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ORIGINAL ARTICLE

Impact of Lipoprotein (a) on the Quantification of LDL-Cholesterol

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SUMMARY

Background: **Accurate LDL-C measurement is essential for cardiovascular risk management. The established methods to determine LDL-C also include Lp(a)-C and potentially distort the actual LDL-C value. The need for Lp(a)-adjusted LDL-C remains debated. Our study aimed to evaluate the impact of Lp(a) on the determination of LDL-C.**

Methods: **We included 3,923 datasets from two cohorts. LDL-C was determined by beta-quantification (LDL-C_{UC}), the reference method recommended by the Lipid Research Clinics, and according to Friedewald (LDL-C_{FW}), Martin/Hopkins (LDL-C_{MH}), and Sampson (LDL-C_{SN}). Correction of LDL-C was performed as follows: corrected LDL-C* = crude LDL-C - (Lp(a) x 0.23 + 1.00). Passing-Bablok regression and Spearman correlation were used for intermethod comparisons.**

Results: **Above 10 mg/dL Lp(a) had a significant effect on LDL-C_{UC}. The effect increased with increasing concentrations of Lp(a) levels and, in relative terms, was most pronounced at lower LDL-C values. For Lp(a) > 58 mg/dL, the actual LDL-C_{UC} was overestimated by ≥ 10%, which was considered clinically relevant. Similar overestimations were observed with the Friedewald, Martin/Hopkins, and Sampson formulas, with Friedewald showing the smallest deviation from LDL-C regardless of Lp(a)-correction. Artificial intelligence models showed that it was not possible to raise the suspicion of elevated Lp(a) from the conventional lipid profile.**

Conclusions: **The influence of Lp(a) on the determination of LDL-C may lead to clinically significant overestimations of the actual LDL-C. Therefore, we recommend using Lp(a)-corrected LDL-C when 1) the Lp(a) concentration is high, 2) the LDL-C concentration is low, and 3) the LDL-C-lowering treatment is less effective than expected.**

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KEYWORDS

lipoprotein(a), low-density lipoprotein cholesterol, beta quantification, PCSK9i therapy, intermethod comparison

LIST OF ABBREVIATIONS

ASCVD - Atherosclerosis-related cardiovascular diseases
CVD - Cardiovascular disease
EAS - European Atherosclerosis Society
ECS - European Cardiovascular Society
FH - Familial hypercholesterolemia
FW - Friedewald equation
HDL-C - High density lipoprotein cholesterol
IQR - Interquartile ranges
LDL-C - Low-density lipoprotein cholesterol
LDL-C_{FW} - LDL-C according to Friedrwald
LDL-CM_{MH} - LDL-C according to Martin/Hopkins
LDL-C_{SN} - LDL-C according to Sampson
LDL-C_{UC} - LDL-C by beta-quantification, crude LDL-CUC
LDL-C_{UC}* - Lp(a)-corrected LDL-CUC
Lp(a) - Lipoprotein(a)
LURIC - Ludwigshafen Risk and Cardiovascular Health study
MD - Mean difference
MH - Martin/Hopkins equation
PCSK9i - Proprotein convertase subtilisin/kexin type 9-inhibitors
SD - Standard deviation
SN - Sampson equation
TG - Triglycerine
VLDL-C - Very low density lipoprotein cholesterol
β-quantification - Combined ultracentrifugation/precipitation method

INTRODUCTION

Over the last decade, lipoprotein(a) (Lp(a)) has become a focus of research as an independent, mainly geneticall-y determined risk factor for atherosclerosis-related cardiovascular diseases (ASCVD). In 2022, the European Atherosclerosis Society (EAS) has recommended the inclusion of lipoprotein(a) into risk assessment [1]. Within the general population, the concentration of lipoprotein(a) ranges between not detectable up to 300 mg/dL and is continuously associated with ASCVD risk. The European Atherosclerosis Society (EAS) defined Lp(a) values above the 75th - 80th percentile as high-risk values and provided population-specific thresholds for Lp(a). In the Caucasian population, the risk for myocardial infarction is 1.6 and 1.9 times higher at Lp(a) in the 67th - 89th and in the 90th - 95th percentile, respectively, compared to values below the 22nd percentile [2].

Lp(a) has a lipid and protein composition similar to low-density lipoproteins (LDL). Compared to LDL, Lp(a) contains apolipoprotein(a), which is covalently bound to apoB100 via a disulfide bridge. Due to their similar composition, the standard methods for determining LDL-C, such as the ultracentrifugation, enzymatic assays or indirect estimation equations, are unable to differentiate between cholesterol contributed by Lp(a) and LDL. Thus, routinely determined LDL-C actually represents the sum of LDL-C and Lp(a)-C and not only LDL-C. However, differentiation may be useful for treatment decisions, as the two lipoproteins differently respond to lipid-lowering. For instance, statins which are recommended by the European Cardiovascular Society (ECS) 2021 as the first-line therapy for LDL-C reduction [3] can only have a minor effect on Lp(a) or can lead to a slight increase. Thus, the lack of differentiation can lead to misclassification, wrong treatment decisions, and adverse clinical consequences [4].

To date, there is neither an approved drug therapy for the reduction of Lp(a) nor a standardised method for determining Lp(a) or Lp(a)-C. The properties of Lp(a), such as the pronounced size and structure heterogeneity of apo(a), with over 40 apo(a)-isoforms, the potential cross-reactivity of apo (a) with plasminogen, or a variance in its cholesterol content make an accurate determination difficult [5,6]. The current standard procedure is to estimate the Lp(a) “mass” with an immunoassay for the apo(a) moiety and to assume that cholesterol contributes a fixed percentage of 30% to the Lp(a) “mass” [6-10]. Opinions on this estimation method and on the general relevance of correcting LDL-C for Lp(a) differ. While some authors argue in favor of a corrected LDL-C to achieve a more accurate diagnosis of hypercholesterolaemia and a more accurate lipid-lowering therapy [3], others question accuracy of the correction method [11] and do not see significant impact on the clinical outcome following differentiation [12,13].

This study aimed to scrutinize the effect of Lp(a) on LDL-C measured by ß-quantification (LDL-C_{UC}), the reference method for LDL-C, on LDL-C estimated according to Friedewald (LDL-C_{FW}) [14], Martin/Hopkins (LDL-C_{MH}) [15], and Sampson (LDL-C_{SN}) [16], and to assess the clinical consequences of this adjustment. We also examined the impact of Lp(a)-adjustment on the assessment of the efficacy of PCSK9i therapy.

