Comparing a novel equation for calculating low-density lipoprotein cholesterol with the Friedewald equation: A VOYAGER analysis

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ABSTRACT

Treating elevated low-density lipoprotein cholesterol (LDL-C) to risk-stratified target levels is recommended in several guidelines. Thus, accurate estimation of LDL-C is required. LDL-C is typically calculated using the Friedewald equation: (total cholesterol) – (non-high-density lipoprotein cholesterol [non-HDL-C]) – (triglycerides [TGs]/5). As the equation uses a fixed value equal to 5 as a divisor for TGs, it does not account for interindividual variability, often resulting in underestimation of risk and potentially undertreatment. It is specifically inapplicable in patients with fasting triglycerides ≥ 400 mg/dL. A novel method of LDL-C calculation was derived and validated by Martin et al.: (non-HDL-C) – (triglycerides/adjustable factor). This equation uses an adjustable factor, the median TG:very-low-density lipoprotein cholesterol ratio in strata defined by levels of TG and non-HDLC, as divisor for TGs, and the adjustable factor ranging from 3 to 12 has been shown to provide more accurate estimates of LDL-C compared with the Friedewald equation using a direct assay as the gold standard.

We used 70,209 baseline and on-treatment lipid values from the VOYAGER meta-analysis database to determine the difference in calculated LDL-C values using the Friedewald and novel equations. In patients with TGs < 400 mg/dL, LDL-C values calculated using the novel equation were plotted against those calculated using the Friedewald equation. The novel equation generally resulted in LDL-C values greater than the Friedewald calculation, with differences increasing with decreasing LDL-C levels; 23% of individuals who reached a LDL-C target of 70 mg/dL with the Friedewald equation did not achieve this target when the novel equation was used to calculate LDL-C; these figures were 8% and 2% for < 100 mg/dL and < 130 mg/dL targets, respectively. In patients with triglycerides ≥ 400 mg/dL, in whom the Friedewald equation is not valid, lipid values calculated using the novel equation were compared with those obtained by β-quantification. Values calculated with the novel equation did not appear to be closely related with those calculated by β-quantification in these patients. In conclusion, the novel equation provides a higher estimation of exact LDL-C values than the Friedewald equation, particularly in patients with low LDL-C levels, which may result in undertreatment of some patients whose LDL-C was calculated using the Friedewald method. However, neither may be suitable for patients with TG ≥ 400 mg/dL.

1. Introduction

There is a well-documented relationship between the magnitude of statin-mediated low-density lipoprotein cholesterol (LDL-C) reduction, and reduction in the risk of major cardiovascular events [1,2]. Consequently, in patients at high cardiovascular risk due to dyslipidemia,

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Table 1

Baseline characteristics and lipid parameters of the 32,258 patients in the VOYAGER database.

Characteristic	N = 32,258
Age, years, mean (SD)	60.0 (11.1)
Men, %	56.7
Race, %	
White	79.9
Black	5.1
Hispanic	4.1
Asian	8.3
Other	2.6
Body mass index, kg/m^2, mean (SD)	28.8 (5.5)
Baseline lipid levels, mg/dL, mean (SD)	
LDL-C	170.9 (38.7)
HDL-C	48.7 (12.7)
Non-HDL-C	205.2 (41.8)
TG, median (interquartile range)	162.2 (120.4, 215.0)
ApoB	159.3 (37.2)
ApoA-1	148.8 (28.7)
ASCVD, %	51
Diabetes, %	29

Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides.

LDL-C reduction is often recommended as the primary treatment goal, with statins as first-line therapy [3,4]. Several guidelines also recommend treating patients to risk-stratified LDL-C target levels (< 160 mg/dL, < 130 mg/dL, and < 100 mg/dL, for patients at low, intermediate, and high cardiovascular risk, respectively, and an optional secondary prevention target of < 70 mg/dL in very-high-risk patients) [4–6]. Thus, accurate estimation of LDL-C is required.

LDL-C is typically calculated using the Friedewald equation, which is based on an analysis of 448 patients from 1972 [7]. The Friedewald equation features a fixed triglyceride (TG):very-low-density lipoprotein cholesterol (VLDL-C) ratio of 5:1, and therefore, does not address the substantial inter-individual variability in TG:VLDL-C ratios. Also, the Friedewald equation is inapplicable for patients with fasting TG ≥ 400 mg/dL, and often underestimates LDL-C levels in patients with TG ≥ 150 mg/dL, potentially resulting in undertreatment of these patients [8]. In patients with TG ≥ 400 mg/dL, β-quantification, a method of lipoprotein measurement using ultracentrifugation, is required to accurately measure LDL-C [9].

