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Original Research

Impact of the Friedewald equation vs 2 validated equations on LDL-C estimates and goal achievement in hospitalized patients with diabetes

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KEYWORDS
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BACKGROUND: In diabetes, there is a lower concordance between estimated and directly measured low-density lipoprotein cholesterol (LDL-C) values. In previous studies, the Martin–Hopkins (MH) and the modified Sampson (mS) equations emerged as novel LDL-C estimating methods with a higher concordance with direct measurement than the Friedewald (F) equation.

OBJECTIVE: Our prior analysis of an entire population of inpatients showed a progressive decline in LDL-C target attainment from low to higher-risk categories, with only 32.5% of patients with diabetes reaching the target. This analysis aimed to compare LDL-C levels calculated using the F, MH, and mS equations in this population, and to evaluate the clinical implications of adopting these approaches on cardiovascular risk categorization — both in the overall cohort and within diabetes and non-diabetes subgroups.

METHODS: Retrospective real-world data were extracted from the Hospital Information System using automated data extraction strategies and stored in a patient-centered repository (the Dyslipidaemia Data Mart). LDL-C was calculated using the F, MH, and mS equations. Goal

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achievement for LDL-C was evaluated using the 3 equations, overall and for diabetic and nondiabetic subgroups. We then assessed the effect of the switch from the traditional method to these novel approaches on patient risk categorization.

RESULTS: A total of 13,834 patients were included. Overall, patients at goal were 35.8% with MH and 32.6% with mS, both lower compared with F (38.9%). The percentage of patients at goal (according to F) who were reclassified as not at goal (according to MH and mS) was significantly higher in diabetes compared with nondiabetes (5.1% vs 2.8% for reclassification from F to MH, $P < .001$; 8.3% vs 5.3% for reclassification from F to mS, $P < .001$). Distance to target was also higher with MH and mS, particularly among patients with diabetes.

CONCLUSION: Accurate LDL-C estimation is critical for the cardiovascular risk management of people with diabetes. The choice of calculation method can significantly influence both target achievement and therapeutic decisions, with the MH and mS equations identifying a larger proportion of patients with diabetes as not at goal compared with the F equation.

Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality[1] in diabetes. Current guidelines suggest a multifactorial approach to reduce cardiovascular risk, emphasizing control of glycated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), albuminuria, systolic blood pressure, and smoking cessation.[2] Despite these efforts, residual cardiovascular risk persists, prompting interest in additional modifiable factors.[3,4]

The emergence of new, highly effective therapeutic interventions over the past decade has underscored the importance of lipid management in diabetes.[5] Lipid-lowering therapies, particularly those targeting LDL-C, have demonstrated robust efficacy in reducing cardiovascular events and mortality in randomized controlled trials, including in patients with type 2 diabetes mellitus (T2DM). These trials have shown a log-linear relationship between each 1 mmol/L reduction in LDL-C and corresponding cardiovascular risk reduction, highlighting the importance of accurate LDL-C estimation in diabetes care.[6]

In routine clinical practice, LDL-C is usually estimated using the Friedewald equation (F).[7] However, this method is less reliable in patients with high triglycerides (TGs) and low LDL-C,[8,9] whose prevalence is increasing worldwide, mainly due to the global metabolic syndrome epidemic and new LDL-C target levels. Indeed, the 2019 update of the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines,[10] and the more recent 2025 update[11] suggest even more aggressive LDL-C goals compared with previous versions (ESC/EAS 2016),[12] particularly for the very high-risk category, leading to treatment intensification. Advances in lipid-lowering therapies now enable many patients to reach extremely low LDL-C values.[13] Similarly, hypertriglyceridemia is a common finding in the general population, largely due to the increasing prevalence of diabetes and metabolic syndrome.[14] The latter is significantly influenced by societal changes such as urbanization, the widespread adoption of the Western diet, and sedentary lifestyles. Furthermore, evidence suggests that the F formula performs worse in people with diabetes compared with those with normoglycemia or prediabetes, due to a lower concordance with directly measured LDL-C.[15] Notably, individuals with diabetes often exhibit both hypertriglyceridemia[16] and very low LDL-C levels (due to cardiovascular risk management). This combination makes them particularly susceptible to inaccuracies in LDL-C estimation via the F formula.

In the last decade, several authors have proposed alternative methods for LDL-C estimation. A common challenge shared by these various approaches is the estimation of very low-density lipoprotein cholesterol (VLDL-C), which, together with high-density lipoprotein cholesterol (HDL-C), LDL-C, and lipoprotein(a), contributes to total cholesterol (TC). Recently, Samuel et al. compared the accuracy of 23 equations and demonstrated that most proposed alternatives to the F equation showed reduced concordance with directly measured LDL-C obtained by Vertical Auto Profile, an alternative ultracentrifugation-based method to the gold-standard β-quantification (BQ). In this analysis, the Martin–Hopkins (MH) equation consistently demonstrated the highest overall accuracy, as well as superior performance across various subgroups, compared with the other equations, including the F formula.[17] The MH equation differs from the F in its method for VLDL-C estimation, since it uses an adjustable patient-specific TG/VLDL-C ratio, derived from non–HDL-C and TG values, thereby improving precision across a range of clinical scenarios[18,19] (see Methods for the detailed formula). More recently, the modified Sampson (mS) equation was developed using a combined database of LDL-C measurements obtained through the reference BQ method from the Mayo Clinic and the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with

Elevated Risk (FOURIER) clinical trial. The equation was derived using least-squares regression analysis, with BQ-measured LDL-C as the dependent variable, aiming to better reflect the known distribution of cholesterol among the major lipoprotein fractions.[20] The terms of the mS equation estimate the cholesterol content of the VLDL-C fraction, which comprises VLDL particles, chylomicrons, and their remnants (see Methods for the detailed formula).

In this context of rapid innovation, it becomes imperative to understand the differential impact of these equations on clinical practice.

We retrospectively evaluated an entire population of inpatients admitted to the hospital during 2021-2022. In our prior analysis, we demonstrated that most patients, particularly those in the high- and very high-risk categories, fail to achieve LDL-C goals. In addition, the use of high-intensity statins and statins plus ezetimibe combination therapy was low or inappropriate, despite the latter being associated with a higher possibility of achieving target levels compared with monotherapy.[21] In this paper, we aim to compare LDL-C estimates, derived from the F, MH, and mS formulas, in the overall population and in diabetic and nondiabetic subgroups. We will also assess changes in LDL-C goal attainment after switching from the F to MH and mS formulas.

