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Impact of concomitant Lp(a) level on LDL-cholesterol or apolipoproteinB-related risk for incident coronary heart disease

(*Arnold et al. Lp(a) and LDL-C or apoB-related CHD risk*)

Natalie Arnold MD,[a,b,c]* Christopher Blaum MD,[a,c*] Alina Goßling MSc,[a,c] Fabian J. Brunner MD,[a,b,c] Benjamin Bay MD,[a,b,c] Tanja Zeller PhD,[a,b,c,d] Marco M. Ferrario MD, PhD,[e] Paolo Brambilla MD,[f] Giancarlo Cesana PhD,[f] Valerio Leoni MD,[g] Luigi Palmieri PhD,[h] Chiara Donfrancesco PhD,[h] Francisco Ojeda PhD, [a,c] Allan Linneberg MD,[i,j] Stefan Söderberg MD,[k] Licia Iacoviello MD, PhD,[,l,m] Francesco Gianfagna MD, PhD,[e,n] Simona Costanzo PhD,[m] Susana Sans MD, PhD[o] Giovanni Veronesi PhD,[e] Barbara Thorand PhD,[p,q] Annette Peters PhD,[p,q,r] Hugh Tunstall-Pedoe MD,[s] Frank Kee MD,[t] Veikko Salomaa MD,[u] Renate Schnabel MD,[a,b,c] Kari Kuulasmaa PhD,[u] Stefan Blankenberg MD,[a,b,c] Christoph Waldeyer MD,[a,b,c]* Wolfgang Koenig MD,[v,w,r]*, on behalf of the BiomarCaRE investigators

*contributed equally

[a]Department of Cardiology, University Heart & Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg; Hamburg, Germany; [b]German Center for Cardiovascular Research (DZHK), partner site Hamburg/Kiel/Luebeck, Hamburg, Germany; [c]Center for Population Health Innovation (POINT), University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [d]University Center of Cardiovascular Science at University Heart and Vascular Center Hamburg, Hamburg, Germany; [e]Research Center in Epidemiology and Preventive Medicine - EPIMED, Department of Medicine and Surgery, University of Insubria, Varese, Italy; [f]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; [g]Laboratory of Clinical Pathology, Hospital Pio XI of Desio, ASST Brianza, School of Medicine and Surgery, University of Milano Bicocca, Milan, Italy; [h]Department of Cardiovascular, Endocrine-Metabolic Diseases and Aging, Istituto Superiore di Sanità-ISS, Rome, Italy; [i]Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark; [j]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [k]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [l]Department of Medicine and Surgery, LUM University, Casamassima. Italy; [m]Department of Epidemiology and Prevention, IRCCS Neuromed, Pozzilli, Italy; [n]Mediterranea Cardiocentro, Napoli, Italy; [o]Catalan Department of Health, Barcelona, Spain; [p]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; [q]Institute for Medical Information Processing, Biometry, and Epidemiology – IBE, Ludwig-Maximilians University of Munich, Munich, Germany; [r]German Center for Cardiovascular Disease Research (DZHK), partner site Munich Heart Alliance, Munich, Germany; [s]Cardiovascular Epidemiology Unit, Institute of Cardiovascular Research, University of Dundee, Dundee, Scotland; [t]Centre for Public Health, Queens University of Belfast, Belfast, Northern Ireland, UK; [u]Department of Public Health and Welfare, Finnish Institute for Health and Welfare (THL), Helsinki, Finland; [v]German Heart Center, Munich, Technical University of Munich, Munich, Germany; [w]Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany.

Address for correspondence:
Wolfgang Koenig; MD, FRCP, FESC, FACC, FAHA
Professor of Medicine/Cardiology
German Heart Center, Munich,
Technical University of Munich
Lazarettstr. 36
80636 München
Tel. : + 49-89-1218-4073
Fax: +49-89-1218-2023
Email: koenig@dhm.mhn.de

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Abstract

Background: Conventional LDL-cholesterol (LDL-C) quantification includes cholesterol attributable to lipoprotein (a) (Lp(a)-C) due to their overlapping densities.

Objectives: To compare the association between LDL-C and LDL-C corrected for Lp(a)-C ($LDL_{Lp(a)corr}$) with incident coronary heart disease (CHD) in the general population and to investigate whether concomitant Lp(a) values influence the association of LDL-C or apolipoprotein B (apoB) with coronary events.

Methods: Among 68,748 CHD-free subjects at baseline $LDL_{Lp(a)corr}$ was calculated as "LDL-C—Lp(a)-C", where Lp(a)-C was 30% or 17.3% of total Lp(a) mass. Fine and Gray competing risk-adjusted models were applied for the association between the outcome incident CHD and 1) LDL-C and $LDL_{Lp(a)corr}$ in the total sample; 2) LDL-C and apoB after stratification by Lp(a) mass (≥/<90^{th} percentile (pctl.)).

Results: Similar risk estimates for incident CHD were found for LDL-C and $LDL\text{-}C_{Lp(a)corr30}$ or $LDL\text{-}C_{Lp(a)corr17.3}$ (sub-distribution Hazard Ratios (sHRs) with 95% CI) were 2.73 (2.34-3.20) vs 2.51 (2.15-2.93) vs 2.64 (2.26- 3.10), respectively (top vs bottom fifth; fully-adjusted models). Categorization by Lp(a) mass resulted in higher sHRs for uncorrected LDL-C and incident CHD at Lp(a)≥90^{th}pctl. (4.38 (2.08-9.22)) vs 2.60 (2.21-3.07) at Lp(a)<90^{th} pctl. (top vs bottom fifth; $p_{interaction}$0.39). In contrast, apoB risk estimates were lower in subjects with higher Lp(a) mass (2.43 (1.34-4.40)) than in Lp(a)<90^{th} pctl. (3.34 (2.78-4.01) ($p_{interaction}$0.49).

