ORIGINAL ARTICLE

Does correction of low-density lipoprotein cholesterol for lipoprotein(a) change the clinical classification of familial hypercholesterolemia? A retrospective study in patients referred to a lipid clinic

Sandra Singh Lukac[1,2], Ljiljana Popovic[1,2], Iva Rasulic[1,2], Ana Petakov[1], Jelena Bogdanovic[1,2], Marija Mitrovic[1], Katarina Lalic[1,2]

[1] University Clinical Center of Serbia, Clinic for Endocrinology, Diabetes and Metabolic Disease, Belgrade, Serbia
[2] University of Belgrade, Faculty of Medicine, Belgrade, Serbia

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Correspondence to:
Sandra Singh Lukac
University of Belgrade, Faculty of Medicine, Belgrade, Serbia
University Clinical Center of Serbia, Clinic for Endocrinology, Diabetes and Metabolic Disease, Belgrade, Serbia
13 Dr Subotica Starijeg Street, 11000 Belgrade, Serbia
Email: bastet224@yahoo.com

Summary

Introduction: Lipoprotein(a) [Lp(a)] contributes to measured low-density lipoprotein cholesterol (LDL-C), potentially affecting the classification of familial hypercholesterolemia (FH). This study evaluated how correcting LDL-C for the estimated cholesterol contribution of Lp(a) affects the clinical classification of FH using the Dutch Lipid Clinic Network (DLCN) criteria.

Materials and Methods: This retrospective observational study included 339 patients evaluated for suspected FH at a tertiary lipid clinic. Corrected LDL-C was calculated by subtracting the estimated cholesterol content of Lp(a) (30% of Lp(a) mass) from pretreatment LDL-C. DLCN scores, recalculated from source data, and all four DLCN categories were determined before and after correction. Changes across categories were tested with the Bowker test of symmetry, and changes at the DLCN ≥6 and ≥3 thresholds with the McNemar test.

Results: LDL-C correction reduced mean LDL-C from 5.02 ± 2.01 to 4.75 ± 2.01 mmol/L ($p < 0.001$). In total, 33 patients (9.7%; 95% CI 7.0–13.4%) moved to a lower DLCN category, and none moved upward (Bowker test, $p < 0.001$). The proportion with probable or definite FH (DLCN ≥6) decreased from 22.4% to 18.3%, and that with DLCN ≥3 from 54.3% to 49.0% (both $p < 0.001$).

Conclusion: Correcting LDL-C for the estimated cholesterol contribution of Lp(a) modestly but significantly changed the clinical DLCN classification of patients with suspected FH, shifting approximately one in ten patients into a lower diagnostic category. Without a genetic reference standard, these findings reflect changes in clinical classification, not improved diagnostic accuracy.

Keywords: familial hypercholesterolemia, lipoprotein(a), LDL-cholesterol, Dutch Lipid Clinic Network, diagnosis

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INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant lipid disorder characterized by elevated plasma low-density lipoprotein cholesterol (LDL-C) levels from birth, leading to premature atherosclerotic cardiovascular disease (ASCVD), particularly coronary artery disease (CAD) in early and middle adulthood (1). The global prevalence of FH is estimated at 1 in 250 individuals, making it one of the most common monogenic disorders associated with cardiovascular risk (2). Despite its frequency and severe clinical implications, FH remains underdiagnosed and undertreated worldwide.

Clinical diagnosis of FH often relies on established criteria such as the Dutch Lipid Clinic Network (DLCN) score, which integrates LDL-C levels, family history, physical findings, and molecular testing where available (3). Among these, LDL-C concentration plays a central diagnostic role. However, LDL-C as conventionally measured includes cholesterol carried not only by LDL particles but also by lipoprotein(a) [Lp(a)], an atherogenic lipoprotein structurally similar to LDL but with an additional apolipoprotein(a) component covalently bound to apolipoprotein B-100 (4,5).

Lipoprotein(a) [Lp(a)] is a structurally unique lipoprotein composed of an apolipoprotein(a) [apo(a)] moiety linked via a disulfide bond to an apolipoprotein B-100–containing LDL-like particle. Genetic variation in the LPA gene is responsible for the vast majority (70–90%) of inter-individual variability in Lp(a) levels, making Lp(a) essentially a genetically determined trait with minimal modulation by diet, exercise, or most lipid-lowering therapies (6–8). Lp(a) has therefore been described as a "locked-in" risk factor – appearing in childhood and remaining stable throughout adulthood (8).

Elevated Lp(a) levels are now well established as an independent and causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve disease (CAVD). Mendelian randomization, genome-wide association, and large population studies consistently demonstrate that higher Lp(a) concentrations translate into increased risk of myocardial infarction, stroke, peripheral arterial disease, and valvular stenosis (9,10).

Importantly, each Lp(a) particle carries a significant cholesterol cargo – estimated at approximately 30–45% of its mass – such that elevated Lp(a) concentrations can lead to considerable "hidden" cholesterol included in routine LDL-C assays. In individuals with markedly high Lp(a) levels, this can lead to overestimation of true LDL-particle cholesterol (11,12). When this occurs in the setting of clinical FH evaluation using LDL-C–driven diagnostic criteria (such as the DLCN), the LDL-C value may be inflated, potentially resulting in a higher DLCN category or a clinical FH diagnosis in the absence of a monogenic cause (13,14).