Methods

Study design and population

This retrospective, observational, cross-sectional study included all adult patients admitted to Fondazione Policlinico Gemelli hospital during the recruitment period that lasted from January 1, 2021, to August 31, 2022. Baseline data were collected using data extraction strategies, based on the design and implementation of a patient-centered data repository (the Dyslipidaemia Data Mart) that extracts, validates, and integrates all relevant data sources for patient characterization and risk assessment.

Baseline was defined as the patient's first hospital admission, and laboratory results were retrieved from the hospital's Laboratory Information System (LIS). Of the initial sample of 109,234 hospitalizations, only patients who met the inclusion and exclusion criteria were included in the present analysis. For a comprehensive and detailed analysis of the selection process, readers are referred to our previous publication.[21] Briefly, from the initial sample of 109,234 hospitalizations, lipid measurements were available for 36,260 hospitalizations (as some patients were admitted to the hospital more than once over the same period, this number comprises 31,296 patients). Following the application of the exclusion criteria, we obtained a sample of 13,834 patients.

Exclusion criteria were the following: (1) age < 18 years, (2) missing or incomplete lipid results (ie, TC and TG measurement only, without use of the LDL-C estimating equations), (3) TGs > 400 mg/dL, (4) LDL-C calculated < 0 mg/dL or > 400 mg/dL, (5) cholesterol and TG measurements conducted less than 36 hours after artificial nutrition and/ or interfering (non–lipid-lowering) drugs, (6) unstable LDL-C results during hospitalization (delta min-max/mean > 30%).

The study protocol conforms to the ethical guidelines of the 1975 Helsinki Declaration and was approved by the Ethics Committee of the Fondazione Policlinico Gemelli Hospital (prot. no. 16,832/23). The study used anonymous data, and, according to national and European regulations, a waiver was applied to the requirement for patient-informed consent.

Lipid measurements

Lipid measurements (TC, HDL-C, and TG) were automatically extracted from the LIS. Technical quality controls were conducted on the data to ensure accuracy of the values. Clinicians independently verified the quality of the results, particularly for patients with LDL-C measurements near the upper limits of the acceptable range. LDL-C was calculated using 3 equations: F, MH, and mS formulas. MH and mS formulas are reported below:

$$\text{LDL-C (MH)} = \text{TC} - \text{HDL-C} - \text{TG/personalized factor*}$$

*The personalized factor is a number that ranges from 3.1 to 9.5 selected from a table based on the patient's non–HDL-C (x-axis) and TG (ordinate axis) values. Non–HDL-C is calculated as follows: TC – HDL-C.

$$\text{LDL-C (mS)} = \text{non–HDLC} - \text{TG}/8{\cdot}37 - (\text{TG} \times \text{non–HDLC})/2640 + \text{TG}^2/17400$$

Diabetes diagnosis and risk category classification

Patient medical history data were integrated to define demographics, comorbidities, and risk factors. CVD risk categories were defined according to the 2019 ESC/EAS Guidelines on dyslipidemia as low (L), moderate (M), high (H), and very high (VH) risk. The CV risk category for each patient at baseline was assessed using information on patient demographics, comorbidities, risk factors, and Systematic COronary Risk Evaluation (SCORE).

To evaluate comorbidities—such as diabetes—structured and unstructured sources were integrated:

- Structured sources: primary and secondary diagnoses reported during hospitalization (ICD9-CM at discharge); payment exemption data extracted from the outpatient data; laboratory and observational parameters extracted from hospital LIS and Observations.
- Unstructured sources: information extracted from clinical reports during hospitalization on therapies using drug name/active ingredient/ Anatomical Therapeutic Chemical (ATC) classification system codes.

Diabetes was identified based on the presence of at least 1 of the following: ICD9-CM codes 250*; payment

exemption codes 013 and 013.250; on antidiabetic therapy excluding metformin extracted from hospitalization clinical reports (clinical diaries, medical histories, discharge letters); HbA1c ≥6.5% before discharge date; or mean fasting blood glucose ≥126 mg/dL for measurements performed between prehospitalization/admission and the fifth day from admission. To select only fasting blood glucose measurements, results were retrieved only if performed together with lipid profile measurements and conducted at least 36 hours after artificial nutrition and/ or interfering (non–-lipid-lowering) drugs.

According to the ESC/EAS guidelines, individuals with diabetes are classified into the following cardiovascular risk categories: moderate (M), high (H), and very high (VH). In order to assign the correct category, data on diabetes duration, type of diabetes (type 1/type 2), risk factors, target organ damage (TOD), and atherosclerotic cardiovascular disease (ASCVD) were extracted and integrated. Patients with T1DM were defined by all diagnoses, including juvenile onset diabetes with the following International Classification of Diseases, 9th Revision - Clinical Modification (ICD9-CM) codes: 250.01|250.03| 250.11|250.13|250.41|250.71|250.73|250.91. To estimate diabetes duration, we used the average age of onset for the Italian population in national annual reports: for people with T2DM ≥70 years, T2DM duration was defined as ≥10 years; for people with T1DM >45 years, T1DM of long duration was defined as >20 years. Data on risk factors (such as hypertension and smoking) were extracted from the Dyslipidaemia Data Mart as already stated.[21] SCORE was calculated for all patients, excluding those already defined as VH risk patients, as such patients require active management of all risk factors without further risk estimation. Patients with TOD were identified by diagnosis of complicated diabetes (ICD9-CM codes 250.4|250.5|250.6|250.7|250.8|250.9) or evidence of albuminuria (the presence of at least 1 measurement exceeding normal range within +/- 90 days from the baseline hospitalization). ASCVD was identified using ICD9-CM codes and exemption codes.

Statistical analysis

Clinical characteristics are presented as medians with IQR for continuous variables, and as numbers and relative percentages for categorical variables.

