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COMPARATIVE ACCURACY OF LDL-CHOLESTEROL ESTIMATION: A META-ANALYSIS OF THE FRIEDEWALD AND MARTIN-HOPKINS EQUATION

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СРАВНИТЕЛНА ТОЧНОСТ НА ОЦЕНКАТА НА LDL ХОЛЕСТЕРОЛА: МЕТААНАЛИЗ НА УРАВНЕНИЕТО НА ФРИДЕВАЛД И МАРТИН-ХОПКИНС

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Abstract. **Introduction:** Low-density lipoprotein cholesterol (LDL-C) is a cornerstone biomarker for cardiovascular risk. The Friedewald formula has long been the standard for estimating LDL-C, however, it has limitations, particularly in patients with hypertriglyceridemia or low LDL-C levels. Several alternative equations, including the Martin–Hopkins (M/H) and Sampson formulas, have been developed to improve accuracy. Among them, M/H has gained recognition for its performance in specific populations, but it represents only one of several refined methods used across professional communities. This study aimed to perform a meta-analysis comparing the accuracy and precision of the Friedewald and M/H formulas in diverse populations, acknowledging that other approaches also exist. **Methods:** A systematic review of articles published between 2018 and 2024 was conducted using PubMed, Embase, Scopus (Elsevier), and Web of Science-eligible studies directly compared both formulas against direct LDL-C measurement in adult populations. A random-effects model was used to pool mean absolute errors (MAEs), root mean square errors (RMSEs), correlation coefficients, and p-values. Heterogeneity was assessed using the I^2 statistic. Results: Eight novel studies, involving a total of 192,094 participants, were included. The M/H formula showed significantly lower MAE (3.6 mg/dL vs. 8.4 mg/dL, $p < 0.001$), lower RMSE (5.1 mg/dL vs. 9.8 mg/dL, $p < 0.001$), and a stronger correlation with direct LDL-C ($r = 0.92$ vs. $r = 0.84$) compared to the Friedewald formula. The superiority of the M/H formula was especially evident in patients with triglycerides >200 mg/dL or LDL-C <70 mg/dL. **Conclusion:** The M/H formula provides more accurate and precise LDL-C estimation than Friedewald, particularly in clinically vulnerable groups. However, it should be considered one of several improved approaches, alongside other equations such as Sampson, which may perform better in certain populations. M/H can be recommended as a strong option, but is not the sole alternative for routine lipid profiling.

Key words: LDL cholesterol, Friedewald formula, Martin-Hopkins formula, cardiovascular risk, lipid profile, triglycerides, meta-analysis

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Резюме. **Въведение:** Холестеролът с ниска плътност (LDL-C) е основен биомаркер за сърдечно-съдовия риск. Формулата на Фридевалд отдавна е стандарт за оценка на LDL-C, но има ограничения, особено при пациенти с хипертриглицеридемия или ниски нива на LDL-C. За подобряване на точността са разработени няколко алтернативни уравнения, включително формулите на Мартин-Хопкинс (M/H) и Сампсън. Сред тях M/H е спечелила признание за ефективността си при конкретни популации, но тя представлява само една от няколкото усъвършенствани методи, използвани в професионалните среди. Целта на това проучване беше да се извърши метаанализ, сравняващ точността и прецизността на формулите на Friedewald и M/H при различни популации, като се отчита, че съществуват и други подходи. **Методи:** Беше проведен систематичен преглед на статии, публикувани между 2018 и 2024 г., като се използваха PubMed, Embase, Scopus (Elsevier) и Web of Science – проучвания, които отговаряха на критериите, директно сравняваха двете формули с директното измерване на LDL-C при възрастни популации. Използва се модел с произволни ефекти за обединяване на средните абсолютни грешки (MAE), средноквадратичните грешки (RMSE), корелационните коефициенти и p-стойностите. Хетерогенността беше оценена с помощта на статистиката I^2. **Резултати:** Бяха включени осем нови проучвания с общо 192 094 участници. Формулата M/H показа значително

по-ниска MAE (3,6 mg/dL спрямо 8,4 mg/dL, p < 0,001), по-ниска RMSE (5,1 mg/dL спрямо 9,8 mg/dL, p < 0,001) и по-силна корелация с директния LDL-C (r = 0,92 спрямо r = 0,84) в сравнение с формулата на Friedewald. Превъзходството на формулата M/H беше особено очевидно при пациенти с триглицериди > 200 mg/dL или LDL-C < 70 mg/dL. **Заключение:** Формулата M/H осигурява по-точна и прецизна оценка на LDL-C в сравнение с Friedewald, особено при клинично уязвими групи. Тя обаче трябва да се разглежда като един от няколко подобрени подхода, наред с други уравнения като Sampson, които могат да дадат по-добри резултати при определени популации. M/H може да се препоръча като силна опция, но не е единствената алтернатива за рутинно профилиране на липидите.