Given these mechanistic and diagnostic considerations, it becomes critical to differentiate elevated LDL-C due to high Lp(a) from that due to classical LDL-receptor pathway defects. Such differentiation may help to interpret the FH phenotype and to identify patients in whom elevated Lp(a) itself warrants clinical attention, particularly in view of emerging Lp(a)-specific therapies.

Several studies have suggested that correcting LDL-C for the cholesterol content attributed to Lp(a) may provide a better estimate of the cholesterol carried by LDL particles and can lead to substantial reclassification of FH probability (15,16). This adjustment may help to distinguish between elevated LDL-C due to LDL receptor pathway defects and that arising from high Lp(a) levels. Identifying the predominant lipid abnormality is relevant for risk stratification.

Lp(a) levels show a minimal response to conventional lifestyle interventions or standard lipid-lowering therapies such as statins or ezetimibe. In recent decades, dedicated efforts have focused on developing therapies that specifically reduce Lp(a) to mitigate its associated cardiovascular risk. With the advent of novel Lp(a)-lowering agents, including antisense oligonucleotides (pelacarsen) and small interfering RNA therapies (olpasiran), currently in advanced clinical development, precise characterization of Lp(a)-related dyslipidemia has gained additional clinical significance (4,17).

This study aimed to evaluate the impact of correcting LDL-cholesterol (LDL-C) for the cholesterol content of lipoprotein(a) [Lp(a)] on the clinical classification of familial hypercholesterolemia (FH) according to the Dutch Lipid Clinic Network (DLCN) criteria.

We hypothesized that adjusting LDL-C for Lp(a) would result in lower LDL-C concentrations and consequently downward reclassification of FH diagnostic categories in a proportion of patients. As no genetic reference standard was available, the study was designed to quantify changes in clinical DLCN classification, not to assess diagnostic accuracy.

MATERIALS AND METHODS

Study design and population

This was a retrospective observational study including 339 individuals evaluated for suspected FH at a tertiary-care lipid clinic at the Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Belgrade, Serbia between 2015 and 2025. Patients were included if baseline lipid measurements, Lp(a) concentrations, and sufficient clinical information for DLCN classification were available. Patients were referred by general practitioners and cardiologists because of elevated LDL-C or premature cardiovascular disease. All consecutive patients in whom Lp(a) had been measured

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were identified from the institutional medical database and medical records. Of 625 patients screened, 286 were excluded because of secondary causes of dyslipidemia or insufficient clinical data for DLCN classification, and 339 were included. All 339 patients had complete data on pretreatment LDL-C, Lp(a), and the individual DLCN components and were included in all analyses of DLCN classification. Participants with secondary causes of dyslipidemia – such as uncontrolled diabetes mellitus, hypothyroidism, nephrotic syndrome, liver disease, or use of lipid-altering medications (other than statins) – were excluded. All data were anonymized prior to analysis. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Clinical Center of Serbia (approval No. 95/15, dated 31 March 2026). Written informed consent was obtained from all participants.

Lipid-lowering treatment. Patients who were not receiving lipid-lowering therapy at the time of evaluation were included with their measured LDL-C. For patients who were already receiving statins at that time, the documented LDL-C value obtained before the initiation of therapy was used. Thus, in all patients, DLCN scoring and the Lp(a) correction were based on pretreatment LDL-C. Data on statin type, intensity, adherence, and duration of treatment were not systematically available and were therefore not analyzed.

Clinical and laboratory measurements

Fasting serum lipid parameters, including serum total cholesterol (TC), HDL-cholesterol (HDL-C), triglycerides (Tg), apolipoprotein A1 (apoA1) and apolipoprotein B (apoB) were measured using standardized enzymatic and immunoturbidimetric assays on an automated analyzer (*Boehringer Mannheim GmbH Diagnostica, Germany*). LDL-C was calculated using the Friedewald formula in 322 patients and measured directly in 17 patients. In these patients, LDL-C was measured using a homogeneous enzymatic colorimetric assay (LDL-Cholesterol Gen.3, Roche Diagnostics GmbH, Mannheim, Germany) on a cobas automated clinical chemistry analyzer. Lipoprotein(a) [Lp(a)] concentrations were determined by an immunoturbidimetric assay using an automated analyzer (Cobas 8000, Roche Diagnostics, Mannheim, Germany). The assay was calibrated according to the manufacturer's protocol, and results were expressed in g/L. Fasting plasma glucose was measured by the hexokinase method. We calculated body mass index (BMI) as weight (kg) divided by height squared (m^2).