Pearson correlation was performed to assess the relation between LDL-C values obtained using the 3 equations (F, MH, and mS) for each included patient. Differences in LDL-C (ΔLDL-C) between the equations were calculated for the entire population, as well as for the diabetic and nondiabetic subgroups.

Changes in LDL-C target attainment after transition from F to MH and mS were assessed for the entire population and the 2 subgroups using McNemar's chi-squared test. The same analysis was performed after stratification of the population by TG class and cardiovascular risk category. Distance to target (DTT) was presented as median (IQR); comparisons between the 2 subgroups were performed with the Mann–Whitney test. The number of patients reclassified from one category to the other (at goal vs not at goal) in the transition from F to MH and from F to mS were compared in the diabetic and nondiabetic subgroups using the chi-squared test. All statistical tests were 2-sided and were performed at the 5% level of significance, unless otherwise stated. Data were analyzed using R software (version 4.2.1).

Results

Patient characteristics and LDL-C values

A total of 13,834 patients were included following the selection process, with 30.5% identified as having diabetes. The prevalence of ASCVD and chronic kidney disease (CKD) was 31.8% and 35.7%, respectively. Several patients were affected by more than 1 comorbidity, including diabetes, CKD, and obesity (17.9% had 2 comorbidities, 3.6% had 3 comorbidities). Overall, median LDL-C (F) was 83.80 (63.20, 107.20), whereas median LDL-C (MH) and median LDL-C (mS) were 86.20 (66.50, 109.30) and 89.30 (69.30, 111.70), respectively.

As expected, BMI and age were higher in the subgroup of patients with diabetes compared with controls ($P < .001$). In patients with diabetes, TGs were significantly higher, while TC, HDL-C, non–HDL-C, and LDL-C (assessed with all the equations) were significantly lower ($P < .001$). ΔLDL-C (MH–F) was 1.50 (−0.60, 4.40) mg/dL, 1.10 (−0.73, 3.80) mg/dL, and 2.30 (0.00, 5.80) mg/dL for the entire population, the subgroup without diabetes, and the subgroup with diabetes, respectively ($P < .001$); whereas ΔLDL-C (mS–F) was 4.80 (3.60, 6.50) mg/dL, 4.50 (3.40, 6.10) mg/dL, and 5.50 (4.10, 7.40) mg/dL for the entire population and the 2 subgroups, respectively ($P < .001$). Baseline features of the enrolled population are reported in Table 1.

The Pearson correlation between F and MH, F and mS, and MH and mS is shown in Table 2.

LDL-C goal achievement

Overall, the percentage of patients at goal was 38.9% with F, 35.8% with MH, and 32.6% with mS. LDL-C goal achievement was significantly greater when assessed with F compared with MH and mS in both the diabetes and nondiabetes subgroups. In the subgroup with diabetes, 32.49% reached LDL-C target levels with F, 27.65% with MH ($P < .001$), and 24.19% with mS ($P < .001$). In the normoglycemic subgroup, the percentage of patients at goal were 41.72%, 39.46%, and 36.33%, respectively. Patients at goal/not at goal in the 2 subgroups with F, MH, and mS are reported in Figure 1.

LDL-C goal attainment was stratified by TG levels (<100 mg/dL, <100-149 mg/dL, 150-199 mg/dL, and 200-400 mg/dL) and cardiovascular risk categories (intermediate,

Table 1. Baseline features of the population.

	Overall	Without diabetes subgroup	With diabetes subgroup	*P* value
Number	13,834	9616	4218	
Age (years)	68.00 (55.00, 78.00)	65.00 (52.00, 77.00)	72.00 (62.00, 80.00)	< .001
Gender (male)	7908 (57.2)	5224 (54.3)	2684 (63.6)	< .001
BMI (kg/m^2)	25.47 (23.05, 28.41)	25.01 (22.76, 27.77)	26.30 (23.88, 29.41)	< .001
Current smokers	1504 (17.2)	1102 (20.8)	402 (11.6)	< .001
SBP (mmHg)	121.62 (114.12, 130.00)	120.67 (113.33, 128.89)	124.00 (116.43, 132.14)	< .001
DBP (mmHg)	71.41 (67.69, 75.56)	71.43 (67.66, 75.70)	71.35 (67.75, 75.25)	.434
ASCVD	4401 (31.8)	2522 (26.2)	1879 (44.5)	< .001
CKD	4937 (35.7)	2931 (30.5)	2006 (47.6)	< .001
TC (mg/dL)	147.00 (120.75, 176.00)	151.00 (125.00, 179.54)	136.00 (111.00, 165.00)	< .001
HDL-C (mg/dL)	37.00 (29.00, 47.00)	39.00 (30.00, 49.00)	34.00 (27.00, 42.00)	< .001
TG (mg/dL)	110.00 (83.50, 147.00)	106.00 (81.00, 142.00)	119.42 (91.00, 159.00)	< .001
Non–HDL-C (mg/dL)	107.00 (85.00, 132.65)	110.00 (88.50, 135.00)	100.00 (78.00, 126.00)	< .001
LDL-C (F) (mg/dL)	83.80 (63.20, 107.20)	87.80 (67.40, 110.00)	74.20 (54.90, 98.60)	< .001
LDL-C (MH) (mg/dL)	86.20 (66.50, 109.30)	89.80 (70.07, 112.10)	78.50 (59.00, 102.10)	< .001
LDL-C (mS) (mg/dL)	89.30 (69.30, 111.70)	92.90 (73.30, 114.70)	80.70 (62.00, 104.00)	< .001
ΔLDL-C (MH-F) (mg/dL)	1.50 (–0.60, 4.40)	1.10 (–0.73, 3.80)	2.30 (0.00, 5.80)	< .001
ΔLDL-C (mS-F) (mg/dL)	4.80 (3.60, 6.50)	4.50 (3.40, 6.10)	5.50 (4.10, 7.40)	< .001

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; F, Friedewald; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MH, Martin–Hopkins; mS, modified Sampson; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Note: Data are expressed as medians (IQR) for continuous variables and as numbers and relative percentages for categorical variables, and *P* value for group comparison.

Table 2. Pearson correlation between LDL-C values calculated with F, MH, and mS equations.