A novel equation estimating LDL-C levels has been derived and validated by Martin et al. using a large sample of lipid profiles (n = 1,350,908) [10]. The novel equation features an adjustable factor for the TG:VLDL-C ratio based on TG and non-high-density lipoprotein cholesterol (non-HDL-C) concentrations. The equation has been shown to provide more accurate estimates of true LDL-C measured by direct assay compared with the Friedewald equation, particularly in individuals with LDL-C < 70 mg/dL and those with elevated TG levels up to 400 mg/dL [10].

The VOYAGER (an indiVidual patient data meta-analysis Of statin therapY in At risk Groups: Effects of Rosuvastatin, atorvastatin, and simvastatin) meta-analysis database contains individual patient data from pooled clinical studies, directly comparing changes in lipid parameters observed during treatment with the 3 statins most commonly used in clinical practice (atorvastatin, rosuvastatin, and simvastatin) [11]. Using the VOYAGER database, the present analysis aimed to investigate the difference in calculated LDL-C levels when using the novel and Friedewald equations. A comparison of the novel method with β-quantification was also performed in patients with TG ≥ 400 mg/dL.
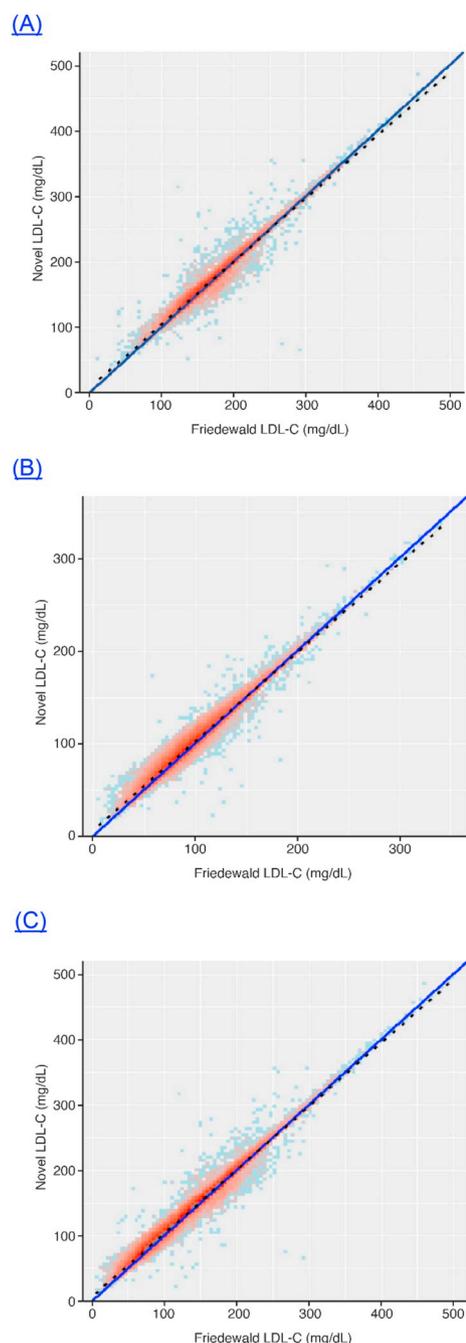

Fig. 1. Comparison of the novel equation versus the Friedewald equation for calculating (A) baseline (B) on-treatment and (C) total LDL-C levels in the VOYAGER meta-analysis database.

Line of equality shown as blue solid; line of regression shown as black dashed.

2. Methods

Detailed patient demographics and methods from the VOYAGER meta-analysis have been reported previously [11]. In brief, the VOYAGER meta-analysis database contains data on 32,258 patients from 37 randomized fixed-dose trials, directly comparing changes in lipid parameters observed with rosuvastatin and either atorvastatin or simvastatin. A total of 70,290 baseline and on-treatment lipid values
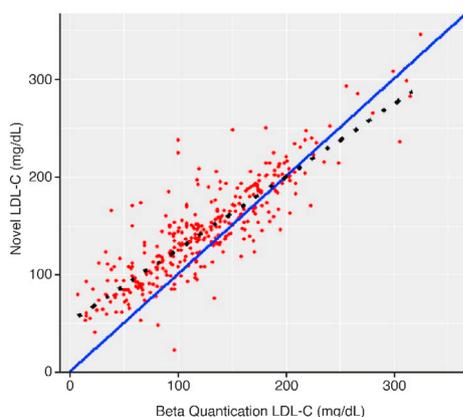
Fig. 2. Comparison of the novel equation versus the β-quantification measure for baseline and on-treatment LDL-C values in patients with TG ≥ 400 mg/dL in the VOYAGER meta-analysis database.
Line of equality shown as blue solid; line of regression shown as black dashed.