MATERIALS AND METHODS

Study population

Our analysis is based on pre-existing lipid data that were available from the following two studies: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study (n = 3,316) and a real-world study of alirocumab and evolocumab treatment (PCSK9i study, n = 700) (Supplemental Table 1). The designs of the studies have been published [17,18].

LURIC is a prospective observational cohort study. A total of 3,316 individuals of German ancestry were recruited between 1997 and 2000 at the Ludwigshafen Heart Center (Germany) [17].

A total of 700 data sets were obtained from a prospective and open label study, abbreviated as PCSK9i study. In this study, 350 patients were recruited at three German University hospitals between 2016 and 2017. Inclusion required participants to have been prescribed PCSK9i therapy (alirocumab 75/150 mg or evolocumab 140 mg once every two weeks). Blood samples were taken twice, before treatment and 4 to 6 weeks under PCSK9i treatment [18]. All studies were conducted in accordance with the Declaration of Helsinki and after approval by the study sites´ institutional review boards. Participants provided written consent.

Out of the 4,016 available data sets, 13 were excluded due to missing data. After thoroughly scrutinizing the three formulas for LDL-C across the entire range of TG (see Supplemental Figures 1 - 3, Supplemental Table 2), only samples with TG concentrations up to 500 mg/dL were included into the further analysis LDL-C, 3,923 in total (LURIC n = 3,245; PCSK9i study n = 678). The Lp(a)-distribution was as follows: < 30 mg/dL, n = 2,616; Lp(a) 30 - 50 mg/dL, n = 429; Lp(a) > 50 mg/dL, n = 876.

Procedures

Laboratory analyses were performed in fasting blood samples. VLDL-C, LDL-C, and HDL-C were determined using exactly the same combined ultracentrifugation/precipitation method (β-quantification) in both studies; it followed the Lipid Research Clinics Program protocol with modifications described previously [19, 20]. The ultracentrifugation was performed with the Beckman 50.4 rotor. Serum samples were centrifuged at 30,000 rpm and 10°C for 18 hours. The volume lost after aspiration of the VLDL-supernatant was replaced with 0.9 % saline and the LDL-fraction was precipitated with phosphotungstic acid/$MgCl_2$. Cholesterol and triglycerides were measured enzymatically with reagents from WAKO on a WAKO 30R analyzer (LURIC) and from Diasys on the Olympus AU640 analyzer in the PCSK9i study. Lipoprotein(a) was determined by immunoturbidimetry using reagents from DiaSys (Holzheim, Germany) and standards from Siemens (Marburg, Germany), and measurements were performed on an Olympus AU640 automatic analyzer [17,18].

Calculated LDL-C/Corrected LDL-C

We calculated LDL-C according to Friedewald (LDL-C_{FW}, [14]), Martin Hopkins (LDL-C_{MH}, [15]), and Sampson (LDL-C_{SN}, [16]) as follows: LDL-C_{FW} = total cholesterol - HDL-C - TG/5 (in mg/dL), LDL-C_{MH} = total cholesterol - HDL-C - TG/adjustable factor (derived from a 180-cell table according to non-HDL-C and TG), and LDL-C_{SN} = total cholesterol/0.948 - HDL-C/0.971 - (TG/8.56 + TG x non-HDL-C/2,140-TG/16,100) - 9.44 (in mg/dL) [14].

We also examined the extended version of the MH formula [11]. It produced results virtually identical to the original MH formula in all analyses (see results). To avoid redundancy, results of the extended MH formula are not reported in detail. The correction of the crude LDL-C value for Lp(a)-C was based on the following equation: corrected LDL-C* = crude LDL-C - (Lp(a) x 0.23 + 1.00). The correction factor of 0.23 for estimating Lp(a) cholesterol is based on a Passing-Bablok regression from the study by Nauck et al., which investigated the relationship between Lp(a) mass and its cholesterol content. This factor replaces the historic estimate of 0.30. As shown in Nauck et al., it is virtually constant across the entire range of Lp(a) concentrations, which is accompanied by different sizes of the apo (a) isoforms [21].

Lp(a)-corrected LDL-C values are marked with an asterisk (e.g. LDL-C_{UC}*), whereas crude LDL-C values are abbreviated without an asterisk (e.g. LDL-C_{UC}).

Statistical analysis

Data are presented as numbers and percentages, medians with interquartile ranges (IQR) or mean differences (MD) with standard deviations (SD). Mean or median differences were calculated 1) by subtracting LDL-C_{UC} (reference method) from the estimated LDL-C using Friedewald (LDL-C_{FW}), Martin/Hopkins (LDL-C_{MH}), or Sampson (LDL-C_{SN}) or 2) by subtracting LDL-C_{UC}* from LDL-C_{UC}. All values are in mg/dL. To convert cholesterol from mg/dL to mmol/L, multiply with 0.02586.

Analyses were performed with Microsoft Excel Parallel Desktop on Windows 11, version 19.2.1 with the Abacus 3.0 extension. The Graphs were created using SigmaStat 4.0.

We used boxplots to analyze the effects of correcting LDL-C_{UC}, LDL-C_{FW}, LDL-C_{MH}, and LDL-C_{SN} for Lp(a) across three concentrations of Lp(a).

We compared the LDL-C reduction under PCSK9i therapy based on LDL-C_{UC} and LDL-C_{UC}*. For each analysis, the values were stratified into three Lp(a)-subgroups: < 30 mg/dL, 30 - 50 mg/dL, and > 50 mg/dL [22]. Using linear regression, we calculated the Lp(a) threshold values at which Lp(a) contributed at a relevant extent to LDL-C. Relevance was defined as a deviation of LDL-C_{UC} from LDL-C_{UC}* by ≥ 10% in this case.

To determine the significance, we used either a paired one-way ANOVA or a *t*-test. A p-value of less than 0.05 was considered statistically significant. Passing-Bablok regression and Spearman correlation test were used to analyze the correlations between the estimated LDL-Cs, the LDL-$C_{UC,}$ and LDL-C_{UC}* [37].

KI-based prediction of Lp(a) levels

We attempted to infer Lp(a) concentrations from total cholesterol, LDL-C, HDL-C, and triglycerides. We used mutual information to capture nonlinear relationships, with permutation tests (1,000 randomizations) to determine significance [38]. Regression models such as lin-

ear regression, random forest, gradient boosting, XGBoost, and neural networks (MLP) were used. Feature scaling was part of the preprocessing [23,24]. Model performance was evaluated using RMSE and R^2. All analyses were performed using the Python scikit-learn library [25].