LDL-C (F) and LDL-C (MH)	r = 0.9900	*P* < .001
LDL-C (F) and LDL-C (mS)	r = 0.9973	*P* < .001
LDL-C (MH) and LDL-C (mS)	r = 0.9972	*P* < .001

Abbreviations: F, Friedewald equation; LDL-C, low-density lipoprotein cholesterol; MH, Martin–Hopkins equation; mS, modified Sampson equation.

high, and very high) in Figures 2 and 3. The percentage of LDL-C goal attainment was significantly lower in patients with diabetes compared with those without across all TG levels, regardless of the formula used ($P < .001$ for all comparisons). Numerically, the use of the MH formula was associated with a greater reduction in the percentage of patients at goal in the diabetes group compared with the nondiabetes group, moving from the lowest to the highest TG levels. The use of MH and mS was associated with a lower LDL-C goal attainment compared with F, both in the diabetes group and the group without diabetes, in the TG strata 100-149 mg/dL, 150-199 mg/dL, and 200-400 mg/dL ($P < .001$ for all the comparisons). In the lowest TG stratum, the same significant difference in LDL-C target categorization was detected between mS and F, whereas the difference between F and MH equations was not significant in patients with diabetes. In contrast, in patients without diabetes, the use of the F equation was associated with lower attainment of the prespecified goal compared with MH ($P < .001$).

Furthermore, individuals with diabetes were significantly less likely to be at goal compared with those without, in all cardiovascular risk categories and regardless of the formula used ($P < .001$ for comparisons). The use of MH and mS led to lower rates of patients at goal, in both the diabetes and nondiabetes groups, compared with F ($P < .001$ for all comparisons).

DTT was significantly higher in the subgroup with diabetes compared with the subgroup without diabetes with all formulas. In the entire population, the median DTT was 9.60 (–13.80, 35.80) mg/dL according to F, 12.70 (–11.30, 38.50) mg/dL with MH, and 15.30 (–7.80, 40.80) mg/dL when LDL-C was assessed with mS (Table 3).

Effects of switch from F to MH and mS on LDL-C target achievement

The majority of patients retained the same classification as that obtained when calculating LDL-C with F. However, the percentage of patients "at goal" (according to F) reclassified as "not at goal" (according to MH) was significantly higher in participants with diabetes compared with those without (5.1% vs 2.8%, $P < .001$). The same was after the switch from F to mS: 8.3% of patients at goal with diabetes became not at goal vs 5.3% of patients without diabetes ($P < .001$). A very small sample of patients not at goal (according to F) was reclassified as at goal (according to MH). The number of these patients was significantly lower in the subgroup with diabetes compared with the nondiabetes subgroup (0.3 vs 0.5%, $P = .03$; Table 4 A). Conversely, no transitions from "not at goal" (according to F) to "at goal" (according to mS) were observed (Table 4 B). DTT increase (ΔDTT) was also significantly greater in individuals with diabetes compared

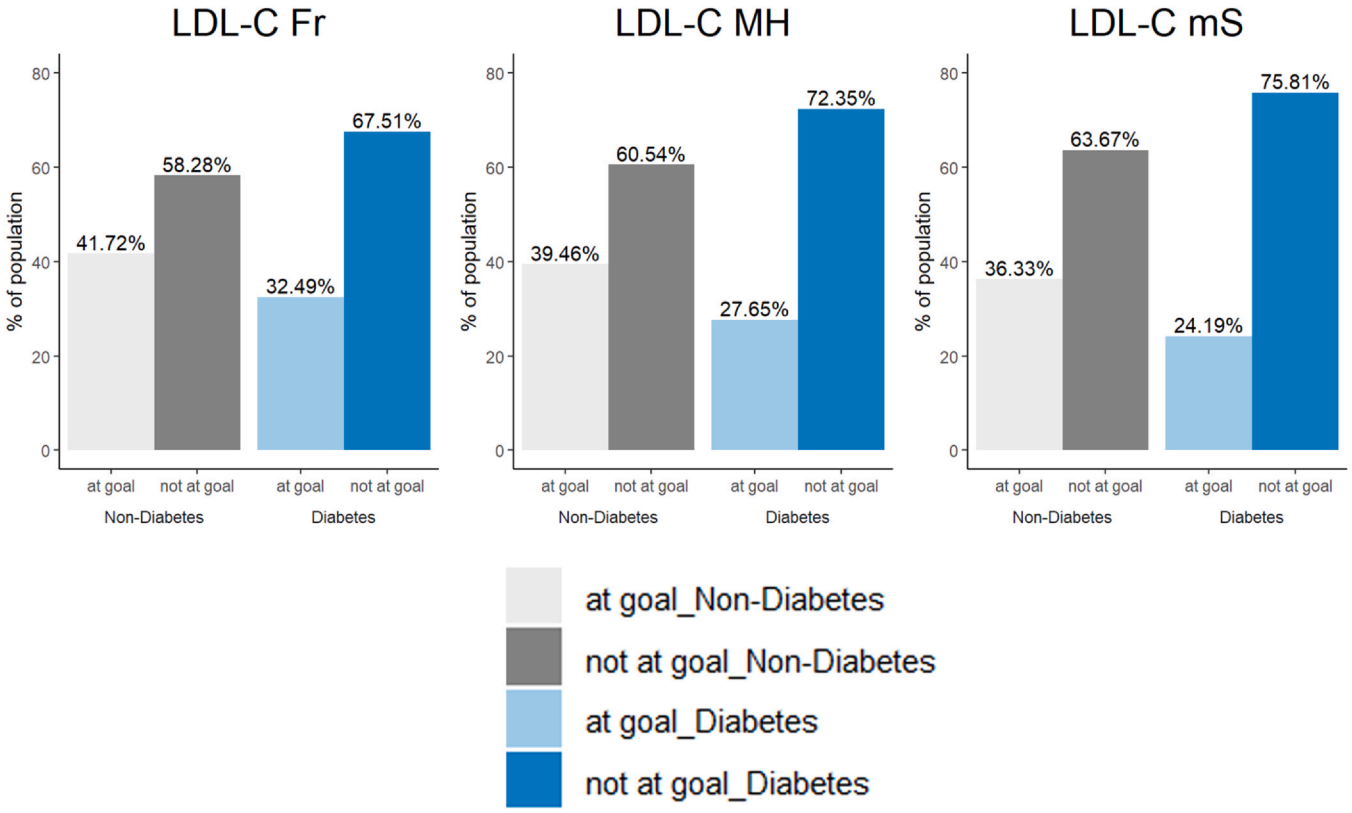

Figure 1. LDL-C goal achievement in diabetes and nondiabetes subgroups with F, MH, and mS. Patients at goal and not at goal are presented as percentages; $P < .001$ for comparison between patients at goal and not at goal in the following groups: subgroup without diabetes with F vs subgroup without diabetes with MH; subgroup with diabetes with F vs subgroup with diabetes with MH; subgroup without diabetes with F vs subgroup without diabetes with mS; subgroup with diabetes with F vs subgroup with diabetes with mS. Abbreviations: F (or Fr), Friedewald equation; LDL-C, low-density lipoprotein cholesterol; MH, Martin–Hopkins equation; mS, modified Sampson equation.