were obtained from the VOYAGER database and used for the present analysis. As calculation of LDL-C using the Friedewald equation is not valid for individuals with fasting TG ≥ 400 mg/dL, β-quantification was used to measure LDL-C directly in 211 baseline samples and 219 on-treatment lipid samples.

Using baseline (n = 31,960) and on-treatment (n = 37,911) lipid values from patients with TG < 400 mg/dL, LDL-C was calculated using both the Friedewald equation: (total cholesterol) – (non-HDL-C) – (TG/5), and the novel equation: (non-HDL-C) – (TG/adjustable factor mg/dL), where the adjustable factor, ranging from 3 to 12, was determined as the median TG:VLDL-C ratio in strata defined by levels of TG and non-HDL-C. The derivation, development, and validation of the novel and Friedewald equations have been described previously [7,10]. Scatterplots showing the LDL-C level calculated using both the Friedewald and novel equations were produced, with each point on the scatterplots representing one lipid sample from the VOYAGER database.

Bland-Altman plots were also used to compare the two methods of LDL-C calculation across TG values. These analyses plot differences between the two methods against the average of the two methods to highlight agreement [12].

Lipid values from patients with TG ≥ 400 mg/dL (n = 338) were also used to calculate LDL-C values using the novel equation. These values were plotted against the LDL-C values in the VOYAGER database, which were obtained by β-quantification.

Concordance was calculated for on-treatment values of LDL-C and was defined as the percentage of LDL-C lipid samples that were classified as < 70 mg/dL or ≥ 70 mg/dL with both the Friedewald and novel method of LDL-C calculation. Discordance was the percentage of on-treatment values where LDL-C was < 70 mg/dL with the Friedewald equation and ≥ 70 mg/dL with the novel equation.

3. Results

The baseline characteristics and lipid parameters of the 32,258 patients included in the VOYAGER database are summarized in Table 1. In 11 of the studies included in VOYAGER database, patients were force-titrated to higher doses of medication during the study period, therefore the total number of lipid samples included in the analysis was 70,209.

Scatterplots showing the baseline, on-treatment, and total LDL-C

values calculated using the Friedewald equation versus the novel equation in patients with TG < 400 mg/dL are shown in Fig. 1. Calculation using the novel equation generally resulted in greater LDL-C values than the Friedewald equation. The differences between the LDL-C values obtained with the two equations were typically small. However, the differences increased with decreasing levels of LDL-C. Overall concordance was 94.9%. Based on an analysis of on-treatment lipid samples, 23% of individuals who reached an LDL-C target of 70 mg/dL with the Friedewald equation (n = 7239) did not achieve this target when the novel equation was used to calculate LDL-C. Furthermore, 8% of individuals who reached an LDL-C target of 100 mg/dL and 2% who reached a target of 130 mg/dL with the Friedewald equation did not achieve this target when the novel equation was used to calculate LDL-C.

A scatterplot showing LDL-C values obtained by β-quantification versus calculation using the novel equation in patients with TG ≥ 400 mg/dL is shown in Fig. 2. The figure highlights that in patients with TG > 400 mg/dL there is poor agreement between the 'gold standard' β-quantification method and the novel method of calculating LDL-C.

Scatterplots showing LDL-C values calculated using the Friedewald equation versus the novel equation in patients with different baseline TG levels are shown in Fig. 3. As observed in Fig. 1, calculation using the novel equation generally resulted in greater LDL-C values than the Friedewald equation, and this was more prominent in those with higher TG levels, TG 150–199 mg/dL and TG 200–399 mg/dL. This is also evidenced in the Bland-Altman plots (Fig. 3b), which show that the difference between the two methods increases as the TG value increases. Concordance was 98% when TG levels were < 100 mg/dL but reduced to 96% when TG levels were 100–149 mg/dL, 93% when TG levels were 150–199 mg/dL, and 89% when TG levels were 200–400 mg/dL.

