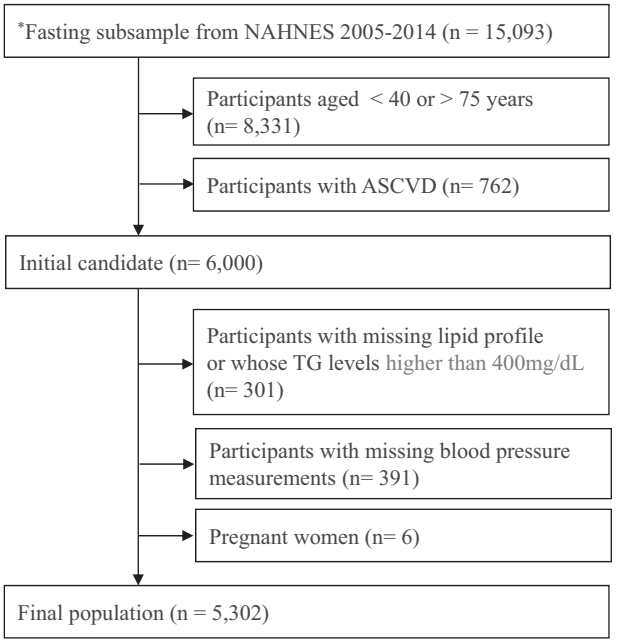


**Figure 1.** Flow diagram for selection of study participants. *Fasted between 8 and 24 hours. ASCVD = atherosclerotic cardiovascular disease (including coronary heart disease, angina, myocardial infarction, and stroke), NAHNES = National Health and Nutrition Examination Survey, TG = triglycerides.

### 2.2. Physical and laboratory examinations

Blood pressure was measured based on standardized protocol. The average of 3 blood pressure measurements was used in this study. Venous blood samples were drawn in the morning session, from which TC, TG, and HDL-C levels were directly measured. In NHANES, LDL-C levels were estimated by the Friedewald equation: $LDL\text{-}C_F = TC - HDL\text{-}C - TG/5$ (in mg/dL).[3] We also calculated LDL-C levels using the novel method: $LDL\text{-}C_N = TC - HDL\text{-}C - TG/\text{adjustable factor}$. The adjustable factor was determined using the 180 strata-specific median TG:VLDL-C ratio from the study by Martin et al.[5]

### 2.3. Eligibility of statin therapy

Among individuals aged between 40 and 75 years without history of ASCVD, eligibility for statin treatment for the primary prevention was determined using the following hierarchical criteria from the 2013 ACC/AHA blood cholesterol guidelines[11]: LDL-C levels ≥190 mg/dL; diabetes and LDL-C levels of 70 to 189 mg/dL; or 10-year ASCVD risk ≥7.5% and LDL-C levels of 70 to 189 mg/dL. Participants who reported to be "taking prescribed medicine" for high blood cholesterol levels were considered to be receiving the medication appropriately based on the guidelines. Therefore, these individuals were included in the statin-eligible population and referred as a medication-receiving population in our study. Individuals who were eligible for initiating statin treatment for the primary prevention but were not receiving cholesterol-lowering medications were defined as the statin-needed population. Therefore, statin-eligible population was the sum of the statin-needed population and the medication-receiving population. Because the medication-receiving population was constant regardless of the LDL-C estimating methods, any changes or discordance in the

**Table 1**

**Weighted characteristics of the overall, statin-eligible*, statin-needed†, and medication-receiving‡ populations based on the 2013 ACC/AHA guidelines according to the different LDL-C estimating methods (Friedewald method vs the Novel method).**