Ключови думи: LDL холестерол, формула на Фридевалд, формула на Мартин-Хопкинс, сърдечно-съдов риск, липиден профил, триглицериди, метаанализ

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Introduction

Low-density lipoprotein cholesterol (LDL-C) is an established risk factor for cardiovascular disease (CVD) and a target for lipid-lowering therapy [1, 2]. LDL-C is typically not measured directly but is estimated using the Friedewald formula, which assumes a fixed ratio for the triglycerides (TG) to very low-density lipoprotein cholesterol (VLDL-C). However, this assumption is sometimes not valid. The Martin/Hopkins (M/H) formula estimates LDL-C using an adjustable factor for the TG: VLDL-C ratio and is expected to improve upon Friedewald when predicting measured LDL-C and apolipoprotein B (ApoB), one molecule of which is associated with an LDL particle. LDL-C estimation plays a vital role in cardiovascular disease (CVD) prevention, diagnosis, and management. The Friedewald formula, introduced in 1972, remains widely used due to its simplicity and ease of application. However, it has known limitations, particularly in individuals with hypertriglyceridemia or low LDL-C levels [3, 4, 5, 6].

LDL cholesterol (LDL-C) plays a central role in lipid management and cardiovascular disease prevention strategies. Traditionally, the Friedewald equation has estimated LDL-C using total cholesterol, high-density lipoprotein (HDL-C), and triglycerides (TG).

Friedewald Equation: LDL-C = Total cholesterol – HDL-C – (Triglycerides/5)

The Friedewald (FW) formula is known to have additional limitations at the extremes of triglyceride concentrations: it tends to be unreliable when triglycerides (TG) exceed 400 mg/dL, as well as at low TG levels below 150 mg/dL [7]. These limitations may result in inaccurate LDL-C estimation and misclassification of cardiovascular risk. A novel method, the M/H formula, developed in 2013, uses a stratified, individualized factor for VLDL-C based on TG and non-HDL-C, offering improved precision.

Martin–Hopkins Equation: LDL-C = Total cholesterol – HDL-C – (Triglycerides/Adjustable factor)

Instead of using a single divisor of 5 for all patients (as in FW), Martin and colleagues created a 180-cell table (also referred to as the strata table) based on: Triglyceride (TG) concentration and Non-HDL cholesterol (non-HDL-C). Each cell in the table gives a specific TG: VLDL-C ratio derived from a large database (> 1.3 million lipid profiles). This ratio is used as the adjustable factor for that specific lipid combination. While a “free” online calculator (Excel-based) is available to automatically compute LDL-C in mg/dL using the M/H formula, challenges remain in integrating this method into laboratory information systems (LIS) in a way that supports automated calculation in mg/dL or mmol/L, limiting its immediate accessibility in some clinical laboratories. In response to these limitations, the Martin–Hopkins method, developed at Johns Hopkins University, utilizes an adjustable factor for estimating very-low-density lipoprotein cholesterol (VLDL-C), thereby enhancing precision. This method has been integrated into several clinical laboratories and electronic medical record systems over the past few years. The M/H formula was the first to demonstrate consistent and clinically meaningful advantages over the FW formula by using an individualized, adjustable factor for VLDL-C derived from triglyceride and non-HDL-C levels. While the FW formula remains the standard in many laboratories due to its simplicity, M/H has demonstrated superior accuracy, particularly in patients with hypertriglyceridemia, low LDL-C, or nonfasting conditions [8, 9]. Over the years, more than 23 alternative equations for LDL-C estimation have been proposed, including population-specific and more recent approaches such as the NIH-Sampson equation. These methods differ in how they estimate the triglyceride-to-VLDL-C conversion, use non-HDL-C, or incorporate apolipoprotein B. The choice of formula is not universal and varies across laboratories and clinical settings, depending on feasibility, local guidelines, and patient population. These approaches differ in their assumptions about triglyceride-to-VLDL-C conversion, adjustments for non-HDL-C, or popula-

tion-specific calibration, reflecting ongoing efforts to improve estimation accuracy [10].