The impact of LDL-C calculation on the efficacy of different statins and doses on reducing LDL-C was also investigated. Compared with the Friedewald method, the novel method of LDL-C calculation resulted in slightly lower mean percentage changes in LDL-C from baseline for atorvastatin (10–80 mg), rosuvastatin (10–40 mg), and simvastatin (10–80 mg) (Fig. 4). However, the differences were minor and consistent across the different statins and doses.

4. Discussion

As guidelines continue to emphasize the importance of treating patients with hypercholesterolemia to risk-stratified goals [4–6], accurate calculation of LDL-C levels in patients at high cardiovascular risk is crucial. The novel equation uses an adjustable factor for the TG:VLDL-C ratio based on individual TG and non-HDL-C concentrations, thus addressing the inter-individual variation in TG:VLDL-C ratios, and providing a more accurate estimation of LDL-C levels than the Friedewald equation. Our results show that use of the novel equation generally results in greater calculated LDL-C values than the Friedewald equation, with this difference most apparent at lower levels of LDL-C and higher levels of TG up to 400 mg/dL. Therefore, the Friedewald equation may underestimate LDL-C levels and subsequently overestimate LDL-C goal attainment. Consequently, individuals at high cardiovascular risk may be undertreated. As the VOYAGER database contains data on the three most commonly used statins, we also investigated whether efficacy of different statins and doses was impacted by method of LDL-C calculation. This study is probably the first and only to demonstrate that the efficacy of statin and dose is not influenced by LDL-C estimation.
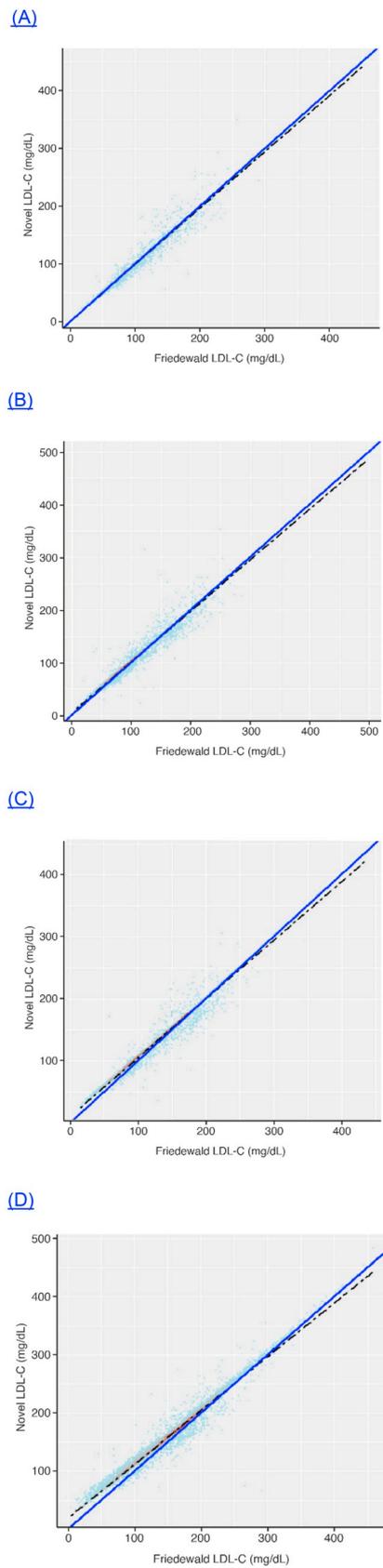
(A)

(B)

(C)

(D)