Correction of LDL-cholesterol for Lp(a)

To account for cholesterol carried within Lp(a) particles, a corrected LDL-cholesterol ($LDL\text{-}C_{(corr)}$) was calculated for each patient using the formula: *$LDL\text{-}C_{(corr)}$ (mmol/L) = LDL-C (mmol/L) – 0.7758 × Lp(a) (g/L), where 0.7758 corresponds to an assumed cholesterol content of 30% of Lp(a) mass converted to mmol/L (0.30 × 1000/386.7) (18,22). Because the cholesterol content of Lp(a) varies between individuals and depends on the assay, sensitivity analyses were performed using alternative assumed cholesterol contents of 20% and 45% of Lp(a) mass (factors 0.517 and 1.164, respectively).* Both measured and Lp(a)-corrected LDL-C values were analyzed to assess the influence of this adjustment on FH classification.

Familial hypercholesterolemia classification

FH diagnosis was determined using the Dutch Lipid Clinic Network (DLCN) criteria, which incorporate clinical findings, family history, physical signs (xanthomas, corneal arcus), LDL-C levels, and genetic results when available. Patients were categorized as definite FH (DLCN >8 points), probable FH (6–8 points), possible FH (3–5 points), or unlikely FH (<3 points). Each patient's DLCN score and diagnostic category were calculated before and after LDL-C correction to determine reclassification rates. DLCN scores were recalculated from the source data according to the original criteria, with only the highest-scoring item within each group (family history, clinical history, physical examination, LDL-C) counted; LDL-C points were assigned using the pretreatment LDL-C to which the Lp(a) correction was applied. Only the LDL-C component of the score was recalculated, while all other components were kept unchanged; consequently, correction could only maintain or lower the DLCN score. In the primary analysis, all four DLCN categories are reported. As a secondary analysis, a DLCN score ≥6 (probable or definite FH), the threshold at which genetic testing is generally recommended, was used as the clinically relevant binary threshold; a DLCN score ≥3 is reported only for comparison, and possible FH (3–5 points) was not regarded as a confirmed diagnosis.

Information on the individual DLCN components was obtained from medical records and was available for all 339 patients. A positive family history (≥1 point) was present in 192 patients (56.6%), a personal history of premature coronary, cerebral, or peripheral vascular disease in 63 (18.6%), tendon xanthomas in 18 (5.3%), and corneal arcus before 45 years of age in 6 (1.8%). Genetic testing was performed in 58 patients (17.1%); in the remaining patients, it was not performed because of technical and financial constraints.

Statistical analysis

Analyses were conducted in IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA). Not all clinical, anthropometric, and laboratory measurements were available for every participant; therefore, the number of observations varied across variables. Analyses were performed

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using all available data for each variable, and the corresponding sample size (N) is reported in the tables. The paired analyses of DLCN classification included only patients with both measured and corrected LDL-C available (n = 339). Continuous variables were summarized as means ± standard deviation (SD) or medians (first–third quartile, Q1–Q3), depending on distribution. Normality was assessed using the Shapiro–Wilk test. Because most variables were not normally distributed, we used nonparametric methods. The Wilcoxon signed-rank test was used to compare measured and corrected LDL-C. Changes across the four ordinal DLCN categories were assessed using the Bowker test of symmetry (McNemar–Bowker test), and a complete reclassification matrix was constructed. As a secondary analysis, changes at the DLCN ≥6 and DLCN ≥3 thresholds were assessed using the McNemar test. Proportions of reclassified patients are reported with 95% confidence intervals (CI) calculated using the Wilson method. Sensitivity analyses were performed stratified by LDL-C method (Friedewald formula vs direct measurement) and using alternative assumed Lp(a) cholesterol contents. Spearman rank correlation was used to assess associations between Lp(a), LDL-C, and Lp(a)-corrected LDL-C. Statistical significance was defined as a two-sided p-value < 0.05.

RESULTS

Study Population

Table 1 presents the baseline demographic and biochemical characteristics of the study population. The cohort comprised 339 individuals, approximately two-thirds of whom were women, with varying clinical likelihood of familial hypercholesterolemia (FH) according to the Dutch Lipid Clinic Network (DLCN) criteria. Participants represented a broad age range typical of a specialized lipid clinic population, with a mean age of approximately 60 years and a mean body mass index within the overweight range. Age was unavailable for 35 patients (10.4%) because it was not recorded in the available medical documentation; other missing data (BMI, apolipoproteins, and fasting glucose) resulted from measurements that were not performed or not documented at the time of evaluation. All lipid measurements used for DLCN scoring were obtained before the initiation of lipid-lowering therapy; LDL-C was measured directly in 17 patients (5.0%) **(Table 1)**.

As expected in a cohort referred for evaluation of suspected FH, total cholesterol and LDL-cholesterol concentrations were elevated. Correction of LDL-C for the estimated cholesterol contribution of lipoprotein(a) [Lp(a)] resulted in a modest reduction in mean LDL-C values, indicating that Lp(a)-derived cholesterol contributes to measured LDL-C levels.

HDL-cholesterol concentrations were within the expected range for a dyslipidemic population. Triglyceride concentrations were markedly skewed and are therefore presented as median (Q1–Q3). Similarly, Lp(a) concentrations showed substantial interindividual variability and a highly skewed distribution, with a median value of 0.161 g/L (Q1–Q3: 0.098–0.470 g/L), reflecting the heterogeneous burden of Lp(a)-associated dyslipidemia within the study population.