| | | Statin-eligible population* | | Statin-needed population† | | |
|---|---|---|---|---|---|---|
| | Overall | Using LDL-$C_F$ | Using LDL-$C_N$ | Using LDL-$C_F$ | Using LDL-$C_N$ | Medication-receiving population‡ |
| Number in sample | 5302 | 2737 | 2750 | 1594 | 1607 | 1143 |
| Weighted§ proportion, % (95% CI) | 100 | 44.8 (42.7–46.9) | 45.0 (42.9–47.1) | 24.2 (22.7–25.8) | 24.4 (22.8–26.0) | 20.6 (19.0–22.3) |
| Age, median (IQR), y | 53 (46–61) | 60 (53–67) | 60 (53–67) | 61 (53–67) | 61 (53–67) | 59 (52–66) |
| Men, % (95% CI) | 53.2 (45.4–48.3) | 55.3 (52.7–58.0) | 55.4 (52.7–58.0) | 61.0 (57.8–64.1) | 61.1 (57.8–64.2) | 51.4 (46.1–56.6) |
| Hypertension, % (95% CI) | 38.0 (36.0–39.9) | 58.0 (55.2–60.8) | 58.2 (55.5–60.9) | 54.1 (50.6–57.4) | 54.5 (51.1–57.8) | 62.7 (59.0–66.2) |
| Diabetes, % (95% CI) | 13.8 (12.7–15.0) | 29.5 (27.2–31.8) | 29.5 (27.3–31.9) | 28.8 (26.1–31.7) | 29.0 (26.2–31.9) | 30.2 (28.7–31.8) |
| Smoking, % (95% CI) | 18.9 (17.0–20.9) | 22.5 (20.4–24.7) | 22.7 (20.6–24.9) | 29.4 (26.6–32.4) | 29.8 (26.8–32.8) | 14.4 (13.8–14.9) |
| Ten-year ASCVD risk‖, median (IQR), % | 4.1 (1.6–9.4) | 10.0 (5.8–16.4) | 10.0 (5.9–16.4) | 11.3 (8.5–17.2) | 11.4 (8.5–17.2) | 7.2 (3.4–15.4) |
| Cholesterol, median (IQR), mg/dL# | | | | | | |
| Total cholesterol | 200 (175–226) | 198 (172–230) | 198 (172–229) | 211 (186–243) | 210 (185–242) | 185 (161–206) |
| Triglycerides | 108 (76–158) | 124 (89–177) | 125 (89–180) | 125 (87–179) | 127 (89–183) | 124 (90–176) |
| HDL-C | 53 (44–64) | 50 (43–61) | 50 (42–61) | 49 (42–62) | 49 (42–62) | 51 (43–60) |
| LDL-$C_F$ | 119 (98–142) | 116 (96–146) | NA | 130 (108–159) | NA | 103 (85–121) |
| LDL-$C_N$ | 120 (99–144) | NA | 119 (99–148) | NA | 133 (109–160) | 106 (87–125) |

ACC = the American College of Cardiology, AHA = the American Heart Association, LDL-C = low-density lipoprotein cholesterol, LDL-$C_F$ = LDL-C estimated using the Friedewald method, LDL-$C_N$ = LDL-C estimated using the novel method, CI = confidence interval, IQR = interquartile range, ASCVD = atherosclerotic cardiovascular disease (coronary heart disease, angina, myocardial infarction, and stroke), HDL-C = high-density lipoprotein cholesterol, NA = not available

* Individuals who were eligible for statin treatment for primary prevention according to the 2013 ACC/AHA guidelines.

† Individuals who were eligible for, but not receiving statin treatment for primary prevention according to the 2013 ACC/AHA guidelines (statin eligible population – medication receiving population).

‡ Individuals who were taking prescribed cholesterol-lowering medications.

§ Fasting subsample weights were used.

‖ Calculated using the pooled cohort equations based on the 2013 ACC/AHA guideline on the assessment of cardiovascular risk.

# To convert the values to mmol/L, multiply by 0.02586.

statin-eligible population was derived from changes in the statin-needed population.

The 10-year ASCVD risk scores were calculated using the pooled cohort equations based on the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk,[18] which include age, sex, race, TC and HDL-C levels, systolic blood pressure, antihypertensive treatment, smoking status, and the presence of diabetes. Because the equations are only available for non-Hispanic Whites and African Americans, the 10-year ASCVD risks for Hispanics or other races were calculated using the equations for non-Hispanic whites. Antihypertensive treatment was determined by self-reported use of prescribed medications for high blood pressure. Diabetes was defined as fasting blood glucose levels ≥126 mg/dL; hemoglobin $A_{1c}$ concentration ≥6.5%; or self-reported use of antidiabetes medications or insulin. Cigarette smoking was determined based on self-reported claims of smoking "every day" or "some days."