with those without ($P < .001$). This difference was observed after switching to both MH and mS (Table 3).

Discussion

This study showed relevant differences in LDL-C values and goal attainment when using the MH and the mS vs the F, despite a high degree of correlation between the 3, in the study population of hospitalized patients in a real-world setting. The enrolled population was highly heterogeneous, since no restrictive criteria were applied in the selection process (except for adult age), and consisted of patients from the general population admitted to any department of the Fondazione Policlinico Gemelli hospital between January 1, 2021, and August 31, 2022.[21]

LDL-C levels were calculated using F, MH, and mS formulas in patients with available lipid profiles that remained stable throughout hospitalization and were free from analytical interferences. Patients with TG values > 400 mg/dL were excluded, as neither F nor MH is currently recommended in this clinical context,[18] while a consensus is still lacking for mS.

The use of the new formulas was associated with an increase in median LDL-C with a median ΔLDL-C (MH–F) at 1.50 (−0.60, 4.40) mg/dL and a median ΔLDL-C (mS–F) at 4.80 (3.60, 6.50) mg/dL. As already stated, a substantial number of patients were not at goal with F, particularly in the high and very high-risk categories. Overall, an even greater number of patients not at goal emerged after the switch from F to MH and to mS, with a non-negligible number of patients previously considered at goal with F being reclassified as not at goal.

In the context of diabetes, these differences were even more pronounced, as there was a higher median ΔLDL-C (MH–F) and ΔLDL-C (mS–F), with a greater number of patients not at goal. Furthermore, the percentage of patients at goal with F reclassified as not at goal with MH and mS was nearly twice as high in patients with diabetes compared with those without. A higher increase in DTT (ΔDTT) was observed in the subgroup with diabetes.

Individuals with diabetes exhibit a high prevalence of "atherogenic dyslipidemia", a lipid abnormality characterized by elevated plasma levels of fasting and postprandial TG-rich lipoproteins (TRLs), an increased presence of small, dense LDL particles, and reduced levels of HDL-C.[22,23] In insulin-resistant states, TRL metabolism becomes