This meta-analysis focuses on comparing the Friedewald and Martin-Hopkins formulas against direct LDL-C measurements to evaluate accuracy and precision across diverse populations, while acknowledging that other alternative formulas exist.

Methods

Search Strategy and Study Selection

A comprehensive literature search was conducted across PubMed, Embase, Scopus (Elsevier), and Web of Science databases using the following keywords: "LDL cholesterol estimation," "Friedewald formula," "Martin-Hopkins equation," "direct LDL-C measurement," and "LDL-C accuracy." Studies published between 2018 and 2024 were considered for inclusion.

Eligible studies met the following criteria:

- Published in peer-reviewed journals
- Conducted in adult populations (≥ 18 years)
- Included a direct comparison of both the FW and M/H formulas with directly measured LDL-C
- Reported quantitative performance metrics such as mean absolute error (MAE) or correlation coefficients
- Sample size of at least 300 participants

Statistical Analysis

All statistical analyses were performed using RevMan version 5.4 and STATA version 17.0. The primary outcome measures were pooled Mean Absolute Error (MAE), Root Mean Squared Error (RMSE), and correlation coefficients (r) comparing LDL-C values estimated by the Friedewald and Martin–Hopkins formulas against directly measured LDL-C values. Correlation coefficients were transformed using Fisher's Z transformation for meta-analysis and then back-transformed for interpretation. A random-effects model was applied throughout to account for heterogeneity across studies. Between-study heterogeneity was quantified using the I^2 statistic, with values above 50% indicating moderate to substantial heterogeneity. Subgroup analyses were performed to explore formula performance in specific clinical contexts, including LDL-C levels < 70 mg/dL, triglycerides > 200 mg/dL, and nonfasting states. Potential publication bias was assessed using Egger's regression test. For accuracy metrics (MAE and RMSE), values were extracted directly from the included studies whenever reported. When not explicitly provided, MAE and RMSE were calculated from the published summary data (mean differences and standard deviations). Pooled estimates in Table 1 represent weighted averages derived through random-effects meta-analysis across all eight studies.

Data Extraction and Quality Assessment

The reviewer extracted key information from each study, including: first author, year of publication, sample size, mean age, triglyceride levels or ranges, LDL-C measurement method, and statistical outcomes (MAE, RMSE, correlation coefficients). Any discrepancies were resolved through consensus. The methodological quality of each included study was assessed using the Newcastle–Ottawa Scale (NOS). All selected studies achieved a minimum score of 7, indicating moderate to high quality.

Results

Study characteristics

The meta-analysis included eight studies with a total of 192,094 participants, directly comparing the Friedewald and Martin-Hopkins formulas against measured LDL-C. Table 1 presents the Pooled accuracy metrics for Friedewald and Martin–Hopkins formulas compared with directly measured LDL-C. Values represent pooled estimates derived from eight included studies using random-effects meta-analysis. The Martin-Hopkins formula consistently outperformed the Friedewald formula across all primary metrics: the pooled MAE was 3.6 mg/dL versus 8.4 mg/dL for Friedewald, and the pooled RMSE was 5.1 mg/dL versus 9.8 mg/dL. The pooled correlation coefficient for Martin-Hopkins (r = 0.92) was higher than Friedewald (r = 0.84), indicating a stronger linear association with directly measured LDL-C values. Differences were statistically significant ($p < 0.001$). By specifying the source studies and sample sizes, we ensure transparency and allow readers to assess the robustness and generalizability of the pooled metrics. Subgroup analyses further confirmed that the Martin-Hopkins formula maintains superior performance in clinically relevant contexts,

Table 1. Pooled accuracy metrics for Friedewald and Martin–Hopkins formulas compared with directly measured LDL-C. Values represent pooled estimates derived from eight included studies using random-effects meta-analysis.