### 2.4. Statistical analysis

We initially investigated the characteristics of the general, statin-eligible, statin-needed, and medication-receiving populations. The statin-eligible and statin-needed populations were determined using the 2 different LDL-C estimating methods alternatively. To investigate the discordance in statin-eligible/needed populations according to the 2 different LDL-C estimating methods, we determined the individuals who would be eligible for initiating statin therapy when using one method but not the other. We repeated the discordance analysis among individuals with high TG (≥150 mg/dL) and low LDL-$C_F$ levels (<70 mg/dL), as the greatest clinical benefit of using the novel method instead of the Friedewald method was seen in this subgroup.[5] The discordance analysis was further repeated according to TG levels with the same cutoff values used by Martin et al[5] (<100, 100–149, 150–199, and 200–399 mg/dL).

All statistical analyses were performed according to the analytic guidelines of NHANES[16] using fasting subsample weights in order to account for complex sampling design and nonresponse of NHANES. By using the sample weights, we extrapolated our results to the population of 101.0 million adults in the United States, aged between 40 and 75 years, without a history of ASCVD, whose TG levels were <400 mg/dL. All statistical analyses were performed using Stata 12.1 (Stata Corp., College Station, TX).

## 3. Results

As described above, 5302 participants were finally included in this study. Figure 1 demonstrates a flow diagram for selection of the study participants. Table 1 shows the characteristics of the overall, statin-eligible, statin-needed, and medication-receiving populations according to the different LDL-C estimating methods. The data are presented as median (interquartile range [IQR]) or as weighted proportion (%) and 95% confidence interval (CI). Among US adults aged between 40 and 75 years without history of ASCVD and with TG levels <400 mg/dL, 53.2% (95% CI, 45.4–48.3) were men with median age of 53 years. The weighted prevalences of hypertension, diabetes, and active cigarette smoking were 38.0% (95% CI, 36.0–39.9), 13.8% (95% CI, 12.7–15.0), and 18.9% (95% CI, 17.0–20.9), respectively. The median 10-year ASCVD risk was 4.1%. In the overall population, 20.6% (95% CI, 19.0–22.3) were taking prescribed cholesterol-lowering medications (medication-receiving population). Assuming that they were taking cholesterol-lowering medications appropriately as per the guidelines, totally 44.8% (95% CI, 42.7–46.9) and 45.0% (95% CI, 42.9–47.1) of the population were eligible for statin treatment for primary

**Table 2**

**Weighted discordance in statin-needed population* based on the 2013 ACC/AHA guidelines according to the different LDL-C estimating methods (Friedewald method vs the Novel method).**

| | Overall (N = 5302, extrapolated N = 101.0 million) | | Triglyceride level ≥150 and LDL-$C_F$ level < 70 (N = 92, extrapolated N = 1.8 million) | |
|---|---|---|---|---|
| | Statin needed when using LDL-$C_F$ but not LDL-$C_N$† | Statin needed when using LDL-$C_N$ but not LDL-$C_F$‡ | Statin needed when using LDL-$C_F$ but not LDL-$C_N$† | Statin needed when using LDL-$C_N$ but not LDL-$C_F$‡ |
| Number in sample | 13 | 26 | 0 | 15 |
| Weighted§, % (95% CI) | 0.2 (0.0–0.8) | 0.4 (0.3–0.6) | NA | 11.6 (4.0–29.3) |
| Extrapolated number | 202.0 thousands | 404.0 thousands | NA | 212.7 thousands |
| Age, median (IQR), y | 53 (48–55) | 53 (49–63) | NA | 62 (48–69) |
| Men, % (95% CI) | 21.3 (0–100) | 61.6 (46.4–74.8) | NA | 53.6 (7.9–94.0) |
| Hypertension, % (95% CI) | 25.5 (2.4–82.6) | 58.2 (0–100) | NA | 87.1 (26.1–99.2) |
| Diabetes, % (95% CI) | 16.1 (0.4–89.8) | 31.5 (0.3–98.6) | NA | 54.8 (1.0–99.3) |
| Smoking, % (95% CI) | 20.4 (0–100) | 43.1 (0.3–99.4) | NA | 51.3 (46.3–56.3) |
| Ten-year ASCVD risk‖, median (IQR), % | 2.2 (2.1–3.7) | 8.5 (6.9–12.4) | NA | 12.4 (9.8–28.4) |
| Cholesterol, median (IQR), mg/dL# | | | | |
| Total cholesterol | 273 (156–285) | 166 (147–283) | NA | 151 (141–166) |
| Triglycerides | 87 (61–94) | 250 (190–294) | NA | 246 (210–258) |
| HDL-C | 64 (63–80) | 39 (35–47) | NA | 35 (32–52) |
| LDL-$C_F$ | 190 (72–192) | 67 (63–182) | NA | 63 (59–67) |
| LDL-$C_N$ | 188 (70–190) | 85 (74–191) | NA | 76 (73–85) |