Fig. 3. a. Comparison of the novel equation versus the Friedewald equation for calculating LDL-C values in the VOYAGER meta-analysis database for (A) TG < 100 mg/dL (B) TG 100–149 mg/dL (C) 150–199 mg/dL and (D) 200–399 mg/dL. b. Bland-Altman comparison of the novel equation versus the Friedewald equation for calculating LDL-C values in the VOYAGER meta-analysis database for (A) TG < 100 mg/dL (B) TG 100–149 mg/dL (C) 150–199 mg/dL and (D) 200–399 mg/dL.
Line of equality shown as blue solid; line of regression shown as black dashed.
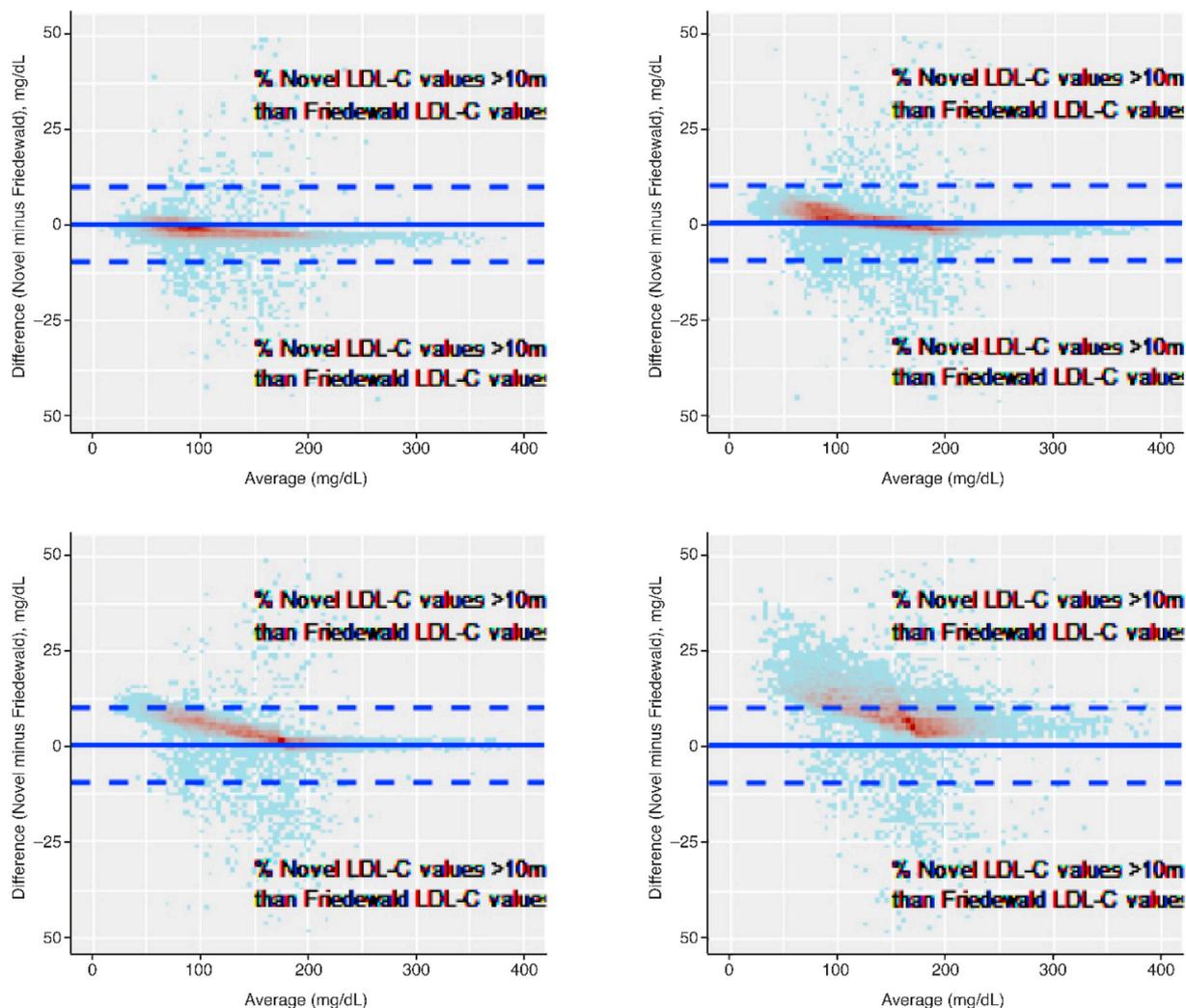
Fig. 3. (*continued*)

When the Friedewald equation was derived, an LDL-C treatment goal of < 70 mg/dL was not yet proposed as an optional secondary prevention target for high-risk patients. An LDL-C level in this range was at the low end or outside the distribution of the data used to derive the Friedewald calculation [10]. Friedewald et al. suggested that in using a fixed TG:VLDL-C ratio may lead to inaccuracies in VLDL-C estimation. Although these inaccuracies would not be crucial at higher LDL-C levels, they may be significant in individuals with lower LDL-C levels and higher TG levels, as VLDL-C would constitute a greater proportion of the equation, thus resulting in larger relative errors in the LDL-C calculation [7,10]. In agreement with this hypothesis, we found that 23% of individuals who reached an LDL-C target of < 70 mg/dL with the Friedewald equation did not achieve this target with the novel equation. Similar results were reported in a recent analysis of nationally representative and clinical cohorts (*n* = 2381), where ~20% of individuals with Friedewald-estimated LDL-C < 70 mg/dL had a value ≥ 70 mg/dL using the novel equation [13].