RESULTS

Exclusion of samples with excessively high triglycerides

As shown in Supplemental Figures 1 - 3 and Supplemental Table 2, LDL-C_{FW} did not substantially deviate from LDL-C_{UC} up to TG 500 mg/dL. For this reason, we only excluded samples with higher TG, although this threshold exceeded the limit originally proposed by Friedewald et al. [14]. Above TG 500 mg/dL, not only LDL-C_{FW} but, to an even greater extent, LDL-C_{SN} and LDL-C_{MH} showed strong deviations from LDL-C_{UC}.

Extended Martin/Hopkins equation

The extended MH formula provided estimates of LDL-C virtually identical to LDL-C_{MH} (Supplemental Figures 2 and 3, correlation coefficient ≥ 0.99). To harness complexity, we therefore abandoned the extended MH formula from the further evaluation.

Clinical characteristics of the study participants

After excluding samples with TG above 500 mg/dL, 3,923 data sets remained, 3,245 samples from the LURIC study and 678 samples from the PCSK9i study (Supplemental Table 1). The participants of the LURIC study are individuals at medium to high CVD risk. The PCSK9i study included patients receiving intensive lipid-lowering therapy and therefore had low LDL-C values (mean crude LDL-C_{UC} before initiation of PCSK9i: 113.0 mg/dL). The patients were middle-aged, with an average of 63 (56 - 71) years, and predominantly male (68% men and 32% women). The median Lp(a)-value was 17 mg/dL in the entire data set, 16 mg/dL in the LURIC study and 25 mg/dL in the PCSK9i study.

Effect of Lp(a) on the LDL-C_{UC}

To analyze LDL-C_{UC} and LDL-C_{UC}* according to increasing Lp(a), we stratified the cohort into three subgroups: < 30 mg/dL, 30 - 50 mg/dL, and > 50 mg/dL (Figure 1). The mean differences between both LDL-C_{UC} and LDL-C_{UC}* increased significantly in parallel to Lp(a) (< 30: mean 3.6 mg/dL; 30 - 50: 10.0 mg/dL; > 50: 22.3 mg/dL; $p < 0.05$). While the increase of LDL-C_{UC} across the Lp(a) strata was expected, LDL-C_{UC}* interestingly also increased. For Lp(a) > 50mg/dL, the median and mean deviations between LDL-C_{UC} and LDL-C_{UC}* were, in absolute terms, six times higher than the deviation at Lp(a) < 30 mg/dL.

This observation is further illustrated in Supplemental Table 4, showing an increasing deviation of LDL-C_{UC} and LDL-C_{UC}*, with increasing Lp(a) values, which becomes more pronounced at higher Lp(a) levels.

Effect of Lp(a) on LDL-C_{FW}, LDL-C_{MH}, and LDL-C_{SN}

Overall, LDL-C_{FW}, LDL-C_{MH}, and LDL-C_{SN} differed only slightly from LDL-C_{UC}. The tendency to overestimate LDL-C_{UC} was evident with all three equations, but to a different extent: LDL-C_{FW} had the smallest deviation from LDL-C_{UC} (mean difference (SD) of 3.3 (17.6) mg/dL), followed by LDL-C_{SN} and LDL-C_{MH} (mean differences of 6.5 (17.1) and 7.5 (18.6) mg/dL, respectively). The deviations were significantly different, but overall, less than 4% of the mean LDL-C_{UC} ($p < 0.001$).

As expected, correcting LDL-C_{UC} for Lp(a)-C enlarged the difference between LDL-C_{UC}* and the formulas: LDL-C_{FW} showed a four-fold and LDL-C_{SN} and LDL-C_{MH} showed two-fold mean differences (LDL-C_{FW}: 11.8 vs. 3.3 mg/dL; LDL-C_{SN}: 14.9 vs. 6.5 mg/dL; LDL-C_{MH}: 16.0 vs. 7.5 mg/dL), when comparing them with LDL-C_{UC}* and LDL-C_{UC}, respectively. Yet, LDL-C_{FW} stayed closest to LDL-C_{UC}* (Table 1).

The absolute differences between LDL-C_{UC}* values and formula-based LDL-C* values were not significantly different compared to the unadjusted analysis, with all statistical significance values and patterns of deviation remaining unchanged (Table 1).

Effect of Lp(a) on LDL-C_{FW}, LDL-C_{MH}, and LDL-C_{SN} according to Lp(a) subgroups

With higher Lp(a) values, the LDL-C_{UC} value increased progressively by about 3 mg/dL per subgroup, whereas the LDL-C_{UC}* value decreased substantially. LDL-C_{FW}, LDL-C_{MH}, or LDL-C_{SN} similarly differed from LDL-C_{UC}/LDL-C_{UC}* across the Lp(a) subgroups (Table 1 and Figure 2A-C). Considering the deviation of the equations to LDL-C_{UC}*, however, a significant increase in the overestimation of LDL-C by the formulas was observed, as the Lp(a)-values increased. At low Lp(a), the mean difference between LDL-C_{FW} and LDL-C_{UC}* was smallest (7.1 mg/dL), followed by LDL-C_{SN} (10.4 mg/dL) and LDL-C_{MH} 11.8 mg/dL ($p < 0.05$). At Lp(a) 30 - 50 mg/dL, the overestimation further increased for each method, and the highest deviations were recorded for Lp(a) > 50 mg/dL, with an average difference of more than 25 mg/dL in all three equations, whereby LDL-C_{FW} showed the smallest difference of 25.3 mg/dL.

The equations did not differ substantially from each other in their correlations with LDL-C_{UC} or with LDL-C_{UC}*. For all Lp(a) groups, the correlation coefficients were ≥ 0.88. (Supplemental Table 3). However, at Lp(a) > 50 mg/dL, the correlation of all three equations with LDL-C_{UC} was significantly stronger compared to the respective correlation with LDL-C_{UC}*. This difference was not observed in the subgroups with lower Lp(a) concentrations.

In the Passing Bablok analysis, the equations showed no significant difference in their slope, regardless of

Table 1. Effect of Lp(a) on LDL-$C_{UC(*)}$, LDL-$C_{FW(*)}$, LDL-$C_{MH(*)}$, and LDL-$C_{SN(*)}$ at different, increasing Lp(a)-concentrations.