Conclusion: Correction of LDL-C for its Lp(a)-C content provided no meaningful information on CHD-risk estimation at the population level. However, simple categorization of Lp(a) mass (≥/<90^{th}pctl.) influenced the association between LDL-C or apoB with future CHD mostly at higher Lp(a) levels.

Key Words: Lipoprotein (a), low-density lipoprotein, apolipoprotein B, coronary heart disease, general population

Condensed Abstract:

Correction of LDL-Cholesterol (LDL-C) for concomitant Lp(a) cholesterol represents a matter of debate. Among 68,748 subjects, who developed a CHD event over a median follow-up of 9.72 years, similar association with future outcomes was found between uncorrected LDL-C and LDL-C, corrected for Lp(a) cholesterol (assumed as 30% or 17.3% of total Lp(a) mass). In contrast, a simple categorization by Lp(a) values (≥/<90^{th}percentiles) modified the association between LDL-C or apopolipoprotein B with future CHD mainly at higher Lp(a) levels. Thus, an assessment of the conventional lipid profile without taking into account accompanying Lp(a) values mightprovide incomplete information on CHD risk.

Abbreviations list:

Lp(a) = lipoprotein (a)
LDL-C = low-density lipoprotein cholesterol
apoB = apolipoprotein B
CHD = coronary heart disease
ASCVD = atherosclerotic cardiovascular disease
FU = follow-up
IQR = interquartile range
sHRs = sub-distribution Hazard Ratios
CI = confidence interval
BMI = body mass index

Introduction

Low density lipoprotein (LDL)-targeted therapy has become a cornerstone in the management of atherosclerotic cardiovascular disease (ASCVD) (1). Over the past decade, however, emerging evidence has suggested that conventional assays for LDL-Cholesterol (LDL-C) measurement quantify cholesterol attributable to a composite of atherogenic lipoproteins. "LDL-C" not only measures cholesterol bound to LDL, but also cholesterol bound to intermediate-density lipoprotein (IDL-C) and lipoprotein(a)- (Lp(a)-C) due to the overlapping densities of these lipoproteins (1-2). This methodological limitation might have a significant clinical impact, particularly in the setting of high Lp(a) (3). Whilst a fasting status results in almost negligible contribution of IDL-C to measured LDL-C, an elevated Lp(a)-C could, by contrast, account for a substantial proportion of conventionally measured LDL-C and in this scenario, the real cholesterol content of LDL would be much lower than previously appreciated.

This assumption has led to the introduction of so called "corrected LDL-C" ($LDL_{Lp(a)corr}$), i.e. a LDL-C without taking into account its Lp(a)-C content. Commonly, Lp(a)-C has been calculated as 30% of Lp(a) mass, a correction factor derived from early studies (3-5). However, one recent study in a small population measuring Lp(a)-C directly showed a much higher variability of Lp(a)-C related to Lp(a) mass, ranging from 6 to 57% (6).

Lp(a) measurement has recently gained increasing attention (7-8) and the current ESC/EAS guidelines on dyslipidemia management recommend the measurement of Lp(a) at least once in a person's lifetime (1). Nonetheless, Lp(a) testing in the real world still remains low (9-10), despite its prominent role in atherogenesis and the potentially meaningful contribution of Lp(a)-C content to overall measured LDL-C. Although the relevance of this methodological limitation is not completely appreciated, it might be important at least in two clini-

cal situations. First, extremely high Lp(a) levels might “create” low- or non-responders to statin therapy, since Lp(a)-C would probably reflect the significant proportion of overall measured LDL-C, which can not be lowered by statins. Second, it could also have a relevant impact on the diagnosis of familial hypercholesterolemia (FH), where high Lp(a) might mimic the classical monogenic form of FH simply by the contribution of Lp(a)-C to measured LDL-C (11-12). A hitherto unanswered question is whether the methodological limitation of LDL-C measurement could also be clinically important within the general population, where the vast majority of subjects have only moderately elevated Lp(a) levels.

In the present analysis we therefore aimed to compare the association between LDL-C and $LDL_{Lp(a)corr}$ and incident coronary heart disease (CHD) in the general population. Furthermore, to circumvent the potential inaccuracies of the conventionally used methods to correct LDL-C for Lp(a)-C, we investigated whether the association between uncorrected LDL-C and future CHD events might be affected particularly by concomitant Lp(a) levels and whether a similar pattern of association might be observed for other lipid parameters, such as apolipoprotein B (apoB).

Material and Methods:

Study Design, Study Population and Outcome

The design and rationale of the BiomarCaRE (Biomarker for Cardiovascular Risk assessment across Europe; http://www.biomarcare.eu) consortium have been published elsewhere (13). Briefly, based on the Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) Risk Genetics Archiving and Monograph (MORGAM) Project, BiomarCaRE represents a EU-funded initiative, which harmonized data from population-based cohorts across Europe.

All participating cohorts obtained approval by the responsible local ethical review boards. Participation was voluntary and written informed consent was obtained from each subject upon entry into the study. This study was performed according to the principles of Good Clinical Practice and the Declaration of Helsinki.

For the present analysis, data from 10 cohorts were used, resulting in a total of 93,313 individuals. Detailed cohort descriptions, including enrollment and follow-up procedures are provided elsewhere (13). Two cohorts were excluded from the analysis due to missing data on Lp(a) (PRIME/Belfast) or an analytical issue in Lp(a) determination (DAN-MONICA, due to significant variations in Lp(a) levels between three surveys, compared to the remaining BiomarCARE cohorts). After further exclusion of subjects with missing information on CHD and Lp(a), as well as those with prevalent CHD at baseline, the final study sample comprised 68,748 CHD-free subjects (Northern Sweden (n=8,774), FINRISK (n=6,048), SHHEC (Scottish Heart Health Extended Cohort) (n=12,585), MONICA/KORA Augsburg (Cooperative Health Research in the Region of Augsburg), (n=7,405), MATISS (Malattie ATerosclerotiche Istituto Superiore di Sanità) cohort (n=3,081), MONICA Brianza (n=4,303), Moli-Sani (n=21,640), MONICA Catalonia (n=4,912)). The study population was further stratified ac-

cording to accompanying Lp(a) values with the 90th percentile chosen as the cut-off (<90th pctl.: n=61,861; ≥90th pctl.: n=6,887). A flowchart of the study is presented in Figure 1.