Effect of Lp(a) correction on LDL-cholesterol

Correcting LDL-cholesterol (LDL-C) for Lp(a)- related cholesterol contribution significantly reduced LDL-C across the study cohort **(Table 1)**. Mean LDL-C decreased from 5.02 ± 2.01 mmol/L before correction to 4.75 ± 2.01 mmol/L after correction. The Wilcoxon signed-rank test confirmed that this reduction was statistically significant ($p < 0.001$), demonstrating that adjustment for Lp(a)-derived cholesterol systematically lowers measured LDL-C concentrations.

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Table 1. Baseline demographic and biochemical characteristics of the study cohort

Age	303	60.2 ± 15.4	years
BMI	329	25.60 ± 4.75	kg/m²
Total cholesterol	339	7.26 ± 2.21	mmol/L
LDL-C (measured)	339	5.02 ± 2.01	mmol/L
LDL-C (corrected for Lp(a))	339	4.75 ± 2.01	mmol/L
HDL-C	338	1.37 ± 0.39	mmol/L
Triglycerides	339	**1.67 (1.18–2.40)**	**mmol/L**
Apolipoprotein B	286	1.47 ± 0.50	g/L
Apolipoprotein A1	283	1.60 ± 0.33	g/L
Fasting glucose	335	5.75 ± 1.84	mmol/L
Lipoprotein(a)	339	**0.161 (0.098–0.470)**	**g/L**
LDL-C measured directly, n (%)	339	**17 (5.0)**	–

*Values are presented as mean ± standard deviation (SD) for normally distributed variables and as median (Q1–Q3) for non-normally distributed variables. Sample sizes differ between variables because of missing clinical, laboratory, or anthropometric data. The number of available observations (N) is reported for each variable.

Table 2. Dutch Lipid Clinic Network (DLCN) diagnostic categories and binary DLCN thresholds before and after LDL-cholesterol correction for the cholesterol contribution of lipoprotein(a)

Binary DLCN thresholds (secondary analysis)*		
DLCN ≥3 (possible, probable or definite FH)	184 (54.3)	166 (49.0)
DLCN <3 (unlikely FH)	155 (45.7)	173 (51.0)
DLCN ≥6 (probable or definite FH)	76 (22.4)	62 (18.3)
DLCN <6	263 (77.6)	277 (81.7)
DLCN diagnostic category (primary analysis)		
Definite FH (>8 points)	33 (9.7)	32 (9.4)
Probable FH (6–8 points)	43 (12.7)	30 (8.8)
Possible FH (3–5 points)	108 (31.9)	104 (30.7)
Unlikely FH (<3 points)	155 (45.7)	173 (51.0)
Total	**339 (100)**	**339 (100)**

Data are presented as n (%). Changes across the four DLCN categories were assessed using the Bowker test of symmetry ($\chi^2 = 33.00$, df = 3, $p < 0.001$); changes at the binary thresholds were assessed using the McNemar test (DLCN ≥6: $\chi^2 = 12.07$, $p < 0.001$; DLCN ≥3: $\chi^2 = 16.06$, $p < 0.001$). **Abbreviations:** FH, familial hypercholesterolemia; DLCN, Dutch Lipid Clinic Network; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a). *Possible FH (DLCN 3–5 points) does not represent a confirmed diagnosis; the DLCN ≥3 threshold is shown only for comparison with the original analysis.

In sensitivity analyses, results were similar in the 322 patients with Friedewald-calculated LDL-C, of whom 30 (9.3%) moved to a lower DLCN category (Bowker test, $p < 0.001$); among the 17 patients with directly measured LDL-C, 3 were downgraded. Using alternative assumed Lp(a) cholesterol contents of 20% and 45%, 21 (6.2%) and 38 (11.2%) patients, respectively, moved to a lower DLCN category (both $p < 0.001$), and the proportion with DLCN ≥6 after correction was 19.5% and 17.4%, respectively.

Impact of LDL-C correction on DLCN classification

Following correction of LDL-cholesterol for the estimated cholesterol contribution of Lp(a), the distribution of patients across the four DLCN diagnostic categories shifted toward lower categories **(Table 2, Table 3 and Figure 1)**. Overall, 33 patients (9.7%; 95% CI 7.0–13.4%) were downgraded by one DLCN category, and none by two or more categories **(Table 3)**. No patient was upgraded, as correction can only lower LDL-C. The distribution of the four categories changed significantly (Bowker test, $\chi^2 = 33.00$, df = 3, $p < 0.001$). In the secondary binary analyses, the number of patients with probable or definite FH (DLCN ≥6) decreased from 76 (22.4%) to 62 (18.3%), i.e., 14 of 76 patients (18.4%; 95% CI 11.3–28.6%) were reclassified below this threshold (McNemar test, $\chi^2 = 12.07$, $p < 0.001$). The number of patients with a DLCN score ≥3 decreased from 184 (54.3%) to 166 (49.0%), i.e., 18 of 184 patients (9.8%; 95% CI 6.3–14.9%) were reclassified as unlikely FH (McNemar test, $\chi^2 = 16.06$, $p < 0.001$). These results describe changes in score-based clinical classification and, without genetic confirmation, do not indicate which classification is more accurate. Furthermore, no significant association was observed between circulating Lp(a) concentrations and Lp(a)-corrected LDL-C (Spearman's $\rho = -0.099$, $p = 0.069$). This is consistent with the intended effect of the correction but does not prove that Lp(a)-derived cholesterol was completely removed.