Lp(a) subgroup	n	Method	Mean LDL-C	Difference to LDL-C_{UC}	%	Difference to LDL-C_{UC}*	%	Mean LDL-C*	Difference to LDL-C_{UC}*	%
All	3,921	ß-quantification (LDL-C_{UC})	116.9 (41.2)			8.5 (9.0)	7.8	108.4 (41.4)		
		Friedewald (LDL-C_{FW})	120.2 (44.1)	3.3 (17.6)	2.8	11.8 (19.6)	10.9	111.7 (44.4)	3.3 (17.6)	3.0
		Martin/Hopkins (LDL-C_{MH})	124.4 (42.8)	7.5 (18.6)	6.4	16.0 (20.3)	14.8	116.0 (43.3)	7.5 (18.6)	6.9
		Sampson (LDL-C_{SN})	123.3 (43.3)	6.5 (17.1)	5.6	14.9 (19.1)	13.7	114.9 (43.6)	6.5 (17.1)	6.0
< 30 mg/dL	2,616	ß-quantification (LDL-C_{UC})	115.2 (39.8)			3.6 (1.83) *	3.2	111.6 (39.7)		
		Friedewald (LDL-C_{FW})	118.7 (43.0)	3.6 (19.0)	3.1	7.1 (19.0) *	6.4	115.2 (42.9)	3.6 (19.0)	3.2
		Martin/Hopkins (LDL-C_{MH})	123.4 (41.7)	8.2 (20.0) *	7.1	11.8 (20.0) *	10.6	119.8 (41.6)	8.2 (20.0) *	7.3
		Sampson (LDL-C_{SN})	122.0 (41.9)	6.9 (18.3)	6.0	10.4 (18.4) *	9.3	118.4 (41.8)	6.9 (18.3)	6.2
30 - 50 mg/dL	429	ß-quantification (LDL-C_{UC})	118.7 (44.5)			10.0 (1.3) *	9.1	108.7 (44.3)		
		Friedewald (LDL-C_{FW})	120.8 (46.6)	2.2 (13.1)	1.9	12.1 (13.0) *	11.1	110.8 (46.4)	2.2 (13.1)	2.0
		Martin/Hopkins (LDL-C_{MH})	124.8 (45.2)	6.2 (14.0)	5.2	16.2 (13.9) *	15.0	114.9 (45.1)	6.2 (14.0)	5.7
		Sampson (LDL-C_{SN})	123.9 (46.1)	5.3 (13.0)	4.5	15.3 (12.9) *	14.0	113.9 (46.0)	5.3 (13.0)	4.9
> 50 mg/dL	876	ß-quantification (LDL-C_{UC})	121.2 (43.1)			22.3 (9.32) *	22.5	98.9 (43.7)		
		Friedewald (LDL-C_{FW})	124.2 (45.5)	3.0 (15.2)	2.5	25.3 (18.0) *	25.6	101.8 (46.2)	3.0 (15.2)	3.0
		Martin/Hopkins (LDL-C_{MH})	127.3 (43.1)	6.1 (16.1)	5.0	28.4 (18.6) *	28.7	105.0 (45.2)	6.1 (16.1)	6.2
		Sampson (LDL-C_{SN})	127.0 (44.7)	5.8 (15.1)	4.8	28.2 (17.9) *	28.5	104.7 (45.9)	5.8 (15.1)	5.9

A total of 3,921 samples from the LURIC and PCSK9i study were categorized into four different Lp(a)-subgroups: < 30, 30 - 50, > 50 mg/dL, and total cohort. Column 2 contains the number of samples in each Lp(a)-subgroup. Column 5 shows the difference between the crude formula-estimated LDL-C and LDL-C_{UC}, column 7, the difference between the crude formula-estimated LDL-C and LDL-C_{UC}*, and column 10, the deviation of LDL-C_{FW}*, LDL-C_{MH}*, and LDL-C_{SN}* from LDL-C_{UC}*. The corrected LDL-C* forms were calculated according to the formula LDL-C - (Lp(a)-C* 0.23 + 1.00). All values are given as mean values and standard deviations in brackets, in mg/dL. In column 6 are the relative differences between formula-estimated LDL-C and LDL-C_{UC}, in column 8 are the relative differences between formula-estimated LDL-C and LDL-C_{UC}*, and in column 11 the difference between estimated LDL-Cs* by the respective equation and LDL-C_{UC}* is given. If there is a significant difference between the LDL-C deviations in a specific Lp(a)-subgroup compared to the other Lp(a)-subgroups, the MD is marked with an asterisk (p < 0.05).

LDL-C_{UC} - crude LDL-C_{UC}, LDL-C_{UC}* - lp(a)-corrected LDL-C_{UC}, LDL-C_{FW} - crude LDL-C_{FW}, LDL-C_{FW}* - lp(a)-corrected LDL-C_{FW}, LDL-C_{MH} - crude LDL-C_{MH}, LDL-C_{MH}* - lp(a)-corrected LDL-C_{MH}, LDL-C_{SN} - crude LDL-C_{SN}, LDL-C_{SN}* - Lp(a)-corrected LDL-C_{SN}, FW – Friedewald equation, SN - Sampson equation, MH - Martin/Hopkins equation.

whether LDL-C_{UC} or LDL-C_{UC}* was used. Furthermore, no difference between the Lp(a)-subgroups could be found for any of the equations (Supplemental Table 3).

Determination of the clinical relevance

We defined a relative difference between LDL-C_{UC} and LDL-C_{UC}* (i.e. the overestimation of LDL-C by the contribution of Lp(a)-C) of more than 10% as clinically relevant. This overestimation was more pronounced 1) the higher the Lp(a) concentration, and 2) the smaller the LDL-C_{UC} value was (Supplemental Table 4 and 5). By using Passing-Bablok regression analysis, we deter-

Table 2. Relative deviation between LDL-C_{UC} and LDL-C_{UC}* at increasing Lp(a)-levels.

	Lp(a) in mg/dL								
LDL-C_{UC}	10	20	30	40	50	70	90	110	130
50	6.00	12.00	18.00	24.00	30.00	42.00	54.00	66.00	78.00
75	4.00	8.00	12.00	16.00	20.00	28.00	36.00	44.00	52.00
100	3.00	6.00	9.00	12.00	15.00	21.00	27.00	33.00	39.00
125	2.40	4.80	7.20	9.60	12.00	16.80	21.60	26.40	31.20
150	2.00	4.00	6.00	8.00	10.00	14.00	18.00	22.00	26.00
175	1.71	3.43	5.14	6.86	8.57	12.00	15.43	18.86	22.29
200	1.50	3.00	4.50	6.00	7.50	10.50	13.50	16.50	19.50
225	1.33	2.67	4.00	5.33	6.67	9.33	12.00	14.67	17.33
250	1.20	2.40	3.60	4.80	6.00	8.40	10.80	13.20	15.60

Based on 3,921 data sets from the LURIC and PCSK9i studies, the percentage deviations of LDL-C_{UC}* from LDL-C_{UC} are shown. Column 1 contains LDL-C_{UC}, the other columns Lp(a). All values are given in mg/dL. Different shades of grey underline the extent of the deviation: light grey, 10 to 20%; medium grey, up to 30%; and dark grey, above 30%.
LDL-C_{UC} - crude LDL-CUC, LDL-C_{UC}* - LDL-C_{UC} corrected for Lp(a)-C. For remaining abbreviations see legend of Table 1.