Formula	MAE (mg/dL)	RMSE (mg/dL)	Correlation (r, 95% CI)	p-value
Friedewald	8.4 (7.2-9.6)	9.8 (9.71-9.89)	0.84 (0.81-0.87)	< 0.001
Martin–Hopkins	3.6 (2.9-4.3)	5.1 (5.06-5.15)	0.92 (0.90-0.94)	< 0.001

including triglycerides > 200 mg/dL, LDL-C < 70 mg/dL, and nonfasting samples. Individual study data are presented in Table 2.

Subgroup Analyses

In subgroup analyses, the Martin–Hopkins formula maintained superior performance across clinically relevant contexts:

- LDL-C < 70 mg/dL: The Martin–Hopkins method exhibited lower estimation error, minimizing misclassification in high-risk patients.
- Triglycerides > 200 mg/dL: Performance of the Friedewald formula deteriorated significantly, while Martin–Hopkins maintained accuracy.
- Nonfasting samples: The Martin–Hopkins method remained robust, supporting its utility in real-world, nonfasting conditions.

Heterogeneity and Publication Bias

Moderate between-study heterogeneity was observed ($I^2 = 66\%$), likely due to differences in population characteristics, LDL-C assay methods, and triglyceride distribution across studies. Nevertheless, the direction and magnitude of the effect were consistent, supporting the robustness of the pooled findings. Egger's test did not indicate significant publication bias ($p > 0.10$), suggesting that the overall effect estimates were unlikely to be influenced by selective reporting. Across all evaluated studies, the Martin–Hopkins formula provided more accurate and consistent LDL-C estimates than the Friedewald equation. This was particularly evident in populations with elevated triglycerides, low LDL-C concentrations, or metabolic disturbances such as diabetes. These results support broader clinical adoption of the Martin–Hopkins equation for routine LDL-C estimation, particularly in patients at higher cardiovascular risk.

Across all studies, the Martin-Hopkins formula generally demonstrated lower estimation errors and stronger agreement with directly measured LDL-C values compared to the Friedewald formula. Notably, in populations with elevated triglycerides, low LDL-C levels, or diabetes, Martin-Hopkins consistently provided more precise LDL-C estimates, which are critical for accurate cardiovascular risk stratification and treatment decisions. Some variability was observed, for example, that while the Martin-Hopkins formula had a smaller mean difference, the Fried Ewald equation exhibited a slightly higher correlation coefficient. This highlights that multiple performance metrics (MAE, RMSE, correlation) should be considered when interpreting formula

Table 2. Summarizes the key findings from the eight studies included in this meta-analysis

Study (year)	n	Key findings
Swapna et al. (2024)	400	Although M/H generally outperformed FW, this study reported a higher correlation for FW. This underscores the need to interpret multiple statistical metrics rather than a single measure.
Dintshi et al. (2022)	1247	Both the M/H and FW formulas show a strong correlation with directly measured LDL-C levels in the general population. However, in the South African diabetic group, the M/H equation performed better across all LDL-C ranges-especially at lower levels around 55 mg/dL and in cases of hypertriglyceridemia at 150 mg/dL. Our results indicate that the M/H formula provides more precise LDL-C estimates than the FW formula.
Alpdemir et al. (2024)	6297	The M/H formula demonstrated significantly greater accuracy in predicting LDL-C levels. While the FW formula is simple and easy to recall, the M/H method can now be conveniently applied without the need for extra software, due to improvements in laboratory information systems
Ferrinho et al. (2021)	1689	The M/H formula showed strong performance and broad applicability, outperforming the FW formula- particularly in cases with LDL-C values below 100 mg/dL, as well as in individuals with diabetes or hypertriglyceridemia.
Song et al. (2021)	129,985	M/H equation presents a potentially cost-effective substitute for direct LDL-C measurement and can be easily implemented in clinical laboratories, regardless of whether dyslipidemia is present. In the Korean adult population, where mild-to-moderate hypertriglyceridemia is relatively common, this formula may offer the most accurate approach for estimating LDL-C levels.
Zafrir et al. (2020)	10,006	The M/H formula showed a notable tendency to reclassify patients into higher LDL-C categories compared to the FW formula, especially among individuals with high triglyceride levels and low LDL-C groups, for whom precise LDL-C estimation is particularly important.
Reiber et al. (2022)	14,906	The FW equation often underestimates LDL-C levels in patients classified as high or very high risk. Our analysis confirms that, in the Hungarian population, the M/H formula-validated against the beta-quantification method, provides more accurate LDL-C estimates than the FW formula.
Martin et al. (2018)	27,564	Among patients reaching low LDL-C levels through PCSK9 inhibitor therapy, the M/H formula provides LDL-C estimates that more closely align with the gold standard preparative ultracentrifugation (PUC) compared to the FW method. By avoiding the underestimation seen with Friedewald's formula, the M/H method may help reduce the risk of undertreatment.

accuracy. Overall, the evidence supports the superior performance of Martin-Hopkins in diverse clinical and demographic settings, reinforcing its potential utility in routine laboratory practice.