In the limited number of lipid samples with TG ≥ 400 mg/dL available in the VOYAGER meta-analysis, and in whom the Friedewald equation is inapplicable, LDL-C values calculated using the novel equation were not close to direct measurements of LDL-C obtained by β-quantification and were generally higher at low levels of LDL-C. In Martin's original comparison of the novel method versus the Friedewald method of LDL-C calculation [10], only patients with TG < 400 mg/dL were included and the novel method was not compared with β-quantification. We therefore believe that this is the first study to show poor agreement between the two methods and suggest that this novel method of LDL-C calculation may be inaccurate in patients with high TG (≥ 400 mg/dL). Consequently, we recommend it is used with caution or even avoided in patients with TG ≥ 400 mg/dL. It should be acknowledged that there was limited number of lipid samples in the VOYAGER database with TG ≥ 400 mg/dL, so this finding warrants further investigation.

In conclusion, the novel equation provides a higher estimate of LDL-C values than the Friedewald equation, particularly in patients with low LDL-C levels, which may result in undertreatment of some patients whose LDL-C was calculated using the Friedewald method. However, the novel equation did not seem to accurately estimate the LDL-C measured directly by β-quantification in patients with TG ≥ 400 mg/dL. However, the clinical significance and implications of our findings may need to be better understood.
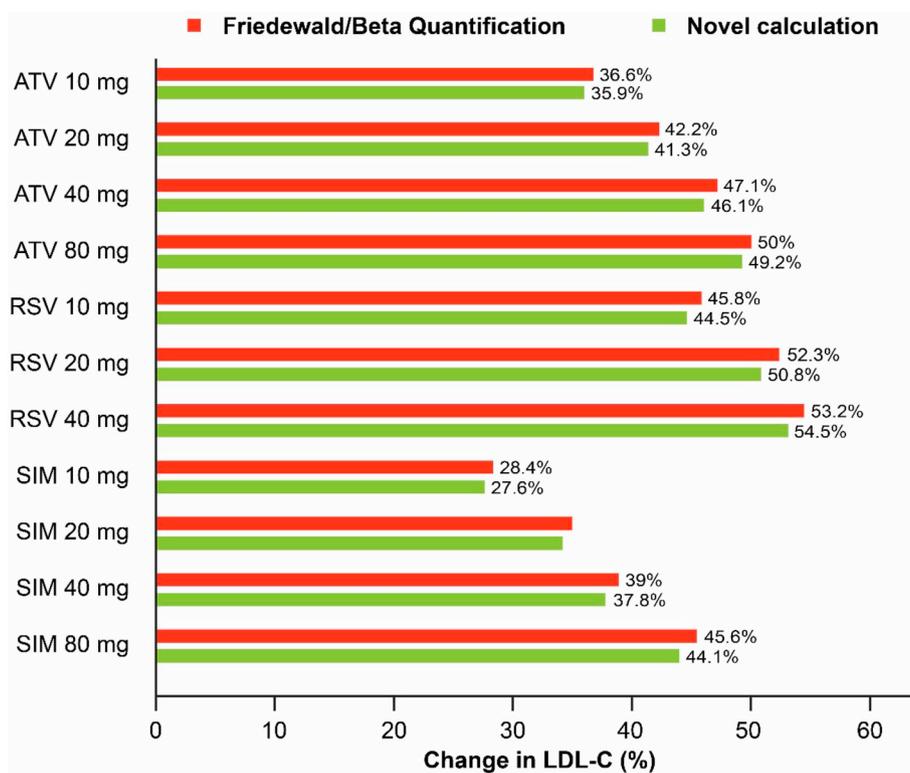
Fig. 4. Mean percentage change in LDL-C for the novel equation versus the Friedewald equation for the different types and doses of statin used in VOYAGER. ATV, atorvastatin; LDL-C, low-density lipoprotein cholesterol; RSV, rosuvastatin; SIM, simvastatin.

Disclosures

BWK is an employee of AstraZeneca; SJN has received research support from AstraZeneca; PL has received speaker fees from AstraZeneca; PJB has received research support and speaker fees from AstraZeneca; MP has received fees for statistical analysis from AstraZeneca; PPT has been involved in a speakers' bureau for Amarin, AstraZeneca, Genzyme, Kowa, and Merck, and is a consultant for Amgen, AstraZeneca, Kowa, Merck, Novartis, Regeneron, and Sanofi.

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