A Prospective Study of Lipoprotein (a) and the Risk of Mortality in Patients with Established Coronary Heart Disease

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Abstract

Background:

Epidemiological and genetic studies show an association between lipoprotein(a) (Lp(a)) plasma levels and cardiovascular risk in general population studies. However, in patients with established coronary heart disease (CHD), it remains less clear whether Lp(a) or *LPA* genetic variants predict long-term mortality.

Methods:

We analyzed the association between Lp(a) plasma concentrations and two *LPA* genetic variants (SNPs, rs10455872, rs3798220) with prevalent CHD phenotypes as well as long-term outcomes in 3,313 participants of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study (median follow-up 9·9 years). Association results for plasma Lp(a) concentrations were validated in five independent studies while genetic association findings were replicated through large scale collaborative analysis within the GENIUS-CHD consortium comprising 24 studies of patients with established CHD.

Findings:

While, we replicate the association of both plasma levels and SNPs prevalence with severity of CHD (tertile 3 of Lp(a) 1·44, 95% CI 1·14 to 1·83; any *LPA* SNP 1·88, 95 % CI 1·40 to 2·53), Lp(a) levels were not associated with all-cause (tertile 3 of Lp(a) 0·95, 95 % CI 0·81 to 1·11; any *LPA* SNP 1·10, 95% CI 0·92 to 1·31) or cardiovascular mortality (tertile 3 of Lp(a) 0·99, 95 % CI 0·81 to 1·2; any *LPA* SNP 1·13, 95% CI 0·90 to 1·40) during follow-up of patients with established CHD. This finding was confirmed in five independent cohorts of 10,195 CHD patients. Similarly, *LPA* SNPs were not associated with subsequent mortality once CHD had been established, a finding confirmed in a meta-analysis of 106,353 participants with 19,332 events from the GENIUS-CHD consortium (all-cause mortality: *LPA* rs3798220 0·94, 95% CI 0·86 to 1·03; *LPA* rs10455872 0·95, 95% CI 0·90 to 1·03; cardiovascular mortality: *LPA* rs3798220 0·95, 95% CI 0·83 to 1·10; *LPA* rs10455872 0·96, 95% CI 0·88 to 1·05).

Interpretation:

In patients with prevalent CHD, neither Lp(a) concentrations nor genetic variants associated with Lp(a) concentrations showed any association with subsequent mortality. These data suggest that Lp(a) as risk marker may be more useful in predicting first CHD event onset rather than progression to death after a CHD event.

Introduction

Worldwide, cardiovascular disease (CVD) remains the leading cause of death[1]. Lipoprotein (a) (Lp(a)) is regarded as an emerging risk factor and potential therapeutic target, based on independent associations with atherosclerosis and CVD events in general population studies[2,3]. In a meta-analysis dated from the year 2000, the combined risk ratio for coronary heart disease (CHD) was 1.7 (95% confidence interval [CI] 1.4 to 1.9) for the top tertile of Lp(a) compared to the lowest tertile in 18 general population studies[4]. The Copenhagen City Heart Study arrived at a virtually identical risk estimate when comparing the highest to the lowest tertile of Lp(a), while reporting higher risks once Lp(a) exceeded the 90th percentile of its frequency distribution[5]. A more recent individual record-based meta-analysis of general population studies excluding participants with a history of CVD at baseline found a continuous, though modest relationship between Lp(a) and the incidence of CHD and stroke, with rates of CHD of 5.6 (95% confidence interval CI 5.4-5.9) and 4.4 (95% CI 4.2-4.6) per 1000 person-years in the highest and in the lowest tertile of Lp(a), respectively[6].

Lp(a) is composed of a low-density lipoprotein (LDL)-like apolipoprotein B (ApoB)-containing core to which one copy of the apo(a) glycoprotein is attached by a disulfide bridge[7-9]. The physiological function of Lp(a) is not known, nor are the precise mechanisms of synthesis and catabolism. It has been suggested that Lp(a) is assembled on the surface membrane of hepatocytes[10] and a number of cell surface receptors have been implicated in the catabolism of Lp(a)[11]. Lp(a) may have effects on the vascular tree similar to LDL, but has been postulated to be potentially more atherogenic due to specific pro-thrombotic effects[3]. The concentrations of Lp(a) in the circulation vary widely and are related to the number of kringle IV type 2 repeats and further sequence variants of the *LPA* gene[12,13]. Two common *LPA* variants, rs10455872 (intronic non-coding) and rs3798220 (missense variant Ile4399Met in the apo(a) protease-like domain), explain a substantial proportion of the variation of Lp(a) and have consistently been linked to the risk of incident myocardial infarction[14,15].

Unlike many other traditional risk factors for CHD, Lp(a) is difficult to modify by life-style changes[3]. PCSK9 inhibitors reduce Lp(a) by 20-30 %[16], but are not yet routinely used for this purpose. Lipoprotein apheresis represents the only currently available approach to substantially lower Lp(a).

The relationship of elevated Lp(a) and future or recurrent cardiac events in patients with established CHD has been studied less extensively and so far appears weaker than in the general population. Further it may be modified by the LDL-cholesterol (LDL-C) concentration[4,17,18]. We therefore sought to examine systematically and at scale the association between Lp(a) and long-term mortality in patients with established CHD.