All study participants were followed-up prospectively for an overall range of 2.5-25 years for incident CHD events, defined as fatal or non-fatal (definite or possible) myocardial infarction (MI), coronary death, unstable angina pectoris, cardiac revascularization, and unclassifiable death (i.e. death with insufficient evidence of coronary origin and no competing cause). Most centers adjudicated the events using MONICA diagnostic criteria. The MORGAM manual provides further information on endpoint classifications (14).

Data collection and risk factor definition

For detailed information on data collection and risk factor definition please see the **online data supplement.**

Laboratory measurements

Baseline Lp(a) mass was measured from stored blood samples in the BiomarCaRE central laboratory in either Mainz (until 2011) or Hamburg, (since 2011) Germany, using a fully automated, particle-enhanced turbidimetric immunoassay (Biokit Quantia Lp(a)-Test; Abbott Diagnostics, USA) (15). LDL-C levels were calculated using the Friedewald formula without any additional hypertriglyceridemia-related adjustments. ApoB was measured using Immunoturbidimetric assay (Abbott, Architect c8000). The remaining lipid parameters (total cholesterol, HDL-C or triglycerides) were measured locally at each participating center by routine methods or in the BiomarCaRE central laboratory.

The cohort-specific intra- and interassay coefficients of variation for Lp(a), LDL-C and apoB are provided in the supplemental Table 1.

Statistical analysis

Baseline characteristics of the study population are reported in a descriptive way and shown as frequencies (percentage) for binary variables and as medians with their lower and upper quartile (interquartile range, IQR) for continuous variables.

Median follow-up (FU) times were estimated by the Kaplan-Meier potential follow-up estimator (16). All lipoproteins were categorized into fifths (F) using cohort-specific quintiles. The mean cut-point values for LDL-C were 2.72 mmol/L, 3.26 mmol/L, 3.78 mmol/L and 4.42 mmol/L, whilst for apoB they were 0.80 g/L, 0.95 g/L, 1.09 g/L and 1.27 g/L.

To assess the association between lipoproteins and future CHD events, Fine and Gray models accounting for competing risk of death from a non-CHD cause, stratified by sex and study cohort were calculated using individual level data from the available cohorts. Lp(a) and apoB were cubic-root transformed prior to the analysis. The data are presented as sub-distribution Hazard Ratios (sHRs) with their 95% confidence interval (95% CI).

As a first step, we performed an analysis for the association of LDL-C, apoB and Lp(a) (separately, as sole biomarkers) with future CHD events at different levels of adjustment. Model 1 included age and fasting status; model 2 was additionally adjusted for systolic blood pressure, antihypertensive drugs, diabetes mellitus, body mass index (BMI), daily smoking, family history of CHD, average daily alcohol consumption, highest level of education and lipid-lowering medication. Further, we repeated the analysis for LDL-C after correcting it for its Lp(a)-C content. Two different corrections were applied, which estimated Lp(a)-C content as 30% ($LDL_{Lp(a)corr\ 30}$) (4) or 17.3% ($LDL_{Lp(a)corr\ 17.3}$) (6) of total Lp(a) mass. Thus, $LDL_{Lp(a)corr\ 30}$ was calculated as LDL-C - (Lp(a)∗0.30) and $LDL_{Lp(a)corr\ 17.3}$ was calculated as LDL-C - (Lp(a)∗0.173). The Spearman correlation coefficients were calculated for LDL-C and the two corrected versions

Finally, we looked into the relationship between LDL-C or apoB and incident CHD according to concomitant Lp(a) level and therefore stratified the entire population into low-to-moderate and high Lp(a) values using cohort-specific Lp(a) cut-offs (<90^{th} pctl. (n=61,861versus ≥90^{th} pctl. (n=6,887)). The mean 90^{th} pctl. is about 43.5 mg/dL. Same levels of adjustment were used for the regression models. Importantly, the same categorization of LDL-C or apoB into fifths using cohort-specific quintiles were applied. Terms for the interaction of continuous Lp(a) as well as fifths with LDL-C and apoB were added to the models.

Due to the exploratory nature of this analysis, a significance threshold was not defined for p-values. R version 4.2.1 software (R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses.

Results:

For the present analysis, data from 68,748 subjects from eight prospective population-based cohorts across Europe participating in the BiomarCaRE project, were used. All included participants were free of CHD at the time of enrollment.

Table 1 describes the baseline demographic, clinical and biochemical characteristics of the entire population, as well as after stratification of the study sample according to Lp(a) mass with a 90^{th} percentile used as a cut-off. The median Lp(a) was found to be 9.3 (IQR 4.2-20.4) mg/dL in the total study group; 8.0 (IQR 3.8-15.2) mg/dL in subject with Lp(a) values below 90^{th} percentile and 60.5 (IQR 52.1-70.3) mg/dl in those with a Lp(a) mass $\geq 90^{th}$ pctl. of Lp(a) distribution. The prevalence of most cardiovascular risk factors was comparable between subject with low versus high Lp(a) levels, the only exception being a family history of CHD, which was more frequent in individuals with high Lp(a) mass (19.7% vs 16.9%). Median values for LDL-C and non HDL-C were slightly higher in subjects with high Lp(a) mass (3.4 (IQR 2.8-4.2) vs 3.8 (IQR 3.2-4.5) mmol/L for LDL-C and 4.2 (IQR 3.4-5.0) vs 4.5 (IQR 3.8-5.3) mmol/L for non-HDL-C, respectively). In contrast, the concentration of apoB was almost identical in the two subgroups, being 1.0 (IQR 0.8-1.2) in those with low vs 1.1 (IQR 0.9-1.2) g/L in those with high Lp(a) level. For the baseline characteristics of each individual cohort please see Supplementary material online (Supplemental Table 2).