ACC = the American College of Cardiology, AHA = the American Heart Association, ASCVD = atherosclerotic cardiovascular disease (coronary heart disease, angina, myocardial infarction, and stroke), CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, IQR = interquartile range, LDL-C = low-density lipoprotein cholesterol, LDL-$C_F$ = LDL-C levels estimated using the Friedewald method, LDL-$C_N$ = LDL-C levels estimated using the novel method, N = number, NA = not available.

* Individuals who were eligible for initiating statin treatment for primary prevention according to the 2013 blood cholesterol guideline of the American College of Cardiology/American Heart Association (ACC/AHA).

† Individuals who were eligible for initiating statin treatment for primary prevention per the 2013 ACC/AHA guideline when using the Friedewald method but the Novel method.

‡ Individuals who were eligible for initiating statin treatment for primary prevention per the 2013 ACC/AHA guideline when using the Novel method but not the Friedewald method.

§ Fasting subsample weights were used.

‖ Calculated using the pooled cohort equations based on the 2013 ACC/AHA guideline on the assessment of cardiovascular risk.

# To convert the values to mmol/L, multiply by 0.02586.

prevention when using the Friedewald method and the novel method, respectively (statin-eligible population). After excluding the medication-receiving population (20.6%) from the overall statin-eligible population, 24.2% (95% CI, 22.7–25.8) and 24.4% (95% CI, 22.8–26.0) of population would become newly eligible for initiating statin treatment for primary prevention when using the Friedewald method and the novel method, respectively (statin-needed population).

Table 2 shows the discordance in the population that would be qualified for initiating statin treatment for primary prevention when using one method for estimating LDL-C but not the other. The weighted proportion of individuals who required initiation of statin treatment based on the Friedewald method but not when using the novel method was 0.2% (95% CI, 0.0–0.8). These individuals had relatively high TC and LDL-$C_F$ levels and low TG levels (median values: 273, 190, and 87 mg/dL, respectively). In contrast, the weighted proportion of individuals who were ineligible for statin treatment by the Friedewald method but would become newly eligible for statin treatment when using the novel method was 0.4% (95% CI, 0.3–0.6). These individuals had a relatively low LDL-$C_N$ level and a high TG level (median values: 67 and 250 mg/dL, respectively). In this population, a large difference was found between the median values of LDL-$C_F$ and LDL-$C_N$ (64 vs. 87 mg/dL, respectively). Among individuals with TG levels of 150 mg/dL or higher and LDL-$C_F$ levels lower than 70 mg/dL, 11.6% (95% CI, 4.0–29.3) was re-classified into the statin-eligible/needed population when using the novel method instead of the Friedewald method. Among individuals whose TG levels are 150 or higher, 1.2% (0.7–2.2) was reclassified to statin-eligible/needed population (Supplement Table 1, http://links.lww.com/MD/C228). According to the discordant analysis based on TG levels, more individuals were re-classified to statin-eligible/needed population by the novel methods as their TG levels became higher (Supplement Table 2, http://links.lww.com/MD/C228).

## 4. Discussion

Among the adults in the United States aged between 40 and 75 years without history of ASCVD and with TG levels lower than 400 mg/dL, the use of the novel method for estimating LDL-C instead of the Friedewald method would result in a small net increase in the statin-eligible/needed population for primary prevention according to the 2013 ACC/AHA cholesterol guidelines (24.4 [95% CI, 22.8–26.0] vs 24.2 [95%CI, 22.7–25.8], respectively). In detail, 0.2% (95% CI, 0.0–0.8) required initiation of statin treatment based on the Friedewald method but not when using the novel method, and 0.4% (95% CI, 0.3–0.6) was ineligible for statin treatment by the Friedewald method but would become newly eligible for statin treatment when using the novel method. Considering the degree of difference between the accuracy of the Friedewald method and that of the novel method in classification of individuals into the right LDL-C category (85.4% vs 91.7%, respectively),[5] our study demonstrated only small discordance in the statin-eligible/needed populations determined using the Friedewald method and the novel method. This might be because of the broadened statin eligibility per the 2013 ACC/AHA guideline that emphasizes more on 10-year predicted ASCVD risks rather than LDL-C levels[12] and the relatively high accuracy of the Friedewald method in estimating the LDL-C level from fasting samples.[7] However, assuming that these estimates are accurate and can be

projected to the US population, there would still be 606,000 US adults who would be affected by the introduction of the novel method for determining the eligibility for statin treatment for primary prevention per the 2013 ACC/AHA guidelines.