DISCUSSION

This study shows that correcting LDL-cholesterol for the estimated cholesterol contribution of lipoprotein(a) significantly affects the clinical classification of familial hypercholesterolemia by reducing measured

Table 3. Reclassification of patients between Dutch Lipid Clinic Network (DLCN) diagnostic categories after correction of LDL-cholesterol for the estimated cholesterol contribution of lipoprotein(a), n

Before \ After correction	Unlikely FH	Possible FH	Probable FH	Definite FH	Total before
Definite FH (>8 points)	0	0	1	32	33
Probable FH (6–8 points)	0	14	29	0	43
Possible FH (3–5 points)	18	90	0	0	108
Unlikely FH (<3 points)	155	0	0	0	155
Total after	173	104	30	32	339

Rows show the DLCN category based on measured LDL-C; columns show the category based on Lp(a)-corrected LDL-C. Cells above the diagonal are zero by construction because correction can only lower LDL-C. Diagonal cells represent patients who remained in the same category. Bowker test of symmetry: $\chi^2 = 33.00$, df = 3, $p < 0.001$. Abbreviations: DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

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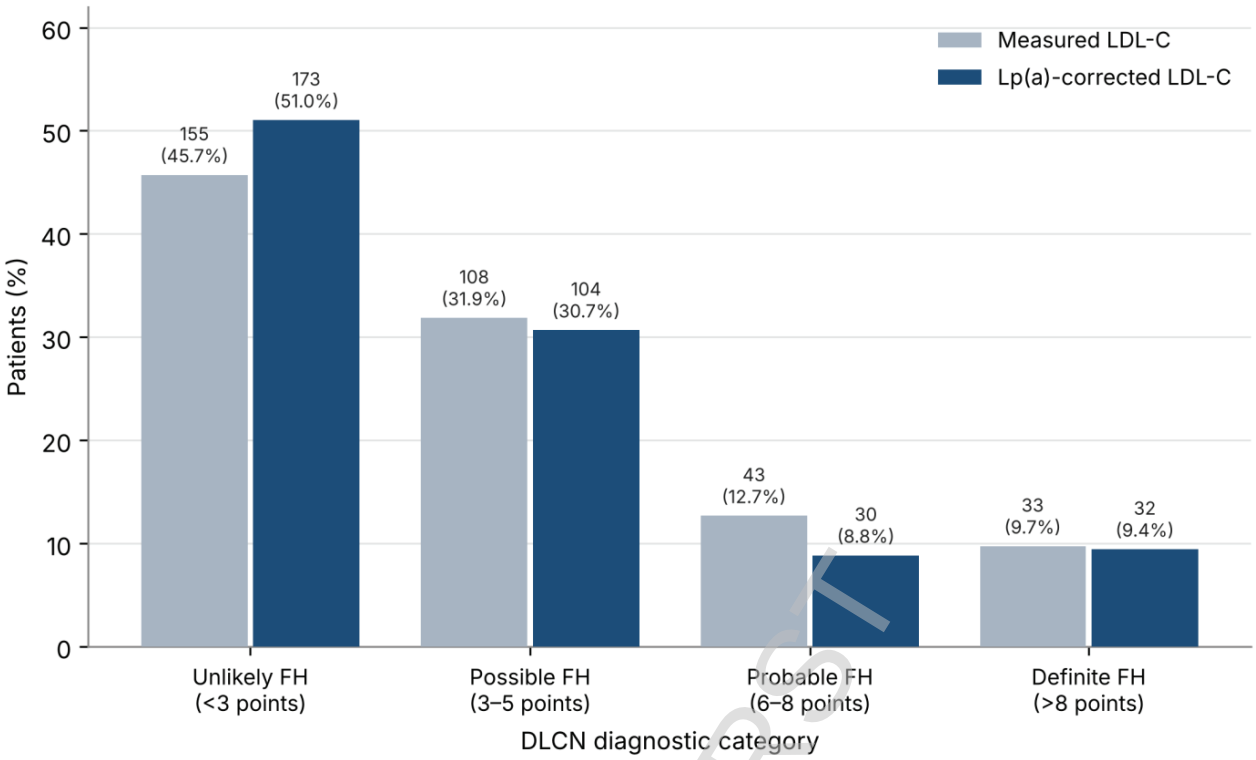


Figure 1. Distribution of patients across the four Dutch Lipid Clinic Network (DLCN) diagnostic categories based on measured and lipoprotein(a)-corrected LDL-cholesterol (n = 339). Bars show percentages; numbers above the bars are n (%). Corrected LDL-C = measured LDL-C − 0.7758 × Lp(a) (g/L). FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a). Figure 1 was prepared with the assistance of Claude (Anthropic); the underlying data and the final figure were verified by the authors.