mined a Lp(a) concentration of 58 mg/dL as the threshold at which the difference between LDL-C_{UC} and LDL-C_{UC}* is more than 10% of the actual LDL-C value (derived from Table 2).
The magnitude of the deviation was also determined by the LDL-C concentration. A lower LDL-C_{UC} value was accompanied by a stronger effect of the correction. As an example, Lp(a) of 50 mg/dL in combination with an LDL-C_{UC} of 50 mg/dL was associated with the difference between LDL-C_{UC} and LDL-C_{UC}* of 30%. In contrast, the same Lp(a) concentration in combination with a LDL-C_{UC} of 250 mg/dL yielded a relative difference of only 6%. Thus, the lower the LDL-C_{UC} value, the earlier a deviation of more than 10% occurred (see Table 2). At LDL-C_{UC} < 50 mg/dL, 61% of the samples deviated by ≥ 10%, compared to 17.3% at LDL-C_{UC} 150 - 175 mg/dL (Supplemental Table 5).

Effect of Lp(a) on LDL-C and LDL-lowering in patients treated with PCSK9i

The effects of PCSK9i therapy on LDL-C_{UC}, LDL-C_{UC}*, LDL-C_{FW}, LDL-C_{SN}, and LDL-C_{MH} according to Lp(a) are shown in Table 3. Although Lp(a) was only minimally affected by PCSK9i therapy (reductions of 25%, 10%, and 18% for Lp(a) < 30, 30 - 50, and > 50 mg/dL, respectively) [18], the absolute reductions of LDL-C estimated by the uncorrected methods were significantly higher compared to reductions of LDL-C_{UC}*. However, the LDL-C_{UC}* values on treatment were significantly lower compared to the uncorrected values ($p < 0.0001$ for all comparisons), suggesting that the LDL-lowering effects are underestimated without correction for Lp(a)-C. This occurs in all subgroups but is most pronounced at high Lp(a) levels.
During PCSK9 inhibitor therapy, all formula-based LDL-C* consistently overestimated LDL-C *reduction compared to the corrected reference (*LDL-C_{UC}*), particularly at low Lp(a) levels. This overestimation diminished at Lp(a) concentrations above 50 mg/dL. Nonetheless, the overall trend of greater LDL-C* reductions with increasing baseline Lp(a) was observed across all formula-based LDL-C* forms and confirmed by the reference method (Table 3).

KI-based prediction of Lp(a) levels using multiple lipid variables

In search of an algorithm which would allow to decide whether high Lp(a) can be suspected from a generic lipid profile, we used artificial intelligence to investigate whether Lp(a) can be predicted from total cholesterol, LDL-C, HDL-C, and triglycerides.
The correlation analysis showed no strong association between Lp(a) and any of the lipid levels. In the mutual information analysis, there were some nonlinear associations, but only the one between HDL-C and Lp(a) was weakly significant ($p = 0.02$). The prediction models (linear regression, random forest, gradient boosting, XGBoost, neural networks) yielded results with low R^2 values and high errors (RMSE ~ 40 - 42), especially at high Lp(a) levels (Supplemental Figures 4 and 5).

DISCUSSION

The key aim of our study was to go beyond the well-established fact that Lp(a)-cholesterol is included in LDL-C measurements, and instead, to systematically quantify its impact across a clinically relevant spectrum of patients and therapeutic settings. We sought to assess how this affects routine LDL-C interpretation and the need for correction in daily practice. To this end, we investigated the effects of Lp(a) on LDL-C values determined

Table 3. Lp(a)-effect on therapy evaluation in PCSK9i patients with regard to different determined LDL-C/LDL-C* forms.

Lp(a) subgroups	Mean Lp(a) baseline (SD)	Mean Lp(a)-C baseline (SD)	Mean baseline (SD)		Mean Lp(a) during therapy	Mean Lp(a)-C baseline (SD)	Mean during therapy (SD)	LDL-C reduction absolute %	
All	52 (57)	13 (13)	LDL-C_{UC}	153 (58) *	43 (48)	11 (11)	75 (48) *	78 *	51.0%
			LDL-C_{FW}	165 (65) *			73 (52) *	92 *	55.8%
			LDL-C_{SN}	168 (63) *			76 (52) *	92 *	54.8%
			LDL-C_{MH}	168 (64) *			77 (51) *	91 *	54.2%
			LDL-C_{UC}*	140 (61)			64 (49)	76	54.3%
			LDL-C_{FW}*	152 (69) *			62 (53) *	90 *	59.2%
			LDL-C_{SN}*	155 (67) *			65 (53)	89 *	57.4%
			LDL-C_{MH}*	155 (68) *			66 (52)	89 *	57.4%
< 30 mg/dL	12 (8)	4 (2)	LDL-C_{UC}	158 (61) *	10 (8)	3 (2)	77 (51) *	97 *	54.8%
			LDL-C_{FW}	173 (71) *			76 (56)	97 *	56.1%
			LDL-C_{SN}	175 (68) *			79 (56) *	96 *	54.9 %
			LDL-C_{MH}	177 (70) *			80 (55) *	97 *	54.8%
			LDL-C_{UC}*	154 (60)			74 (51)	80	51.9%
			LDL-C_{FW}*	169 (71) *			72 (56)	96 *	56.8%
			LDL-C_{SN}*	171 (68) *			75 (55)	95 *	55.6%
			LDL-C_{MH}*	173 (70) *			77 (55) *	96 *	55.5%
30 - 50 mg/dL	42 (4)	11 (1)	LDL-C_{UC}	160 (59) *	39 (10)	10 (2)	76 (43) *	84 *	52.5%
			LDL-C_{FW}	170 (61) *			71 (45) *	99 *	58.2%
			LDL-C_{SN}	172 (60) *			74 (45) *	98 *	57.0%
			LDL-C_{MH}	173 (59) *			76 (43) *	97 *	56.1%
			LDL-C_{UC}*	149 (59)			60 (44)	83	55.7%
			LDL-C_{FW}*	159 (61) *			55 (43) *	97 *	61.0%
			LDL-C_{SN}*	161 (60) *			57 (43)	96 *	59.6%
			LDL-C_{MH}*	162 (59) *			58 (42)	96 *	59.2%
> 50 mg/dL	111 (54)	26 (12)	LDL-C_{UC}	145 (53) *	99 (47)	24 (11)	72 (43) *	73 *	50.3%
			LDL-C_{FW}	154 (55) *			70 (47) *	84 *	54.4%
			LDL-C_{SN}	156 (55) *			72 (48) *	84 *	53.8%
			LDL-C_{MH}	155 (54) *			72 (46) *	83 *	53.5%
			LDL-C_{UC}*	119 (56)			50 (44)	70	58.8%
			LDL-C_{FW}*	128 (58) *			49 (49)	80 *	62.5%
			LDL-C_{SN}*	130 (58) *			51 (49)	80 *	61.5%
			LDL-C_{MH}*	129 (57) *			51 (48)	79 *	61.2%