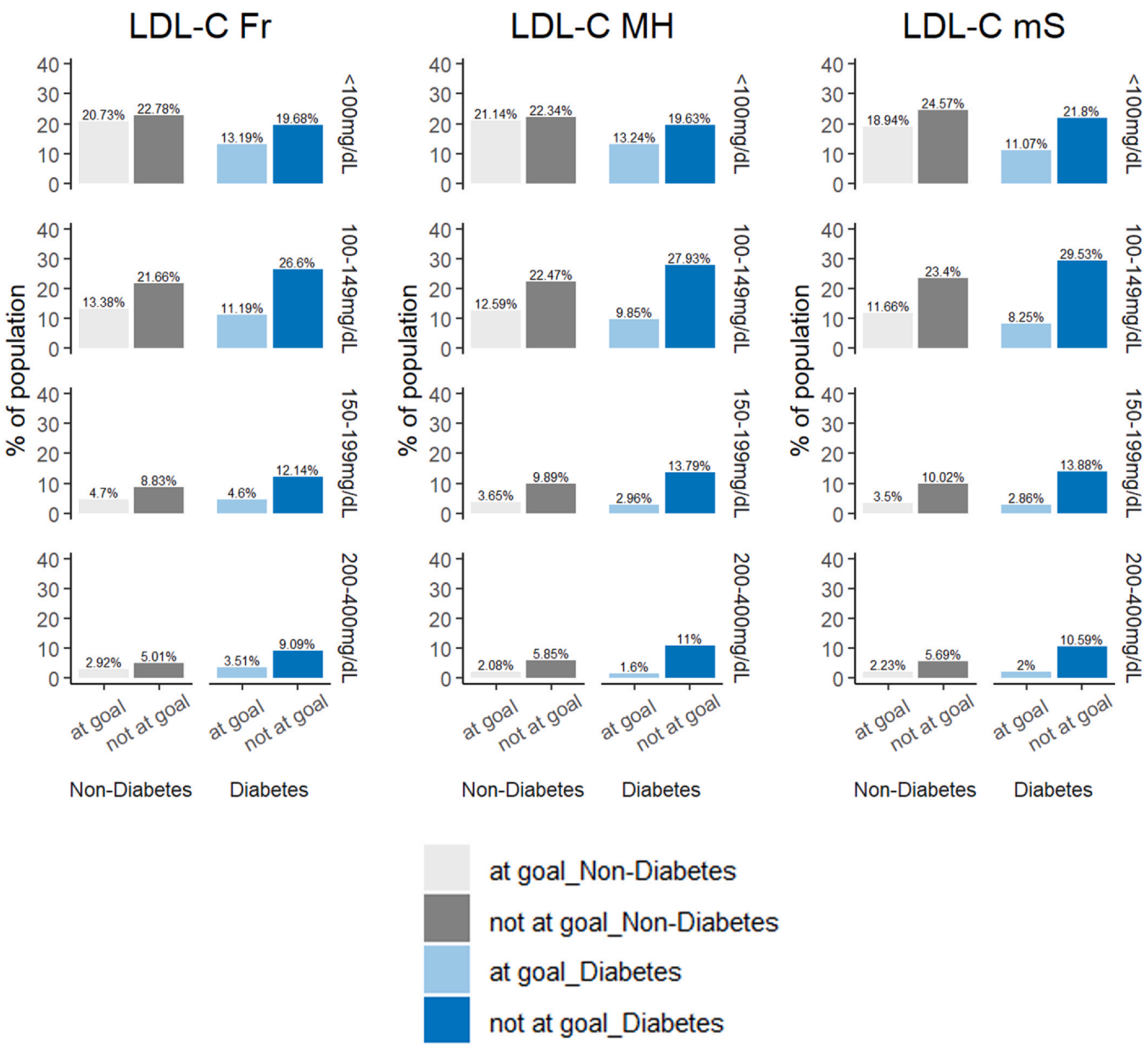

Figure 2. LDL-C goal achievement in diabetes and nondiabetes groups, according to triglyceride strata. Patients at goal and not at goal are presented as percentages. In the triglyceride class < 100 mg/dL, $P < .001$ for comparison between patients at goal and not at goal in the subgroup without diabetes with F vs the subgroup without diabetes with MH; nonsignificant for comparison between the diabetes subgroup with F vs the diabetes subgroup with MH; $P < .001$ for comparison between the subgroup without diabetes with F vs the subgroup without diabetes with mS and for the subgroup with diabetes with F vs the subgroup with diabetes with mS. In the triglyceride strata 100-149 mg/dL, 150-199 mg/dL, and 200-400 mg/dL, $P < .001$ for comparison between on-target/off-target patients in the following groups: subgroup without diabetes with F vs subgroup without diabetes with MH; subgroup with diabetes with F vs subgroup with diabetes with MH; subgroup without diabetes with F vs subgroup without diabetes with mS; subgroup with diabetes with F vs subgroup with diabetes with mS. Abbreviations: F (or Fr), Friedewald equation; LDL-C, low-density lipoprotein cholesterol; MH, Martin–Hopkins equation; mS, modified Sampson equation.

dysregulated, involving multiple interconnected metabolic abnormalities.[24] VLDL particles, the main TRLs synthesized by the liver, are produced in response to the uptake of free fatty acids from adipose tissue depots. In this complex scenario, both the overproduction and delayed clearance of TRL and their remnants contribute to their accumulation.[25] These remnants, including chylomicron and VLDL remnants, contain a markedly higher cholesteryl ester content per particle—approximately 40 times higher than LDL—thereby substantially increasing their atherogenic potential.[26] Furthermore, cholesteryl ester transfer protein (CETP) promotes TG enrichment of HDL particles (facilitating their accelerated catabolism). CETP also enriches LDLs, making them a better substrate for hepatic lipase and