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LDL-cholesterol concentrations and shifting patients toward lower Dutch Lipid Clinic Network (DLCN) diagnostic categories. This finding is consistent with the conceptual understanding that routine LDL-C measurements capture cholesterol carried not only by LDL particles but also by Lp(a), such that "LDL-C" is systematically overestimated in individuals with elevated Lp(a) (12,18–20). Several clinical and laboratory studies have highlighted that this overestimation can be particularly relevant in FH evaluation, where fixed LDL-C thresholds form a central component of diagnostic algorithms (13,21,22). Our data therefore provide further empirical support for the notion that uncorrected LDL-C may overstate the severity of LDL-related dyslipidemia in a subset of patients with high Lp(a), with potential consequences for clinical classification.

Because correction can only lower LDL-C while all other DLCN components remain unchanged, the observed reclassification was necessarily downward and, to a large extent, a mathematical consequence of the correction. When the correction was applied consistently to the same pretreatment LDL-C that was used for DLCN scoring, its effect was modest: approximately one in ten patients moved to a lower category, and no patient moved by more than one category. Without an independent reference standard, such as genetic testing, our data show that correction changes clinical classification, but cannot establish whether the corrected or uncorrected classification more accurately identifies patients with monogenic FH.

The extent of reclassification we observed after applying Lp(a)-correction aligns with prior analyses in FH cohorts and lipid clinic populations. Thayabaran et al. (12) demonstrated that adjusting LDL-C for Lp(a)-cholesterol in a large referral cohort improved the specificity of DLCN-based FH diagnosis, reclassifying a significant proportion of patients – particularly those without pathogenic variants – to lower probability categories. In Danish lipid clinics, Hedegaard et al. (19) reported that approximately one-quarter of individuals who met clinical FH criteria did so largely because of elevated Lp(a), rather than monogenic FH. They showed that incorporating Lp(a)-related information attenuated the apparent prevalence of phenotypic FH. Similar evidence from the Italian LIPIGEN network and other registries supports the role of *LPA* risk genotypes and high Lp(a) concentrations as important contributors to the FH phenotype in mutation-negative patients, with LDL-C correction reducing the proportion who exceed conventional diagnostic thresholds (23–25). In this context, our finding that the proportion of individuals meeting DLCN-based FH criteria fell significantly, albeit modestly, after correction reinforces the view that high Lp(a) can masquerade as, or amplify, the biochemical signature of FH and that Lp(a)-corrected LDL-C may help disentangle these overlapping phenotypes (20).

Methodologically, the absence of a significant association between circulating Lp(a) concentrations and Lp(a)-corrected LDL-C is consistent with the intended

effect of the correction, namely reducing the estimated contribution of Lp(a)-derived cholesterol to measured LDL-C. However, this finding does not confirm that the Lp(a)-derived cholesterol component was completely removed. Willeit et al. (18) showed in a large prospective study that calculating LDL-C corrected for Lp(a)-cholesterol alters CVD risk categorization, and that corrected LDL-C may better reflect the risk conveyed by LDL per se, independent of Lp(a). However, it is important to recognize that most correction methods are based on a fixed assumption of cholesterol content within Lp(a) particles. In contrast, biochemical and modeling studies indicate substantial interindividual variation in Lp(a)-cholesterol content. Rosenson et al. (26) recently proposed a formula to estimate Lp(a)-cholesterol from molar Lp(a) values, underscoring both the potential of more precise correction and the uncertainty that still surrounds the optimal way to quantify Lp(a)-derived cholesterol in routine practice. These considerations suggest that while Lp(a)-corrected LDL-C is conceptually attractive and practically useful, it remains an approximation rather than a direct measurement, and clinicians should clearly acknowledge its limitations in decision-making (22,26).

Our findings are consistent with the growing body of evidence describing the complex interplay between familial hypercholesterolemia (FH), lipoprotein(a) [Lp(a)], and cardiovascular risk. FH and elevated Lp(a) are among the most common inherited lipid disorders, and their coexistence is associated with a particularly high risk of atherosclerotic cardiovascular disease (ASCVD). Multiple cohort studies and meta-analyses have demonstrated that elevated Lp(a) confers additional ASCVD risk beyond that attributable to LDL-cholesterol alone, supporting its role as an independent causal cardiovascular risk factor. These findings underscore the importance of routine Lp(a) measurement in patients with suspected or confirmed FH to improve cardiovascular risk stratification (27–30). Contemporary reviews and consensus documents emphasize that elevated Lp(a) can both confound the clinical diagnosis of FH – by inflating LDL-C and DLCN scores – and act as an independent risk driver that warrants recognition irrespective of whether FH is ultimately confirmed. Our observation that correcting LDL-C for Lp(a) systematically reduces DLCN scores should therefore be interpreted in the context of this "double-hit" paradigm, in which uncorrected LDL-C may inflate DLCN-based classification but high Lp(a) still signals a need for aggressive ASCVD risk management (31).