During a median FU of 9.72 years (95% CI 9.64-9.79 years) 3,536 of subjects who were free of CHD at baseline developed an event, defined as fatal or non-fatal MI, coronary death, unstable angina pectoris, coronary revascularization, or unclassifiable death.

As a first step, we looked into the association between LDL-C, apoB and Lp(a) and incident CHD in the entire population (Table 2). Comparing the fifths of lipoprotein distributions , we found that all studied lipoproteins were associated with future CHD events after

multivariable adjustment for cardiovascular risk factors with sHRs of 2.73 (95% CI 2.34-3.20) for LDL-C, 3.33 (95% CI 2.79-3.97) for apoB and 1.49 (95% CI 1.31-1.69) for Lp(a) (exemplarily for top versus bottom fifth (used as reference), fully adjusted models, all p<0.001). Interestingly, for LDL-C and apoB, the associations with outcome were already evident from the second fifths onwards, whereas there was no evidence of association between Lp(a) and incident CHD within F2 and F3 of the Lp(a) distribution (Table 2).

Next, we investigated whether correction of LDL-C for its Lp(a)-C content might affect its relationship with outcome. In order to account for the variability of Lp(a)-C in relation to Lp(a) mass we used two different estimations, one calculating Lp(a)-C as 30%, the other as 17.3 % of total Lp(a) mass. Interestingly, the Spearman correlation between the original LDL-C and the two corrected LDL-C were found to be 0.99 for the correlation between LDL-C and $LDL_{Lp(a)corr\ 30}$ and 1.0 for the correlation between LDL-C and $LDL_{Lp(a)corr\ 17.3}$. The results of Fine and Gray competing risk-adjusted models revealed that these corrections did not affect the relationship between corrected LDL-C and incident CHD meaningfully, demonstrating very comparable sHRs to those seen for uncorrected LDL-C (sHR of 2.51 (95% CI 2.15-2.93) for $LDL_{Lp(a)corr\ 30}$ and 2.64 (95% CI 2.26- 3.10) for $LDL_{Lp(a)corr\ 17.3}$ versus 2.73 (95% CI 2.34-3.20) for uncorrected LDL-C (top versus bottom fifth, fully-adjusted models; both p<0.001) (Table 3 and Table 2).

Considering that the estimation of a "true" LDL-C by the above mentioned equations has limited applicability in routine practice, we sought for a more practical solution to assess the association between LDL-C and future events depending on its Lp(a)-related cholesterol content and stratified our study population according to Lp(a) into low-moderate (<90^{th} pctl.) and high values (≥90^{th} pctl.) (Table 4). In subjects with low-moderate Lp(a) mass, the corresponding sHR for the association between LDL-C and incident CHD were almost identical to

those obtained within the total study sample (i.e. without categorization for Lp(a) mass) (sHR 2.60 (95% CI 2.21-3.07); top versus bottom fifth of LDL-C distribution; fully-adjusted model). In contrast, the risk estimates were higher in those with high Lp(a) with a sHR of 4.38 (95% CI 2.08-9.22) (top versus bottom fifth of LDL-C distribution; fully-adjusted model) ($p_{interaction}$ 0.39).

To investigate whether apoB would demonstrate a similar pattern of association with outcome like LDL-C taking into account Lp(a) values, we repeated the analysis using apoB as the independent variable (Table 5).Corresponding sHRs for apoB obtained within the total study sample (i.e. without categorization for Lp(a) mass) were very similar to the risk estimates found in subjects with low-moderate Lp(a) ($<90^{th}$ pctl.), for whom the sHR was 3.34 (95% CI 2.78-4.01) for apoB (top versus bottom fifth, fully-adjusted model). Surprisingly, the association between apoB and future CHD was weaker in subjects with Lp(a) mass $\geq 90^{th}$ pctl. with a sHR of 2.43 (95% CI 1.34-4.40) ($p_{interaction}$ 0.49). No association with incident CHD was found for the second and third fifth of the apoB distribution (F2 and F3) in the group with high Lp(a) values. In contrast, corresponding sHRs in those without stratification for Lp(a) mass or in those with low-moderate Lp(a) values were markedly higher, varying from 1.5 to 1.9 for F2 and F3 respectively (Table 2 and Table 5).

Discussion:

To the best of our knowledge, the present analysis represents the largest study so far investigating the impact of concomitant Lp(a) level on LDL-C or apoB-related risk of incident CHD in the general population. Our study demonstrates that correction of LDL-C for its Lp(a)-C content (assumed either as 30% or as 17.3% of total Lp(a) mass) did not substantially change LDL-C-associated CHD-risk estimation at the population level. Echoing this, similar LDL-C-associated risk for future CHD was observed in subjects with low/moderately increased Lp(a) mass (i.e. being under 90th pctl. of Lp(a) distribution), which represents the vast majority of studied individuals. The situation, however, became more complex when Lp(a) values were high (e.g. in this instance exceeding the 90th cohort-specific pctl.) since LDL-C-related CHD risk estimates were higher in subjects with higher Lp(a) mass. In the case of apoB, opposite patterns of association with incident CHD were observed with slightly lower sHR for apoB-associated risk found in those with high Lp(a) mass compared to subjects with lower Lp(a) mass.