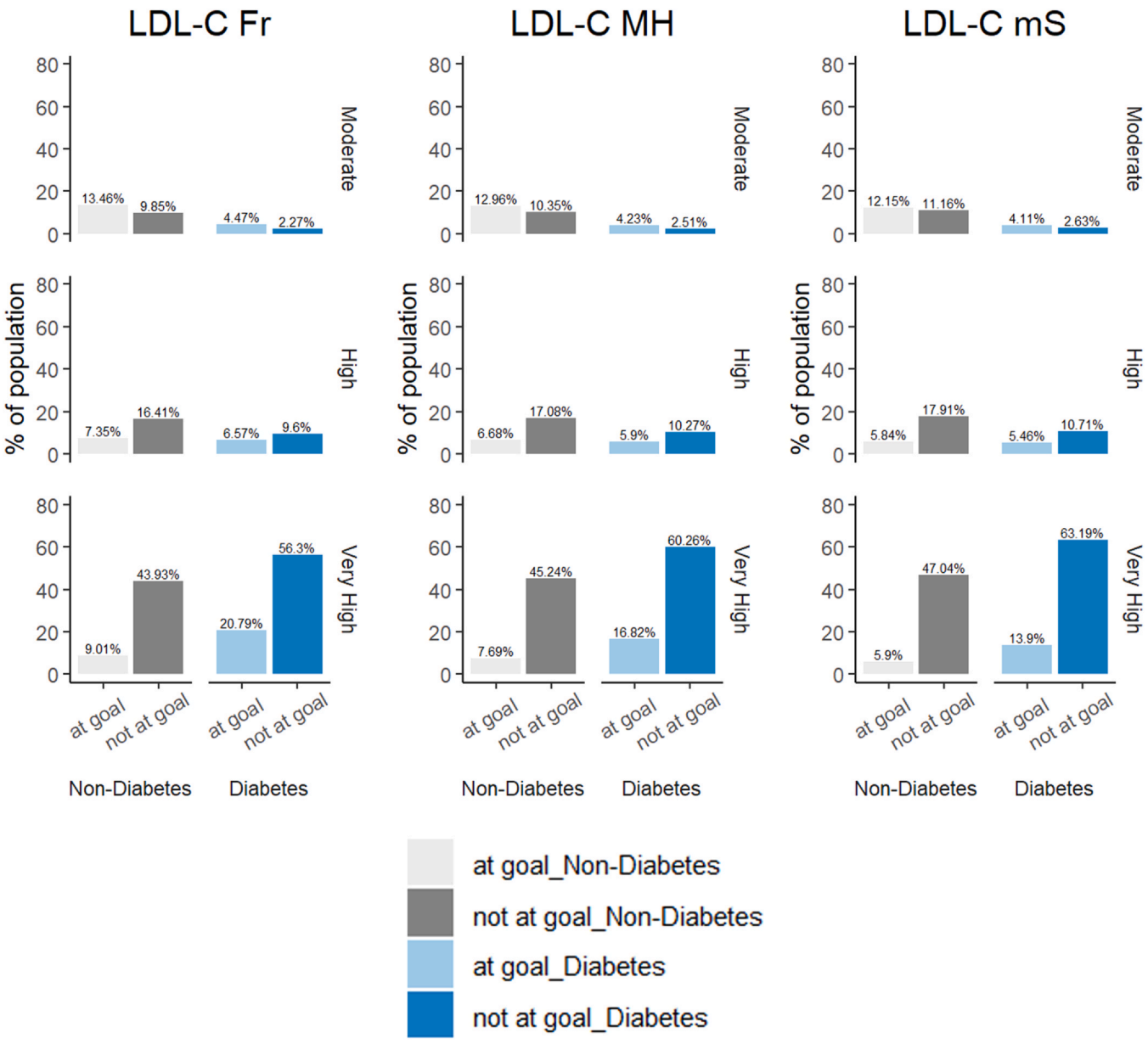

Figure 3. LDL-C goal achievement in diabetes and nondiabetes groups, according to cardiovascular (CV) risk category strata. Patients at goal and not at goal are presented as percentages. In the M, H, and VH CV risk categories, $P < .001$ for comparison between patients at goal and not at goal in the following groups: subgroup without diabetes with F vs subgroup without diabetes with MH; subgroup with diabetes with F vs subgroup with diabetes with MH; subgroup without diabetes with F vs subgroup without diabetes with mS; subgroup with diabetes with F vs subgroup with diabetes with mS. Abbreviations: F (or Fr), Friedewald equation; H, high; LDL-C, low-density lipoprotein cholesterol; M, moderate; MH, Martin–Hopkins equation; mS, modified Sampson equation; VH, very high.

Table 3. Distance to target (DTT) in diabetes and nondiabetes with F, MH, and mS.

	Overall	Nondiabetes	Diabetes	*P* value
DTT (F) (mg/dL)	9.60 (–13.80, 35.80)	7.50 (–18.00, 34.60)	13.20 (–6.30, 38.60)	< .001
DTT (MH) (mg/dL)	12.70 (–11.30, 38.50)	9.80 (–15.70, 36.80)	17.50 (–2.40, 42.20)	< .001
DTT (mS) (mg/dL)	15.30 (–7.80, 40.80)	12.60 (–12.50, 39.30)	19.70 (0.50, 44.20)	< .001
ΔDTT (MH-F) (mg/dL)	1.50 (–0.60, 4.50)	1.10 (–0.70, 4.00)	2.30 (0.00, 5.80)	< .001
ΔDTT (mS-F) (mg/dL)	4.90 (3.60, 6.50)	4.60 (3.40, 6.10)	5.50 (4.10, 7.40)	< .001

Abbreviations: F, Friedewald equation; LDL-C, low-density lipoprotein cholesterol; MH, Martin–Hopkins equation; mS, modified Sampson equation.

Note: DTT is presented as median (IQR), ΔDTT for subtraction of median LDL-C(F) from median LDL-C(MH) and LDL-C(mS), and *P* value for comparison between nondiabetes and diabetes.

Table 4. Reclassification of patients (at goal vs not at goal): (A) after the switch from Friedewald to Martin–Hopkins; (B) after the switch from Friedewald to modified Sampson.

(A)

Friedewald → Martin–Hopkins	Classification persistence	Overall	Nondiabetes	Diabetes	*P* value
not at goal → not at goal	classification unchanged	60.7%	57.7%	67.2%	< .001
not at goal → at goal	classification changed	0.5%	0.5%	0.3%	.03
at goal → not at goal	classification changed	3.5%	2.8%	5.1%	< .001
at goal → at goal	classification unchanged	35.3%	38.9%	27.4%	< .001

(B)

Friedewald → modified Sampson	Classification persistence	Overall	Nondiabetes	Diabetes	*P* value
not at goal → not at goal	classification unchanged	61.1%	58.3%	67.5%	< .001
not at goal → at goal	classification changed	0%	0%	0%	NA
at goal → not at goal	classification changed	6.3%	5.3%	8.3%	< .001
at goal → at goal	classification unchanged	32.6%	36.4%	24.2%	< .001

Data are presented as percentages; *P* value for comparison between nondiabetes and diabetes.
Abbreviation: NA, not applicable.

leading to the production of smaller and more atherogenic LDL particles.[22,23] In conclusion, a higher proportion of TGs in VLDL particles and other lipoproteins is generally observed in diabetes. Therefore, individuals with diabetes are expected to have a higher TG/VLDL-C ratio.

In this study, patients who were reclassified from "at goal" to "not at goal" (indicating a higher LDL-C value when calculated using the MH and the mS compared with the F) had a higher TG/VLDL-C ratio, according to the corresponding strata of the MH table and the terms obtained by least-squares regression analysis of the mS equation. The main limitation of the F formula is the assumption of a fixed TG/VLDL-C ratio, which reduces accuracy in cases of low LDL-C and high TGs. TG/VLDL-C ratio is not a fixed parameter, and it is likely influenced by genetic factors and patient-specific clinical features, including the presence or absence of diabetes.

By incorporating a more accurate calculation of VLDL-C, these novel approaches to LDL-C estimation provide a significant advantage over the F formula and represent a step towards a more personalized and patient-centered medicine. These formulas could prevent both underestimation and overestimation of cardiovascular risk, with possible implications for therapeutic choices. Notably, the underestimation of cardiovascular risk remains a critical challenge, as it may leave high-risk patients undertreated. In this perspective, the use of the novel formulas significantly reduces this risk. Our data show that only 0.3% of patients with diabetes and 0.5% of those without were reclassified from "not at goal" to "at goal" following implementation of the MH equation. In contrast, a greater proportion of individuals who were previously classified as "at goal" were reclassified as "not at goal", as described above. The use of the mS equation eliminated the risk of underestimation in this population, as no patients categorized as "not at goal" by F were found to be "at goal" when using mS. This likely makes mS the safer option in this clinical context. Furthermore, patients with higher ΔLDL-C (defined as the difference between MH or mS and F) typically present with higher TGs, thus also carrying the additional risk related to the higher prevalence of remnant lipoproteins. In these cases, therefore, a comprehensive management of all cardiovascular risk factors is necessary, and a more accurate LDL-C estimate may help reduce inappropriate treatments. Previous studies have shown lower concordance between directly measured and calculated remnant cholesterol than that currently observed for LDL-C. Remnant cholesterol is calculated by subtracting LDL-C from non–HDL-C; therefore, inaccuracies in the LDL-C calculation directly affect remnant values. This is particularly relevant given the growing interest in their role in atherosclerosis.[27]