A total of 678 datasets from PCSK9i-study were examined. Data shown are divided into three Lp(a)-subgroups, each with crude and lp(a)-corrected forms of LDL-C_{UC}, LDL-C FW, LDL-C SN, and LDL-C MH. The corrected LDL-C* forms were calculated by the formula: LDL-C - (0.23 * Lp(a) + 1.00). The values are given as mean values and the corresponding standard deviation in brackets behind them (in mg/dL). Column 4 shows the mean value of LDL-C/LDL-C* forms before the start of PSCK9i-therapy, while column 7 shows them during PSCK9i-therapy. The achieved LDL-C reduction was given in absolute amount (column 8) and percentage (column 9). Mean LDL-C(*) forms were marked with an asterisk when they differ significantly from mean LDL-C_{UC}*; LDL-C reductions were marked with an asterisk when they differ significantly from LDL-C_{UC}* ($p < 0.0001$). For abbreviations see legend of Table 1.

by ß-quantification (LDL-C_{UC}) and on LDL-C using the formulas by Friedewald, Sampson, and Martin/Hopkins. Our main findings were: Above a concentration of 10 mg/dL, Lp(a) contributed significantly to LDL-C across all methods. The impact of Lp(a)-C on LDL-C_{UC} increased in parallel to increasing Lp(a). This trend was in relative terms more pronounced in the presence of low LDL-C_{UC}. Above an Lp(a)-value of 58 mg/dL, the overestimation of the actual LDL-C_{UC} value was on average $\geq$ 10%, which we considered as clinically rele-

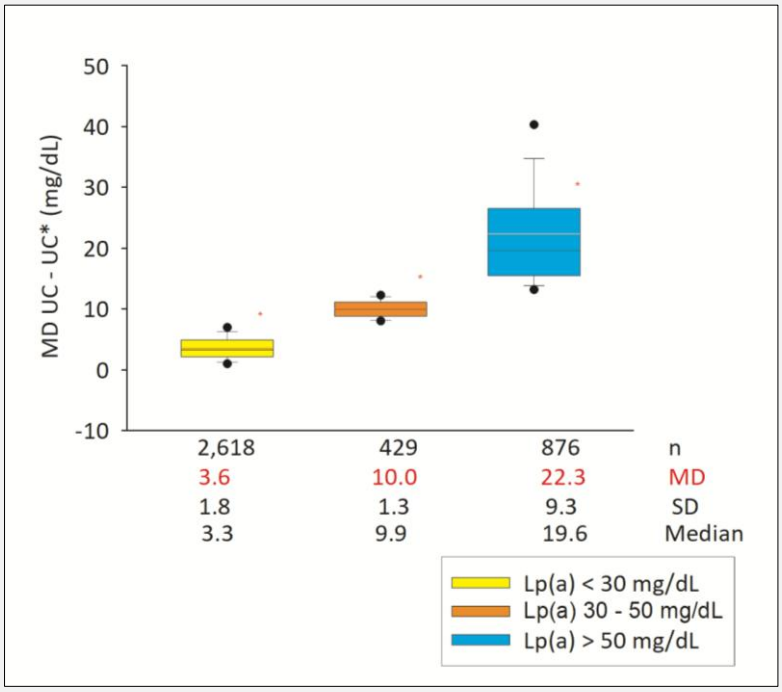

Figure 1. Deviation between LDL-C_{UC} and LDL-C_{UC}* according to ranges of Lp(a).

LDL-C_{UC}* was calculated from LDL-C_{UC} as LDL-C - (Lp (a)*0.23 + 1.00). The red center line of the boxes represents the mean value (50th percentile), the black line the median. The black box contains the 25th to 75th percentiles. The black whiskers mark the 10th and 90th percentiles. The outliers (5th and 95th percentile) are indicated as black dots. Each boxplot represents one of the 3 Lp(a) ranges in different colors (yellow: Lp(a) < 30 mg/dL; orange: 30 - 50 mg/dL; turquoise: > 50 mg/dL). The red asterisks mark significant differences to the two other Lp(a) subgroups. The MDs differed significantly between the three subgroups at p < 0.05.
Lp(a) - lipoprotein(a), LDL-C - low density lipoprotein-cholesterol, LDL-C_{UC} - crude LDL-C_{UC}, LDL-C_{UC}* - Lp(a)-corrected LDL-C_{UC}, MD - mean difference, SD - standard deviation.

vant. The percentage of samples with deviations ≥ 10% increased, the lower the LDL-C_{UC} value was. This significant overestimation of LDL-C was also observed when we used the formulas of Friedewald, Martin/Hopkins, and Sampson for LDL-C.

To further investigate the impact of Lp(a) on the determination of LDL-C_{UC}, we corrected LDL-C_{UC} [21] to generate LDL-C_{UC}*. LDL-C_{FW}, LDL-C_{MH}, and LDL-C_{SN} were highly correlated with both LDL-C_{UC} and LDL-C_{UC}*. At Lp(a) above 50 mg/dL the equations correlated significantly stronger with LDL-C_{UC} than with LDL-C_{UC}*, suggesting that Lp(a)-C is included in the LDL-C values obtained from the equations. Across the entire range of Lp(a) values, LDL-C_{FW} was closest to LDL-C_{UC} and LDL-C_{UC}*, followed by LDL-C_{SN} and LDL-C_{MH}. *The absolute differences between* LDL-C_{UC}* *and the formula-based LDL-C** values were consistent with the unadjusted analysis, maintaining stable significance levels and difference patterns.

Our results are relevant to the assessment of lipid-lowering therapy. When LDL-C was determined without correction for Lp(a)-C, the beneficial effects of PCSK9i therapy were underestimated. In fact, the number of patients achieving their therapeutic goal for LDL-C is higher when using corrected LDL-C rather than uncorrected methods. When analysing the corrected formula-based LDL-C values, we observed a similar trend to the reference method, with a greater relative LDL-C reduction as baseline Lp(a) levels increased. All formula-based approaches significantly overestimated the accurate LDL-C reduction, particularly at low Lp(a) levels. The differences between the formulas remained stable, consistent with the uncorrected comparisons.