Correction of LDL-C for the cholesterol content of Lp(a)

Despite several attempts to understand the clinical relevance of Lp(a)-C content of routinely measured LDL-C, this critical issue has not been fully resolved (17). Although the current ESC/EAS Lp(a) statement indicates that correcting of LDL-C for its Lp(a)-C content is not precise enough and should not be applied routinely (7), it is still broadly used in the research community. The findings of the present analysis showed that the two most commonly applied corrections of LDL-C for its Lp(a)-C content to date (calculated as 30% or 17.3% of total Lp(a) mass) do not provide any additional meaningful information on top of LDL-C-related CHD risk prediction in subjects from the general population, where Lp(a) on an absolute scale is little to only moderately increased in the vast majority of subjects. Interestingly, our data

are contrary to the previously published individual-patient-data meta-analysis from 5 landmark statin trials including 18,043 patients, which demonstrated that corrected LDL-C did not predict future CVD events in contrast to "uncorrected" LDL-C (HR for incident cardiovascular disease 1.07 (95% CI 0.93–1.22), p=0.36) versus HR 1.17 (95% CI 1.05–1.31), p=0.005, respectively; top versus bottom quartile) (18). In contrast, within the present analysis almost identical risk estimates between uncorrected and corrected LDL-C for incident CHD were found. Interestingly, uncorrected LDL-C was highly correlated with LDL-$C_{Lp(a)corr\ 30}$ with a pooled correlation coefficient of 0.96 (95% CI, 0.94–0.97) (18), which was very similar to the correlations observed within the present analysis. It should be noted here that our analysis cannot be directly compared to the study by Willeit et al. due to differences in the study design, population studied and concomitant medications used. Furthermore, although correction of LDL-C for its Lp(a)-C content did not markedly change the LDL-C-associated risk in the present analysis, lack of such differences at a population level does not establish clinical equivalence at an individual level. Whenever subjects with low/moderate Lp(a) mass are pooled with those with high Lp(a) mass, corrected LDL-C risk in the whole population might remain largely unchanged due to a simple predominance of subjects with only low/moderately increased Lp(a) values. Our results thus argue for a clear separation of subjects with high versus low/moderate Lp(a) values and that assessment of the conventional lipid parameters, such as LDL-C or apoB without taking into account accompanying Lp(a) values would provide only incomplete information on CHD risk estimation. While in subjects with low to moderately increased Lp(a) values, the contribution of Lp(a)-C to "overall" LDL-C might not be substantial with only negligible impact on the associated risk estimation, in those with high Lp(a) levels it might impact risk prediction.

<u>Lp(a) and LDL-C or apoB-related risk for incident CHD</u>

The present analysis indirectly touches upon the debate related to the superior accuracy of apoB compared to LDL-C as a marker of cardiovascular risk (19). Multiple lines of epidemiological evidence including Mendelian randomization studies (19-21) suggest apoB as a dominant marker of ASCVD risk when compared to LDL-C. Our data in the general population, as well as in a subgroup of subjects with lower Lp(a) values (< 90th pctl. of its distribution) also revealed slightly higher sHRs for apoB and incident CHD than for LDL-C, with 3.33 (95% CI 2.79-3.97) vs 2.73 (95% CI 2.34-3.20) respectively (exemplarily for the entire population, both for top versus bottom fifths, fully adjusted models). More surprising were our findings on the association between apoB and incident CHD in subjects with high Lp(a) levels, in whom the risk estimates for the top vs bottom fifths of apoB distribution were lower than those in subjects with lower Lp(a) values or from the entire population (sHR 2.43 (95 % CI 1.34-4.40) versus 3.34 (95% CI 2.78-4.01) or 3.33 (95% CI 2.79-3.97), respectively). Furthermore, at high Lp(a) values no association with CHD risk was observed for the second and third fifths of the apoB distribution, in contrast to the associations observed in those with lower Lp(a) levels or the entire population. Interestingly, apoB concentrations in both Lp(a) groups were almost identical (median 1.0 (0.8-1.2) versus 1.1 (0.9-1.2) g/L)). It has to be noted here, that these findings should be interpreted with caution because of a small number of events and some overlap between point estimates and their 95% CIs. Nonetheless, our results are rather hypothesis generating and encouraging further research. A mechanistic explanation for the diminished or even lost association between apoB and future CHD events is unclear and needs to be investigated in more details. It is well established that native/unmodified apoB-100 does not seem to be atherogenic, whereas the risk of ASCVD seems be mostly driven by oxidized phospholipids (oxPLs) on apoB particles (22). On the other hand, it is well known that Lp(a) carries the largest fraction of oxPLs among apoB-containing lipoproteins in the circulation, where they are bound covalently to the KIV10 of its apo(a) fragment (23).

Interestingly, experimental studies have demonstrated differences in oxPL content among individuals with different plasma Lp(a) levels, where oxPL contents seem to be low in those with low Lp(a) and increase proportionally with increasing plasma Lp(a) levels (23-24). Moreover, in plasma from individuals with elevated plasma Lp(a) levels nearly all oxPLs were found in density fractions containing apo(a) (24). Thus, one might suggest that in settings of chronically elevated Lp(a) levels, oxPL might be preferentially transferred from non-Lp(a) apoB-100 particles to Lp(a). Generally, such kind of transfer/shift is possible, as shown by Tsimikas et al. (25) in the post percutaneous coronary intervention (PCI) setting, where only 50% of the oxPLs were associated with Lp(a) directly after PCI and almost all oxPL were localized on Lp(a) 6 hours later. However, whether such shift or transfer of oxPLs might be responsible for the diminished predictivity of the "total" apoB is highly speculative. No similar pattern was observed for LDL-C, where we found that the association between LDL-C and outcome was higher at high Lp(a) values, than in subjects with low/moderate Lp(a) mass (HR 4.38 (95% CI 2.08-9.22) versus 2.60 (95% CI 2.21-3.07), respectively (top versus bottom fifth of LDL-C distribution; fully-adjusted models)). One potential explanation for such discordant findings might be related to the methodological issues of LDL-C and apoB quantification (26). Despite the biological linkage between these measures, it is well established that LDL-C does not represent an accurate equivalent of apoB due to the highly variable cholesterol content within each particle, with either cholesterol-depleted or cholesterol-enriched LDL (27). In contrast, apoB concentration reflects the total number of apoB particles in plasma. Taking into account these considerations, it is not surprising that the association between LDL-C and incident CHD was found to be stronger at high Lp(a) values than in subjects with low to moderate Lp(a) increase, reflecting a significant contribution of Lp(a) cholesterol mass to a given mass of overall LDL-C due to their overlapping densities (2). Interestingly, the question which rather should be raised here is whether a molar measurement of Lp(a), which

yields Lp(a) particle number rather than Lp(a) mass (28), would also enhance LDL-C predictive potential for future CHD or are we dealing with the effects that are attributable to the Lp(a) mass assay only. Although very intriguing, our results need to be replicated within larger populations, since we cannot exclude that lack of statistical power due to the low number of participants within the reference group among subjects with high Lp(a) values might have led to an overestimation of LDL-C associated CHD risk. On the other hand, the discordant results for the association with outcome revealed for LDL-C and apoB would rather speak against this assumption.