Discussion

This meta-analysis of eight studies, including more than 192,000 participants, demonstrates that the Martin–Hopkins equation provides significantly improved accuracy compared to the traditional Friedewald formula for LDL-C estimation. Across populations with normolipidemia, diabetes, hypertriglyceridemia, and low LDL-C, the M/H formula consistently showed lower mean absolute errors, reduced root mean squared errors, and stronger concordance with direct LDL-C measurements. These findings highlight the clinical importance of accurate LDL-C estimation for risk stratification and therapeutic decision-making in cardiology. Nevertheless, LDL-C estimation is a dynamic and evolving field. More than 23 alternative formulas have been published to address the limitations of FW, including the Sampson method [11]. Among these, the M/H equation, introduced in 2013, was the first to demonstrate clear, clinically validated superiority through individualized adjustment of the VLDL-C factor based on triglycerides and non-HDL-C [12]. However, its reliance on lookup tables or electronic tools can pose barriers to integration into laboratory information systems (LIS). The NIH-Sampson equation, developed in 2020 and validated in over 250,000 samples, offers comparable or superior accuracy to M/H, particularly at low LDL-C and elevated triglycerides. An enhanced version that incorporates apolipoprotein B further refines estimation [10]. Unlike M/H, the Sampson equations can be directly programmed into LIS without reference tables, facilitating broad implementation. These methods have already been adopted by major laboratories and are recommended by national guidelines in Canada, Mexico, Poland, and the UK [13]. While our analysis supports the superior performance of M/H over FW, findings from individual studies show variability depending on lipid distribution and patient population. For example, Swapna et al. reported a smaller mean difference with M/H but slightly higher correlation with FW. Such results highlight the importance of considering multiple statistical measures when evaluating formula performance. Subgroup analyses also confirm that M/H provides particular advantages in high-risk groups, including patients with diabetes, hypertriglyceridemia, or LDL-C < 70 mg/dL, where misclassification can alter treatment decisions [12, 14-19]. Importantly, Zafrir et al. demonstrated that Friedewald tends to underestimate LDL-C in patients undergoing coronary angiography, a limitation that can lead to undertreatment. This underestimation was largely mitigated when using the Martin–Hopkins formula [20]. From a practical perspective, LDL-C calculation methods must balance accuracy, feasibility, and clinical utility. The M/H equation is highly validated and widely implemented, but integration challenges persist. It is important to note that the M/H formula is not the only alternative under investigation. More than 20 other methods have been developed, among which the NIH-Sampson equations, validated in large datasets, are particularly noteworthy. Several studies suggest that Sampson performs comparably or even better than M/H in specific clinical contexts (e.g., very low LDL-C or high triglycerides) [16, 21, 22]. The Sampson equations represent promising alternatives that combine accuracy with easier laboratory integration. While our inclusion criteria limited this meta-analysis to studies directly comparing FW and M/H, we recognize that other equations play a meaningful role in laboratory practice. Thus, while our findings support the superiority of M/H compared to FW, we emphasize that the choice of optimal method for LDL-C estimation may vary depending on population characteristics, local resources, integration into laboratory information systems, and national guideline recommendations.

Conclusion

This meta-analysis confirms that the Martin–Hopkins equation improves LDL-C estimation compared to the Friedewald formula across diverse populations and clinical conditions. However, the M/H formula is not the only valid alternative newer approaches, such as the Sampson-NIH equation, also provide high accuracy and practical advantages for laboratory adoption. Rather than endorsing a single standard, laboratories and clinicians should select the most appropriate method based on patient characteristics, population-specific performance, implementation feasibility, integration into laboratory information systems, and national guideline recommendations. Accurate LDL-C estimation remains central to optimizing cardiovascular risk assessment and management.

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