Our findings are in line with the current literature [3,12, 26]. Kinpara et al. [3] observed a significant overestimation of the actual LDL-C when Lp(a)-C is not taken into account. In their analysis, the median difference between the calculated LDL-C_{FW} and LDL-C_{UC}* increased with rising Lp(a)-levels, with LDL-C_{FW} overestimating LDL-C* by 20.4 % at the highest Lp(a) values (> 50 mg/dL) [3]. Saeedi et al. [12] and Li et al. [26] also observed a significant overestimation of the actual LDL-C value by using the Friedewald equation. In both studies the effect increased with increasing Lp(a). Ac-

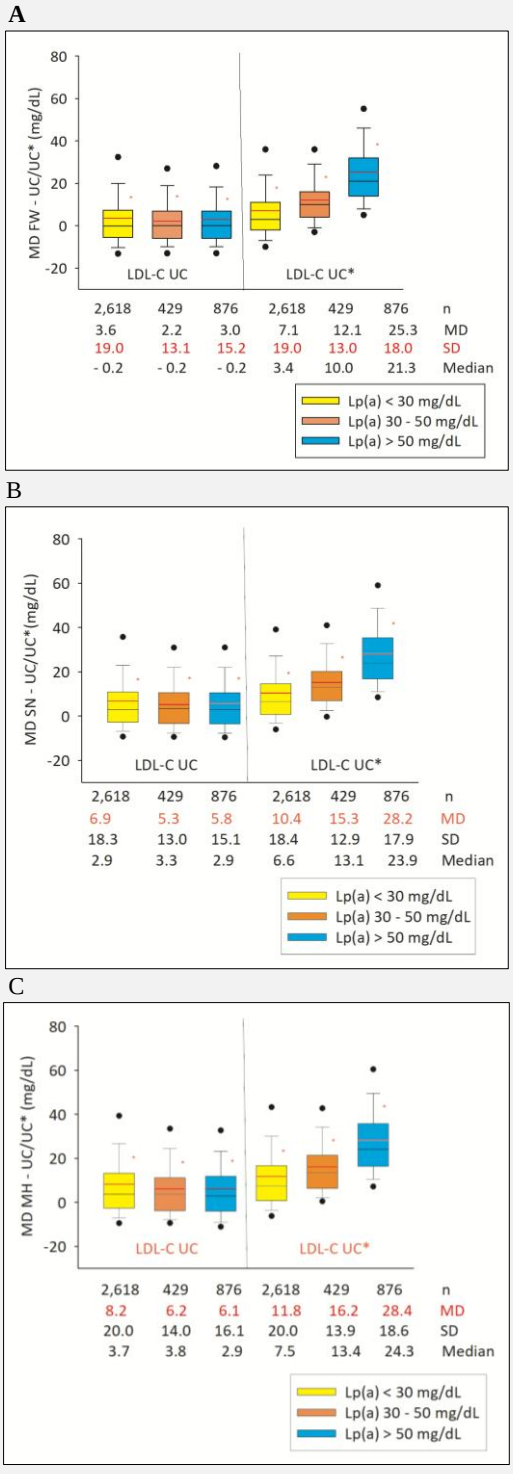

Figure 2. Effect of Lp(a) on LDL-C_{FW} (2A), LDL-C_{SN} (2B), and LDL-C_{MH} (2C) according to Lp(a).
On the left side of each panel, the formula-generated LDL-C is compared to LDL-C_{UC}, on the right side, the formula-generated LDL-C is compared to LDL-C_{UC}*. LDL-C_{UC}* = LDL-C - (Lp(a)*0.23 + 1.00)). The red center line denotes the mean value (50th percentile), the black line denotes the median. The black box contains the 25th to 75th percentiles. The black whiskers mark the 10th and 90th percentiles. The outliers (5th and 95th percentile) are indicated as black dots. Each boxplot represents one of the 3 Lp(a) ranges in different colors (yellow: Lp(a) < 30 mg/dL; orange: 30 - 50 mg/dL; turquoise: > 50 mg/dL). Panel 2A refers to the Friedewald equation, Panel 2B to the Sampson equation, and Panel 2C to the Martin/Hopkins equation. The red asterisk marks boxplot, if it shows significant differences 1) between LDL-C_{UC} and LDL-C_{UC}* and 2) between LDL-C_{UC} and the estimated LDL-C.
LDL-C_{UC} - crude LDL-C_{UC}, LDL-C_{UC}* - lp(a)-corrected LDL-C_{UC}, FW - Friedewald equation, SN - Sampson equation, MH - Martin/Hopkins equation. For other abbreviations see legend of Figure 1.

cording to Saeedi et al., LDL-C_{FW} was up to 40% higher than LDL-C* [12]. Li et al. found an overestimation of the actual LDL-C value between 4.1 and 21.4%, with the overestimation increasing in parallel to the Lp(a) levels [26]. To clarify the clinical relevance, some authors investigated the effect of Lp(a) on the classification of familial hypercholesterolemia (FH) [8,11,27]. For instance, Willeit et al. [27] showed that a significant percentage of patients was classified into lower LDL-C categories by using LDL-C*. This trend increased with increasing LDL-C levels: 30.2% at LDL-C 70 - 100 mg/dL, 35.1% at LDL-C 100 - 130 mg/dL, 32.9% at LDL-C 130 - 190 mg/dL, and 41.1% at LDL-C $\geq$ 190 mg/dL of the patients were reassigned to lower LDL-C categories [27]. As FH is defined as a disorder caused by an impaired catabolism of LDL, but not Lp(a), it remains an entirely open question whether or not LDL-C and Lp(a)-C should be lumped together for the diagnosis of FH or whether LDL-C* should be considered instead.

In the current literature, there seems to be broad consensus on a more accurate differentiation of LDL-C into actual LDL-C* and Lp(a)-C and that LDL-C* should be used in particular in the case of high Lp(a) [3,9]. Until now, only lipoprotein electrophoresis with subsequent enzymatic staining for cholesterol allows the direct determination of Lp(a)-C which is satisfactorily accurate once Lp(a) exceeds 10 mg/dL [21]. As this method is not widely available, a correction for Lp(a)-C has to be derived from the mass or molar concentration of the Lp(a) particles [28-30]. Usually Lp(a)-C is estimated by multiplying the Lp(a) mass by 0.3. Kronenberg et al. argued against a routine correction of LDL-C for Lp(a) and only suggested using LDL-C* for 1) patients with a clinically suspected FH-diagnosis and elevated Lp(a)-values and 2) patients with "statin resistance" [31]. This recommendation was followed by other authors who saw a higher risk in the inaccurate estimation of Lp(a)-C, assuming a fixed ratio of cholesterol to the Lp(a) concentration, than in neglecting Lp(a)-C in general [11,32].