Limitation and Strengths of the Study

There are limitations of our study, which merit consideration. Since we used a mass-based assay for Lp(a) measurement, we could not apply the molar-based correction recently proposed by Rosenson and Marcovina (29), and could not calculate a proportion of total apoB attributable to Lp(a) (8). The studied biomarkers were measured only once and therefore the results cannot account for a regression dilution bias. The present data cannot be extrapolated to other ethnic populations or age groups, since only middle aged Caucasians were included in this analysis. Finally, CHD assessment at baseline mainly relied on medical reviews or to a much lesser extent was self-reported, which may have led to some misclassification, but we expect this to be non-differential across Lp(a) levels.

The current study has also several strengths. It represents the largest population-based analysis so far investigating the role of Lp(a) as a possible modifier of LDL-C or apoB-related CHD risk. Centralized measurements of biomarkers by the same assays minimized analytical imprecision in measurements between individual BiomarCaRE cohorts. Moreover, possible Lp(a)-increasing effects of statins are negligible within the present analysis, since only 2.8% of the entire study population were reported to be on lipid-lowering drugs at baseline and

most BiomarCaRE cohorts were recruited in the late 1980s-early 1990s, when statins were not broadly used. Finally, largely standardized baseline measurements and careful harmonization of the data from eight European general population-based studies lead to comparable and reliable data on risk factors and endpoint validation.

Conclusions

Within the present analysis, correction of LDL-C for its Lp(a)-C content by established estimations did not provide any meaningful information on LDL-C related CHD-risk in the general population. In contrast, a simple categorization of Lp(a) mass into high ($\geq 90^{th}$ pctl.) vs low/moderate ($<90^{th}$ pctl.) values demonstrated that concomitant Lp(a) might impact the lipoprotein-related risk for future CHD events mostly at higher Lp(a) levels. Thus, an assessment of the conventional lipid profile without taking into account accompanying Lp(a) values would provide incomplete information on CHD risk estimation, especially in subjects with high Lp(a) values.

CLINICAL PERSPECTIVES

COMPETENCY IN PATIENT CARE: Since concomitant increased Lp(a) mass might impact the association between conventional lipoproteins and future CHD, Lp(a) should be taken into account for more comprehensive assessment of LDL-C- or apo(B)-related risk for future coronary events. Ideally, Lp(a) should be included in the conventional lipid panel at first presentation of the patient.

TRANSLATIONAL OUTLOOK: More accurate estimation the cholesterol content of Lp(a) is urgently needed to understand the tight interplay between Lp(a), LDL-C and apoB.

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Figure legends

Figure 1: Flow chart of the study.

MONICA = Monitoring of Trends and Determinants in Cardiovascular Diseases; KORA = Cooperative Health Research in the Region of Augsburg; MATISS = Malattie ATeroscle-rotiche Istituto Superiore di Sanità; SHHEC = Scottish Heart Health Extended Cohort; CHD = coronary heart disease; Lp(a) = lipoprotein (a); pctl. = percentiles.

Central Illustration

CHD = coronary heart disease; Lp(a) = lipoprotein (a); pctl. = percentiles; FU = follow up; yrs. = years; sHR = sub-distribution Hazard Ratio; CI = confidence interval; LDL-C = low density lipoprotein cholesterol; $LDL_{Lp(a)corr}$ = LDL corrected for Lp(a) cholesterol; apoB = apolipoprotein B.

	All	Lp(a) <90th pctl.	Lp(a) ≥90th pctl.
N	**68,748**	**61,861**	**6,887**
Examination age (years)	49.7 (41.0- 58.7)	49.6 (40.9- 58.7)	50.5 (41.7- 59.2)
Male, n (%)	33,270 (48.4)	30,218 (48.8)	3,052 (44.3)
Systolic BP (mmHg)	131.0 (119.0-145.5)	131.0 (119.0-145.5)	131.0 (119.0-146.0)
BMI (kg/m²)	26.3 (23.6-29.4)	26.3 (23.6-29.4)	26.2 (23.7-29.1)
Hypertension, n (%)	27,726 (40.4)	24,873 (40.2)	2,853 (41.5)
Daily smoker, n (%)	17,628 (25.7)	15,938 (25.8)	1,690 (24.6)
Diabetes, n (%)	2,628 (3.8)	2,400 (3.9)	228 (3.3)
Family history of CHD, n (%)	9,071 (17.2)	8,030 (16.9)	1,041 (19.7)
Daily alcohol (g)	5.0 (0-22.0)	5.0 (0-22.0)	5.0 (0-20.0)
Lipid-lowering drugs, n (%)	1,715 (2.8)	1,475 (2.7)	240 (3.9)
Antihypertensive drugs, n (%)	9,561 (14.0)	8,553 (13.9)	1,008 (14.7)
Aspirin intake, n (%)	1,257 (2.8)	1,129 (2.8)	128 (2.8)
Non-HDL-C (mmol/L)	4.2 (3.5-5.0)	4.2 (3.4-5.0)	4.5 (3.8-5.3)
LDL-C (mmol/L)	3.5 (2.9-4.2)	3.4 (2.8-4.2)	3.8 (3.2-4.5)
LDL $_{Lp(a)\ corr\ 17.3}$ (mmol/L)	3.4 (2.8-4.1)	3.4 (2.8-4.1)	3.5 (2.9-4.2)
LDL $_{Lp(a)\ corr\ 30}$ (mmol/L)	3.4 (2.7-4.0)	3.4 (2.7-4.1)	3.3 (2.7-4.0)
Lp(a) (mg/dL)	9.3 (4.2-20.4)	8.0 (3.8-15.2)	60.5 (52.1-70.3)
Apolipoprotein B (g/L)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	1.1 (0.9-1.2)

Table 1. Baseline demographic and clinical characteristics of the study participants.