Accurate LDL-C estimation may thus represent an additional challenge for clinicians aiming to manage cardiovascular risk in patients.[28] The 2019 update of ESC/EAS guidelines[10] introduced new, more ambitious LDL-C goals, recently confirmed in the 2025 update,[11] since meta-analyses have demonstrated the reduction of coronary heart disease death and major adverse cardiovascular events connected to the reduction of LDL-C in high-risk patients.[28] A linear relationship between LDL-C reduction and a lower incidence of cardiovascular events has also been demonstrated in patients with diabetes.[6] However, retrospective registries have revealed suboptimal rates of LDL-C goal attainment in outpatients affected by diabetes, with only modest improvements in recent years, probably associated with the gradual increase in lipid-lowering therapies (such as high-intensity statins, statin–ezetimibe combination therapy,[21] and PCSK9 inhibitors).[29]

Our study demonstrated that discrepancies in LDL-C calculation are more pronounced in patients with diabetes. Higher TG levels, together with lower non–HDL-C levels (likely due to the more frequent use of lipid-lowering therapies), are associated with a generally higher TG/VLDL-C ratio and a higher DTT increase (ΔDTT) when using a novel validated equation characterized by better concordance with the reference BQ method. Using the F formula, clinicians have a greater likelihood of

underestimating cardiovascular risk, making it a less reliable option in the general population, particularly among individuals affected by diabetes.

In conclusion, these findings underscore the importance of accurate LDL-C estimation methods for effective cardiovascular risk management.

Limitations and strengths

This study has several limitations. First, as it retrospectively evaluated hospitalized patients, data on direct LDL-C measurements via BQ were not available. Consequently, we could not assess which of the novel validated estimating equations has the best concordance with the gold standard for direct LDL-C measurement in this population. As a result, a direct comparison between MH and mS is beyond the scope of this research. However, extensive literature has already demonstrated the superior concordance of MH and mS with direct LDL-C compared with F, making additional confirmation from this dataset redundant.[15,18–20,30–33] This allowed us to focus on indirect comparisons between the 2 novel equations and the F formula. Second, another important limitation of this study is the cross-sectional design. While these findings could suggest the inferiority of the F formula in terms of safety, the study design does not permit the establishment of possible causality between LDL-C (MH) and LDL-C (mS) and cardiovascular events or mortality. Thus, further research is needed to determine whether more accurately estimated LDL-C values calculated with MH and mS (and generally higher than those assessed with F) are proportionally associated with events (or with a reduction due to prompt treatment intensification). Third, the inclusion of severely ill patients could have overestimated goal attainment, as discussed in our prior analysis.[21] Furthermore, we acknowledge that the binary classification of patients into diabetes and nondiabetes subgroups does not capture the heterogeneity of diabetes or the prediabetic state, nor the possible correlations between different degrees of insulin deficiency and/or resistance and lipid parameters. Unfortunately, a more detailed metabolic characterization is not easily available in population-based studies.

This study also has several strengths. First, we used advanced data extraction strategies through the implementation of Dyslipidaemia Data Mart, a patient-centered data repository that extracts, integrates, and validates data from multiple sources, thereby minimizing errors and ensuring high-quality patient characterization. This approach allowed an in-depth analysis of a large and valuable sample size. Second, since no restrictive criteria were applied, these findings have a high generalizability and reproducibility. While previous studies primarily focused on highly selected cohorts already receiving secondary or tertiary care, this study assessed an entire population in a real-world setting, thereby highlighting significant gaps in LDL-C target achievement without the influence of inclusion bias. To our knowledge, this is the first study to compare 3 LDL-C estimation methods in relation to LDL-C goal attainment in the general population, and specifically among inpatients in a real-world setting. In addition, all lipid measurements were performed in the same laboratory, eliminating potential discrepancies in TC, HDL-C, and TG measurements that can arise using different methods. Further, through the implementation of 2 different validated equations, our results highlight a measurable risk of LDL-C goal achievement overestimation when LDL-C is assessed with the F, which is higher in individuals with diabetes compared with those without. Therefore, these findings provide a compelling rationale for moving beyond the traditional LDL-C estimation method.

Conclusions

Accurate estimation of LDL-C remains a cornerstone in cardiovascular risk stratification and the management of patients, especially those in the higher risk categories, such as individuals with diabetes. Our findings show that the choice of LDL-C estimation method can substantially affect the proportion of patients classified as meeting or missing recommended LDL-C goals. The choice of formula can, therefore, have a significant impact not only on goal attainment but also on subsequent therapeutic decisions.

In the era of personalized medicine, the MH and the mS approaches align better with the need for tailored risk management strategies, minimizing the likelihood of misclassification. In our analysis of an entire population of inpatients, the 2 novel validated estimating equations identified a larger proportion of patients as being at goal compared with the F equation, and the percentage of patients was even higher in the subgroup of patients with diabetes compared with the subgroup without. Similarly, patients with diabetes showed a greater increase in DTT following the transition from the traditional formula to the new ones.

Future prospective studies are needed to validate these findings and to explore whether the use of the MH and the mS equations in routine clinical practice leads to reduced cardiovascular events and mortality, particularly among patients with diabetes.

CRediT authorship contribution statement

Umberto Capece: Writing – original draft, Conceptualization. **Chiara Iacomini:** Methodology, Data curation. **Cassandra Morciano:** Conceptualization. **Shawn Gugliandolo:** Conceptualization. **Amelia Splendore:** Conceptualization. **Alfredo Cesario:** Methodology. **Carlotta Masciocchi:** Methodology. **Gianfranco Di Giuseppe:** Investigation. **Gea Ciccarelli:** Investigation. **Adriana Avolio:** Conceptualization. **Michela Brunetti:** Data curation. **Laura Soldovieri:** Data curation. **Francesca Cinti:** Investigation. **Teresa Mezza:** Investigation. **Stefano Patarnello:** Methodology. **Andrea Giaccari:** Writing – review & editing. **Nicoletta Di Giorgi:** Writing – review & editing, Data curation.

Ethical approval

The study protocol conforms to the ethical guidelines of the 1975 Helsinki Declaration and was approved by the Ethics Committee of the Fondazione Policlinico Gemelli Hospital (prot. no. 16832/23). The study used anonymous data, and, according to national and European regulations, a waiver was applied to the requirement for patient-informed consent.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that they did not use AI for the preparation and editing of this manuscript, and they take full responsibility for the content of the publication.

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Declaration of competing interest

The authors declare that they have no competing interests or personal relationships that could have influenced the work reported in this paper.

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