Especially, the estimation of Lp(a)-C with a fixed factor of 0.3 has been challenged, because biochemical analyses claimed that the cholesterol content of Lp(a) varied between 30% to 45% of the total Lp(a)-mass [33-36]. Consistent with this finding, Fatica et al. [7] reported that at low LDL-C levels (10 - 39 mg/dL), about 25% of LDL-C was contributed by Lp(a)-C, whereas at higher LDL-C levels (40 - 99 mg/dL), approximately 15% of the LDL-C were due to Lp(a)-C. A deviation from the commonly set 30% was also found in our previous analysis, which estimated the proportion of cholesterol at around 23% of total Lp(a). Therefore, in our analyses, the approximation "(Lp(a) * 0.23 + 1.00)" was used for Lp(a)-C, which corrects the LDL-C value slightly less.

Our artificial intelligence analyses showed that Lp(a) cannot be reliably predicted from total cholesterol, LDL-C, HDL-C, and triglycerides. The models often underestimated Lp(a) and failed to capture its variability, especially at high levels, suggesting Lp(a) is largely independent of conventional lipid values. Hence, Lp(a) determinations cannot be replaced by artificial intelligence at the current knowledge.

Based on our findings, we suggest the use of LDL-C* when 1) the Lp(a)-value is above 58 mg/dL, 2) the LDL-C value is below 100 mg/dL, or 3) the effect of lipid-lowering treatment on LDL-C is less than expected or even absent. A correction for Lp(a) is not required when the Lp(a)-value is below 10 mg/dL. Our recommendations are in line with those of other authors [2,3, 8,26]. The distortion of the actual LDL-C by high Lp(a) value may lead to an incorrect diagnosis and/or treatment decision and follow-up care with clinical consequences for the patient [3,11,12,26].

Strengths and limitations

Our study offers robust, data-driven insights into LDL-C correction for Lp(a), addressing a clinically relevant gap in the absence of randomized controlled endpoint studies.

We used the gold standard method (beta-quantification) to determine LDL-C levels, in which Lp(a)-C is entirely included in the LDL fraction. Thus, our correction may be more accurate compared to studies using enzymatic assays or VAP for LDL-C, in which Lp(a)-C may in part be included into other lipoprotein fractions (VLDL, HDL) [11,12]. To our knowledge, this is the first study investigating the effect of Lp(a)-C on LDL-C_{MH} and LDL-C_{SN}, and there is only limited data on LDL-$C_{FW.}$ [13,26]. This addresses a major gap in the literature and significantly enhances the analytical validity and clinical relevance of Lp(a)-related LDL-C correction.

We applied Lp(a) corrections to formula-based LDL-C values, but these offered no additional insights, as the correction factor was effectively neutralized and results closely matched those of the reference method. This highlights the need for dedicated, formula-specific correction approaches, which remain unavailable to date. Another aspect that has barely been investigated so far was the impact of Lp(a)-C on the apparent therapeutic effect of PCSK9i.

Our study is distinguished by several key strengths: 1) a large and validated cohort of 3,923 samples, 2) a comprehensive comparison of all three major Lp(a)-correction formulas against the gold standard (beta-quantification), 3) the inclusion of patients undergoing PCSK9 inhibitor therapy, and 4) the application of AI-supported methods to investigate Lp(a)-C derivation. These elements provide novel insights and offer significant practical implications for clinical lipid management.

The main limitations of our study include the reliance on an estimated Lp(a)-C value derived from a Passing-Bablok regression analysis by Nauck et al., which improves upon the conventional correction factor of 0.30 but remains an approximation. As shown by Nauck et al., this correction factor is largely independent of the Lp(a) particle heterogeneity. Our estimation of Lp(a)-C

is based on this model-based approach, and therefore, does not strictly align with the current recommendations of the National Lipid Association (NLA), which currently do not support LDL-C correction [39]. As no international standardized method for LDL-C correction or direct Lp(a)-C measurement exists, our method represents a pragmatic compromise within current methodological limitations. Importantly, the clinical relevance of this correction is limited at low Lp(a) concentrations (< 10 mg/dL), where deviations generally remain below 2 mg/dL and have a minor impact on interpretation. However, as Lp(a) levels exceed 50 mg/dL, the potential of distortion increases noticeably. Given the Lp(a) median of 17 mg/dL and mean of 32.5 mg/dL observed in our cohort, the overall impact on our results is expected to be moderate, with only 22.3% samples exceeding the threshold where correction may be required [11]. Another limitation is the use of mg/dL to report lipid parameters, including Lp(a)-C. While molar units (nmol/L) are more precise and guideline-recommended, mg/dL is widely used in clinical practice and in the majority of available studies. Due to the isoform-dependent variability in Lp(a) molecular weight and the absence of standardized conversion factors, reporting in mg/dL represents a pragmatic and widely accepted compromise that ensures comparability with previous data [40]. Finally, while a predominantly German cohort may limit generalizability, it provides a well-defined and homogenous population that enables more precise and controlled investigations.

CONCLUSION

With the exception of lipoprotein electrophoresis, established methods in routine lipid analysis cannot accurately differentiate between LDL-C and Lp(a)-C. An overestimation of LDL-C may result in misclassifications of dyslipidemia and misinterpretation of effects of lipid-lowering medicines, especially in high-risk ASCVD patients [3,7,29]. In conclusion, we recommend the use of LDL-C* at 1) high Lp(a) concentrations, 2) low LDL-C values, and 3) in an unexpectedly low response to LDL-lowering medicines.

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Declaration of Interest:
The authors declare the following financial interests/ personal relationships that could be seen as potential conflicts of interest:
S. Drobnik, A. Koloi, U. Kassner, A. Dressel, W. Drobnik have nothing to declare. H. Scharnagl: Abbott Diagnostics, Amgen, Sanofi. T. Hollstein: AMGEN, Daiichi Sankyo, Eli Lilly, MSD, Novartis, Novo Nordisk, Sanofi, Science & Stories GmbH, Techniker Krankenkasse, SOBI, Recordati Pharma. M. Nauck: Amgen, Biorad, Sysmex, Novartis, Novonordisk, Radiometer, Technopath. W. März: AMGEN, Sanofi, Amryt Pharmaceuticals, Abbott Diagnostics, Akzea Therapeutics, Novartis Pharma, SOBI, employment with SYNLAB Holding Deutschland GmbH.

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