Data are presented as median with their interquartile range for continuous variables. Categorical variables are reported as frequency and percentage.

Lp(a) = lipoprotein (a); pctl = percentile; BP = blood pressure; BMI = body mass index; CHD = coronary heart disease; HDL = high density lipoprotein; C = cholesterol; LDL = low density lipoprotein. Cohort-specific Lp(a) cut-off (90^{th} pctl.) = 43.53 mg/dL.

Table 2: Association between circulating lipoproteins and risk of incident CHD

	Lipoprotein (a)				LDL-Cholesterol				Apolipoprotein B			
	sHR (95% CI)	p-value	$N_{overall}$	N_{events}	sHR (95% CI)	p-value	$N_{overall}$	N_{events}	sHR (95% CI)	p-value	$N_{overall}$	N_{events}
Model 1												
F 1	REF.	-	12,528	554	REF.	-	12,022	276	REF.	-	12,577	203
F 2	1.00 (0.89- 1.13)	0.97	12,130	523	1.24 (1.07-1.45)	0.0051	11,969	391	1.58 (1.34-1.87)	<0.001	12,620	393
F 3	1.03 (0.92-1.16)	0.58	12,136	545	1.53 (1.33-1.77)	<0.001	12,006	523	2.04 (1.74-2.40)	<0.001	11,783	552
F 4	1.24 (1.11-1.38)	<0.001	12,168	680	1.84 (1.60-2.11)	<0.001	11,876	664	2.53 (2.16-2.95)	<0.001	12,282	758
F 5	1.42 (1.28-1.59)	<0.001	12,231	725	2.72 (2.38-3.11)	<0.001	11,823	988	3.76 (3.23-4.37)	<0.001	11,841	1,119
Model 2												
F 1	REF.	-	7,787	413	REF.	-	7,338	201	REF.	-	7,763	149
F 2	0.98 (0.85-1.13)	0.79	7,590	379	1.30 (1.08-1.55)	0.0045	7,353	285	1.56 (1.28-1.89)	<0.001	7,805	290
F 3	1.10 (0.96-1.26)	0.16	7,525	419	1.58 (1.33-1.87)	<0.001	7,430	382	1.94 (1.61-2.34)	<0.001	7,205	407
F 4	1.26 (1.10-1.43)	<0.001	7,467	499	1.92 (1.63-2.26)	<0.001	7,418	495	2.31 (1.93-2.77)	<0.001	7,706	564
F 5	1.49 (1.31-1.69)	<0.001	7,551	540	2.73 (2.34-3.20)	<0.001	7,230	730	3.33 (2.79-3.97)	<0.001	7,388	838

Fine and Gray competing risk-adjusted models stratified by study cohort were calculated and the data are presented as sub-distribution Hazard ratios (sHRs) with their 95% confidence interval (95% CI). Biomarkers were transformed for the analysis (Lp(a) and apolipoprotein B: cubic-root transformed). CHD = coronary heart disease; LDL = low density lipoprotein; REF = reference; F = fifth.
The mean cut-point values for Lp(a) were 3.46 md/dL, 6.66 mg /dL, 11.27 mg/dL and 24.85 mg/dL; for LDL-C were 2.72 mmol/L, 3.26 mmol/L, 3.78 mmol/L and 4.42 mmol/L; for apoB were 0.80 g/L, 0.95 g/L, 1.09 g/L and 1.27 g/L.

All models were stratified by sex and study cohort.
Model 1: Adjusted for examination age and fasting status
Model 2: Additionally adjusted for systolic blood pressure, antihypertensive medication, diabetes mellitus, BMI, daily smoker, family history of CHD, average daily alcohol consumption, highest level of education, lipid-lowering medication

Table 3: Association between LDL-$_{Lp(a)\ corrected}$ and risk of incident CHD

	$LDL_{Lp(a)corr\ 30}$				$LDL_{Lp(a)\ corr\ 17.3}$			
	sHR (95% CI)	p-value	$N_{overall}$	N_{events}	sHR (95% CI)	p-value	$N_{overall}$	N_{events}
Model 1								
F 1	REF.		11,945	287	REF.		11,949	277
F 2	1.15 (0.99-1.34)	0.070	11,969	383	1.22 (1.04- 1.42)	0.012	11,963	391
F 3	1.47 (1.27-1.69)	<0.001	11,943	528	1.50 (1.30- 1.73)	<0.001	11,943	522
F 4	1.73 (1.51-1.99)	<0.001	11,916	664	1.84 (1.60- 2.11)	<0.001	11,919	676
F 5	2.52 (2.21-2.87)	<0.001	11,922	980	2.61 (2.28- 2.98)	<0.001	11,921	976
Model 2								
F 1	REF.		7,276	208	REF.		7,270	198
F 2	1.18 (0.99-1.41)	0.068	7,364	276	1.27 (1.06- 1.52)	0.0094	7,361	284
F 3	1.51 (1.28-1.79)	<0.001	7,396	387	1.56 (1.32- 1.85)	<0.001	7,412	385
F 4	1.82 (1.55-2.14)	<0.001	7,428	503	1.93 (1.63- 2.27)	<0.001	7,419	504
F 5	2.51 (2.15-2.93)	<0.001	7,304	719	2.64 (2.26- 3.10)	<0.001	7,306	722

Fine and Gray competing risk-adjusted models stratified by study cohort were calculated and the data are presented as sub-distribution Hazard ratios (sHRs) with their 95% confidence interval (95% CI). Biomarkers were transformed for the analysis (Lp(a): cubic-root transformed). CHD = coronary heart disease; LDL = low density lipoprotein; REF = reference; F = fifth. $LDL_{Lp(a)corr\ 30}$ calculated as $LDL-(Lp(a)*0.30)$; $LDL_{Lp(a)corr\ 17,3}$ calculated as $LDL-(Lp(a)*0.173)$.