As shown in Table 2, the individuals who became newly eligible for the statin treatment for primary prevention when using the novel method instead of the Friedewald method had a relatively high TG level and a low LDL-C level. In this population, there was also a large gap between the estimated LDL-C levels by the Friedewald method and the novel method (median LDL-$C_F$ = 64 mg/dL and LDL-$C_N$ = 87 mg/dL). Because the lower cutoff level of LDL-C for primary prevention statin treatment per the guideline is 70 mg/dL, such difference between the LDL-$C_F$ and LDL-$C_N$ levels might lead to the discordance in statin eligibility. This difference was probably because of the falsely underestimated LDL-$C_F$ levels considering the previous studies that reported a substantial LDL-C underestimation by the Friedewald method at low LDL-C and high TG levels.[5,7,19] In the study by Martin et al,[5] only 49.9% of individuals with TG levels of 150 mg/dL or higher and estimated LDL-$C_F$ levels lower than 70 mg/dL was found to actually have LDL-C levels lower than 70 mg/dL on using the direct measurement. In contrast, the novel method showed a higher accuracy with less underestimation of LDL-C levels in this population.[5,7,8] To further investigate the effect of the novel method in this population, we repeated the discordance analysis in the subgroup of individuals with TG levels of 150 mg/dL or higher and LDL-$C_F$ levels lower than 70 mg/dL. In this subgroup, 11.6% (95% CI, 4.0–29.3) would be re-classified into the statin-eligible population when using the novel method instead of the Friedewald method. Therefore, reassessment of individuals' statin eligibility using the novel method may be beneficial, particularly when their TG level is 150 mg/dL or higher and LDL-$C_F$ level is lower than 70 mg/dL.

Our study was only focused on fasted (≥8 hours) individuals, because NHANES was designed to examine TG and LDL-C levels only in a subsample of participants who were randomly selected for a fasting blood test. Although the 2013 ACC/AHA guidelines prefer fasting lipid profiles,[11] experts have supported the fact that non-fasting lipid measurements would be acceptable for estimation of initial risk for primary prevention.[20] A recent European guideline further recommends routine use of non-fasting lipid profiles.[21] However, in the non-fasting samples, the Friedewald method becomes less accurate and the clinical benefit of using the novel method may be maximized.[7] In this context, further study may be beneficial to investigate the effect of applying the novel method instead of the Friedewald method to non-fasting samples when determining statin eligibility.

There are limitations in our study. First, our results rely on the accuracy and representativeness of the NHANES data for the current US population. Second, we could not determine the exact impact of the novel method on the individuals who were taking prescribed cholesterol-lowering medications. We also assumed that the cholesterol-lowering medications were prescribed appropriately based on the guidelines. Third, self-reported medical history and medication use might not be accurate. Fourth, NHANES 2005–2014 did not provide data regarding peripheral arterial disease (PAD) history which is also considered an ASCVD. Therefore, individuals with PAD could not be excluded from this study. Fifth, we could not determine the reference statin-eligible/needed population using the directly measured LDL-C levels. Sixth, day-by-day variability of TG levels depending on diet and exercise could not be fully considered. However, our study included a large number of fasted samples to minimize this aspect. Despite the above limitations, to our knowledge, our study is the first to investigate the clinical effect of using the novel method for estimating LDL-C levels instead of the Friedewald method on determination of the statin eligible population per the current guidelines in representative population of adults in the United States.

In conclusion, the use of the novel method for estimating LDL-C in fasting samples instead of the Friedewald method would be associated with a small net increase in statin-eligible/needed population for primary prevention and reclassification of 606.0 thousand US adults based on the 2013 ACC/AHA guidelines. Reassessment of individuals' statin eligibility using the novel method may be beneficial, particularly when their TG level is 150 mg/dL or higher and LDL-$C_F$ level is lower than 70 mg/dL.

## Author contributions

**Conceptualization:** Doosup Shin.
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**Software:** Doosup Shin.
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