From a diagnostic perspective, several recent studies have explored how Lp(a) measurement and correction might be operationalized within FH care pathways. Tromp et al. (20) used genetically estimated Lp(a) levels to adjust LDL-C and reclassify FH probability in a large nationwide referral cohort, showing that Lp(a)-adjusted LDL-C meaningfully refines DLCN category assignment and ASCVD risk estimation, while warning that inappropriate correction thresholds could lead to missed monogenic FH diagnoses. Olmastroni et al. (25) demonstrated that *LPA* risk genotypes can explain an FH-like phenotype in a subset of patients without detectable mutations in classical FH genes, and that LDL-C adjustment based on Lp(a) concentrations reduces the proportion of individuals exceeding the 5 mmol/L LDL-C threshold used in many guidelines. Other groups have proposed incorporating Lp(a) directly into modified diagnostic algorithms, either as an additional criterion or via Lp(a)-inclusive risk models, to balance the risk of overdiagnosis against the danger of overlooking high-risk individuals who might benefit from early, intensive therapy. The reclassification we observed after LDL-C correction illustrates the potential impact of such strategies, but also highlights the need for prospective validation and clear consensus on which patients, Lp(a) levels, and clinical settings warrant routine correction (12).

The potential clinical implications of Lp(a)-corrected LDL-C should be interpreted with caution. Evidence from outcome studies suggests that when both LDL-C and Lp(a) are elevated, residual ASCVD risk remains high even after aggressive LDL-C lowering. Lp(a) may emerge as a dominant risk factor once LDL-C is well controlled (32–34). Prospective analyses and post hoc evaluations of PCSK9 inhibitor trials have shown that Lp(a) lowering contributes independently to cardiovascular risk reduction, and that individuals with high Lp(a) derive greater benefit from PCSK9 inhibition, even when LDL-C appears "at goal". These data support recent calls for Lp(a) screening in FH and high-risk populations, not only to refine diagnosis but also to identify patients who may benefit from emerging Lp(a)-targeted therapies. Our results show that some patients fall below traditional LDL-C thresholds after correction. However, Lp(a)-associated cholesterol remains atherogenic, and a lower corrected LDL-C value does not justify less intensive lipid-lowering treatment; rather, patients with high Lp(a) may require more intensive management of their overall cardiovascular risk (26).

Finally, our study should be viewed in the context of evolving international guidance on FH and Lp(a). Contemporary consensus statements and position papers from expert societies emphasize that FH remains underdiagnosed and undertreated globally, and that clinical scores such as the DLCN remain essential tools where genetic testing is limited. At the same time, these documents increasingly highlight the importance of Lp(a) measurement in FH workup, recommend at least once-in-a-lifetime Lp(a) testing, and acknowledge the potential role of Lp(a)-corrected LDL-C in selected scenarios, particularly in patients with very high Lp(a) or borderline LDL-C values. Our findings are congruent with this evolving paradigm: they support routine Lp(a) measurement in lipid clinics, demonstrate that LDL-C correction can significantly modify FH classification,

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and underscore that any correction strategy must be integrated with comprehensive clinical assessment, genetic testing where available, and careful consideration of individual ASCVD risk (35). Future research should focus on standardizing Lp(a) assays (preferably in nmol/L), refining and validating correction formulas across diverse populations, and determining how best to combine corrected LDL-C, apolipoprotein B, and Lp(a) metrics in algorithms that optimize both diagnostic accuracy and long-term cardiovascular outcomes (36).

Limitations and future directions

The present study has several limitations. Most importantly, genetic testing was performed in only 58 patients (17.1%) because of technical and financial constraints, and no independent reference standard was available; therefore, our findings reflect changes in clinical DLCN classification rather than improved diagnostic accuracy, and we cannot determine whether reclassified patients have monogenic FH. Second, its retrospective cross-sectional design precludes assessing longitudinal outcomes and evaluating the relationship between Lp(a)-corrected LDL-cholesterol and future cardiovascular events. Third, the study population consisted of patients with suspected familial hypercholesterolemia referred to a specialized lipid clinic, which may limit the generalizability of the findings to broader populations. In addition, not all clinical and laboratory variables were available for every participant, resulting in variable sample sizes for some descriptive variables. Fourth, DLCN scores were derived from retrospectively recorded pretreatment LDL-C values and clinical data, which may have introduced misclassification. Fifth, LDL-C was calculated using the Friedewald formula in most patients and measured directly in a small number of patients. However, results were similar in patients with Friedewald-calculated LDL-C.

The correction of LDL-cholesterol was based on a published estimate of the cholesterol contribution of lipoprotein(a). Although this approach has been used in several previous studies, the proportion of cholesterol carried by Lp(a) may vary among individuals owing to differences in lipoprotein composition and apo(a) isoform size. Consequently, the correction formula may not provide an equally accurate estimate for every patient, and the fixed 30% assumption is uncertain and assay-dependent. For this reason, sensitivity analyses with alternative assumptions (20% and 45%) were performed.