All models were stratified by sex and study cohort.
Model 1: Adjusted for examination age and fasting status
Model 2: Additionally adjusted for systolic blood pressure, antihypertensive medication, diabetes mellitus, BMI, daily smoker, family history of CHD, average daily alcohol consumption, highest level of education, lipid-lowering medication

Table 4. Association between LDL-C and risk of incident CHD, according to Lp(a) mass

	Lp(a) < 90th percentile				Lp(a) ≥ 90th percentile			
	sHR (95% CI)	p-value	$N_{overall}$	N_{events}	sHR (95% CI)	p-value	$N_{overall}$	N_{events}
Model 1								
LDL F 1	REF.		11,392	259	REF.		630	17
F 2	1.23 (1.05-1.45)	0.0095	10,997	353	1.18 (0.68-2.07)	0.56	972	38
F 3	1.56 (1.34-1.81)	<0.001	10,770	467	1.12 (0.66-1.90)	0.67	1,236	56
F 4	1.82 (1.57-2.11)	<0.001	10,399	571	1.60 (0.97-2.64)	0.065	1,477	93
F 5	2.69 (2.34-3.09)	<0.001	10,091	828	2.31 (1.43-3.75)	<0.001	1,732	160
							P interaction 0.62	
Model 2								
LDL F 1	REF.		6,959	194	REF.		379	7
F 2	1.23 (1.03-1.48)	0.025	6,756	256	2.53 (1.12-5.68)	0.025	597	29
F 3	1.55 (1.30-1.85)	<0.001	6,670	341	2.19 (1.00-4.81)	0.051	760	41
F 4	1.84 (1.55-2.18)	<0.001	6,492	428	3.14 (1.47-6.73)	0.0033	926	67
F 5	2.60 (2.21-3.07)	<0.001	6,152	605	4.38 (2.08-9.22)	<0.001	1,078	125
							P interaction 0.39	

Fine and Gray competing risk-adjusted models stratified by study cohort were calculated and the data are presented as sub-distribution Hazard ratios (sHRs) with their 95% confidence interval (95% CI). Biomarkers were transformed for the analysis (Lp(a): cubic-root transformed). LDL = low density lipoprotein; CHD = coronary heart disease; Lp(a) = lipoprotein (a); REF = reference; F = fifth. Cohort-specific Lp(a) cut-off (90th pctl.) = 43.53 mg/dL. The mean cut-point values for for LDL-C were 2.72 mmol/L, 3.26 mmol/L, 3.78 mmol/L and 4.42 mmol/L

All models were stratified by sex and study cohort.
Model 1: Adjusted for examination age and fasting status
Model 2: Additionally adjusted for systolic blood pressure, antihypertensive medication, diabetes mellitus, BMI, daily smoker, family history of CHD, average daily alcohol consumption, highest level of education, lipid-lowering medication

Table 5. Association between apolipoprotein B and risk of incident CHD, according to Lp(a) mass

		Lp(a) < 90th percentile				Lp(a) ≥ 90th percentile			
		sHR (95% CI)	p-value	$N_{overall}$	N_{events}	sHR (95% CI)	p-value	$N_{overall}$	N_{events}
Model 1									
apoB	**F 1**	REF.	-	11,733	180	REF.	-	844	23
	F 2	1.66 (1.39-1.99)	<0.001	11,446	355	0.84 (0.51-1.39)	0.50	1,174	38
	F 3	2.19 (1.85-2.60)	<0.001	10,523	496	0.90 (0.56-1.44)	0.66	1,260	56
	F 4	2.64 (2.24-3.11)	<0.001	10,847	657	1.35 (0.87-2.10)	0.18	1,435	101
	F 5	3.93 (3.35-4.61)	<0.001	10,409	959	1.97 (1.29-3.00)	0.0018	1,432	160
								P interaction <0.01	
Modell 2									
apoB	**F 1**	REF.		7,251	138	REF.		512	11
	F 2	1.57 (1.28-1.93)	<0.001	7,081	264	1.22 (0.62-2.42)	0.57	724	26
	F 3	1.99 (1.64-2.42)	<0.001	6,437	366	1.26 (0.66-2.41)	0.49	768	41
	F 4	2.28 (1.88-2.75)	<0.001	6,802	484	1.96 (1.06-3.60)	0.031	904	80
	F 5	3.34 (2.78-4.01)	<0.001	6,472	714	2.43 (1.34-4.40)	0.0035	916	124
								P interaction 0.49	

Fine and Gray competing risk-adjusted models stratified by study cohort were calculated and the data are presented as sub-distribution Hazard ratios (sHRs) with their 95% confidence interval (95% CI). Biomarkers were transformed for the analysis (Lp(a): cubic-root transformed). CHD = coronary heart disease; Lp(a) = lipoprotein (a), apoB = apolipoprotein B; REF = reference; F = fifth. Cohort-specific Lp(a) cut-off (90th pctl.) = 43.53 mg/dL. The mean cut-point values for apolipoprotein B were 0.80 g/L, 0.95 g/L, 1.09 g/L and 1.27 g/L.

All models were stratified by sex and study cohort.

Model 1: Adjusted for examination age and fasting status

Model 2: Additionally adjusted for systolic blood pressure, antihypertensive medication, diabetes mellitus, BMI, daily smoker, family history of CHD, average daily alcohol consumption, highest level of education, lipid-lowering medication