Furthermore, Lp(a) concentrations were reported in grams per liter rather than molar units (nmol/L). Because no universal conversion factor exists between mass- and molar-based measurements, direct comparison with studies reporting Lp(a) in nmol/L should be interpreted with caution. Future prospective studies in larger, multicenter cohorts, particularly among patients with genetically confirmed familial hypercholesterolemia, are needed to determine whether Lp(a)-corrected LDL-cholesterol improves cardiovascular risk prediction and clinical decision-making.

CONCLUSION

Correction of LDL-cholesterol for the cholesterol contribution of lipoprotein(a) significantly, although modestly, shifted patients with suspected familial hypercholesterolemia toward lower Dutch Lipid Clinic Network (DLCN) diagnostic categories, with approximately one in ten patients moving to a lower category, indicating that elevated Lp(a) can meaningfully contribute to measured LDL-cholesterol and to DLCN-based clinical classification. Without genetic confirmation, these results reflect changes in clinical classification rather than a demonstrated improvement in diagnostic accuracy.

From a clinical perspective, these findings support the European Atherosclerosis Society recommendation that Lp(a) should be measured at least once during adulthood. In individuals with elevated Lp(a), reliance on uncorrected LDL-cholesterol may overestimate the cholesterol carried by LDL particles and influence DLCN-based classification. Lp(a)-corrected LDL-cholesterol may be considered as complementary information in the evaluation of suspected FH; however, its diagnostic value should be validated against genetic testing, and it should not be used to justify less intensive lipid-lowering therapy, because Lp(a)-associated cholesterol remains atherogenic (12,18,20,37).

The clinical relevance of this approach is likely to increase with the emergence of Lp(a)-targeted therapies, including the antisense oligonucleotide pelacarsen and the small interfering RNA (siRNA) agent olpasiran, both of which have demonstrated substantial reductions in Lp(a) concentrations in phase II and III clinical trials. As the role of Lp(a) in cardiovascular disease continues to evolve, routine Lp(a) measurement together with consideration of Lp(a)-corrected LDL-cholesterol may become an increasingly important component of precision medicine approaches for the diagnosis and management of familial hypercholesterolemia (36,38).

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DA LI KOREKCIJA LDL-HOLESTEROLA ZA LIPOPROTEIN(A) MENJA KLINIČKU KLASIFIKACIJU FAMILIJARNE HIPERHOLESTEROLEMIJE? RETROSPEKTIVNA STUDIJA KOD PACIJENATA UPUĆENIH U LIPIDOLOŠKI CENTAR

Sandra Singh Lukač[1,2], Ljiljana Popović[1,2], Iva Rasulić[1,2], Ana Petakov[1], Jelena Bogdanović[1,2], Marija Mitrović[1], Katarina Lalić[1,2]

Sažetak

Uvod/Cilj rada: Lipoprotein(a) [Lp(a)] doprinosi ukupno izmerenoj koncentraciji LDL-holesterola (LDL-h), što može uticati na klasifikaciju familijarne hiperholesterolemije (FH). Cilj studije bio je da proceni uticaj korekcije LDL-h za procenjeni holesterolski doprinos Lp(a) na kliničku klasifikaciju FH prema kriterijumima Dutch Lipid Clinic Network (DLCN).

Metode: Retrospektivna opservaciona studija obuhvatila je 339 pacijenata sa sumnjom na FH, ispitivanih u tercijarnom lipidnom centru. Korigovani LDL-h izračunat je oduzimanjem procenjenog holesterolskog sadržaja Lp(a) (30% mase Lp(a)) od LDL-h pre terapije. DLCN skor je ponovo izračunat iz izvornih podataka, a sve četiri DLCN dijagnostičke kategorije određene su pre i nakon korekcije. Promene između kategorija ispitane su Bowker-ovim testom simetrije, a promene na pragovima DLCN ≥6 i ≥3 McNemar-ovim testom.

Rezultati: Korekcija LDL-h smanjila je srednju vrednost LDL-h sa 5,02 ± 2,01 na 4,75 ± 2,01 mmol/L ($p < 0,001$). Ukupno su 33 pacijenta (9,7%; 95% CI 7,0–13,4%) prešla u nižu DLCN kategoriju, a nijedan u višu (Bowker-ov test, $p < 0,001$). Udeo pacijenata sa verovatnom ili sigurnom FH (DLCN ≥6) smanjen je sa 22,4% na 18,3%, a udeo sa DLCN skorom ≥3 (moguća, verovatna ili sigurna FH) sa 54,3% na 49,0% (oba $p < 0,001$).

Zaključak: Korekcija LDL-h za procenjeni holesterolski doprinos Lp(a) umereno, ali značajno je promenila kliničku DLCN klasifikaciju pacijenata sa sumnjom na FH, pomerajući približno svakog desetog pacijenta u nižu dijagnostičku kategoriju. Bez genetskog referentnog standarda, ovi rezultati odražavaju promenu kliničke klasifikacije, a ne poboljšanje dijagnostičke tačnosti.

Ključne reči: familijarna hiperholesterolemija, lipoprotein(a), LDL-holesterol, Dutch Lipid Clinic Network, dijagnoza

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