Methods

LURIC study

Between 1997 and 2000, the Ludwigshafen Risk and Cardiovascular Health (LURIC) study enrolled 3,316 German patients undergoing coronary angiography[19]. The study design and examinations at baseline have been described[19]. Written informed consent was obtained from all patients. Participants with acute illnesses other than acute coronary syndromes (ACS), such as malignancy or other chronic non-cardiac diseases within the past five years were excluded. Clinically stable patients (except for ACS) with available coronary angiogram data were enrolled. Information on death during follow-up was obtained from the local Public Health Departments. Cardiovascular mortality was defined as death due to fatal myocardial infarction, sudden cardiac death, death after cardiovascular intervention, stroke and other causes of death caused by cardiovascular diseases.

The study was performed in accordance with the Declaration of Helsinki. An approval by the competent Ethics Committee (Ärztekammer Rhineland-Palatinate, Germany) was obtained. No patients were lost to follow-up.

Validation cohorts

Association findings for Lp(a) plasma levels and outcomes were validated in 10,195 participants of the Homburg Cream and Sugar (HCS) study, the KAROLA study, the WENBIT/WECAC study, the PROSPER study and the ATHEROGENE study. For details on these cohorts please see appendix pages 2-3.

GENIUS-CHD consortium

Genetic association results for SNPs in the *LPA* locus and all-cause, as well as cardiovascular mortality were validated through a collaborative individual participant level analysis through the Genetics of Subsequent Coronary Heart Disease (GENIUS-CHD) consortium (www.genius-chd.com)[20]. This is a recently formed grouping of multiple international studies of patients with CHD (either stable disease or ACS), who have had blood or tissue samples stored for analysis or have genotyping data and have then been prospectively followed for subsequent events, such as death. Studies with available *LPA* SNP data from the wider GENIUS-CHD consortium were included, and are described in the appendix, page 1.

Laboratory methods and procedures

In LURIC, blood sampling for measuring Lp(a) plasma levels (LPA Test, Rolf Greiner Biochimica, Flacht, Germany) was performed at the day of coronary angiography. Details for the other cohorts are described in the appendix pages 4-5.

Statistical analysis

Continuous data are presented as mean ± SD when normally distributed or as median and interquartile ranges for variables with skewed distribution. Categorical data are presented as percentages. Statistical differences between continuous variables were determined using one-way ANOVA, Kruskal–Wallis test, or chi-squared test for categorical variables.

In LURIC, the association between Lp(a) plasma levels divided in tertiles as well as LPA SNP carrier status and all-cause as well as cardiovascular mortality was studied using Cox regression analyses with/without adjustment for age, sex, diabetes mellitus, systolic blood pressure, body mass index, smoking status, estimated glomerular filtration rate and LDL-cholesterol.

In sensitivity analyses we determined the association between Lp(a) plasma levels and mortality in LURIC in patients with/without statin treatment or divided into two groups using a cut-off at LDL-C of 130 mg/dL. Moreover, to examine the proportion of variance of Lp(a) caused by the *LPA* SNPs rs10455872 and rs3798220, η^2 was calculated.

Positive LPA SNP carrier status was defined as heterozygosity or homozygosity for the minor alleles of rs10455872 and/or rs3798220. In HCS, KAROLA, WENBIT/WECAC, PROSPER and ATHEROGENE, similar analyses were performed to examine the association between tertiles of Lp(a) and the composite cardiovascular end-points. Results of crude models as well as models adjusted for the following well-established cardiovascular risk factors, i.e. age, sex, diabetes mellitus, systolic blood pressure, body mass index, smoking status, estimated glomerular filtration rate, and LDL-cholesterol are reported. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported.

To determine the association between tertiles of Lp(a) as well as LPA SNP carrier status and Friesinger score, generalized linear models were used to estimate the marginal (adjusted) means of Friesinger score. Adjustments were made for age, sex, diabetes mellitus, systolic blood pressure, body mass index, smoking status, estimated glomerular filtration rate and LDL-cholesterol.

To analyze the association of the Lp(a) SNPs with cardiovascular outcome in the GENIUS-CHD consortium, meta-analyses using log hazard ratios and their standard errors derived from unadjusted Cox regression models of the association of rs10455872 and rs3798220 with fatal cardiovascular events and all-cause mortality from every cohort included were performed. Standard normal random effects meta-analysis was performed using the R-package 'metaplus' (v 0.7-8).

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Results

3,313 participants of LURIC with Lp(a) measurements and genotyping were included in the present analyses. Baseline characteristics of these participants are shown in **Table 1**. Besides LDL-C and gender distribution, the prevalence of traditional cardiovascular risk factors such as age, reduced estimated glomerular filtration rate (eGFR), diabetes mellitus, smoking, or hypertension was not significantly different across tertiles of Lp(a) (tertile 1 ≤ 10·0 mg/dL, tertile 2 10·1-26·0 mg/dL, tertile 3 > 26·0 mg/dL). The prevalence of CHD at baseline was 77·9 %. Following the strategy of a recent meta-analysis[4], we divided Lp(a) in tertiles, thereby also minimizing the influence of different methodology used to measure Lp(a). In patients within the highest study-specific tertile of Lp(a), the prevalence of angiographically defined CHD was greater (81·9 % vs. 75·7 %) as compared to those in the lower tertile of Lp(a).

LPA genetic variants and Lp(a) levels

In LURIC, *LPA* SNP rs10455872 data were available in 3058 participants and *LPA* SNP rs3798220 data in 3286 participants. 524 participants (15·9 %) carried any *LPA* minor allele; ten participants carried a minor allele in *LPA* SNP rs10455872 and rs3798220. As previously reported[14], in participants with Lp(a) plasma levels within the highest tertile, the frequencies of the minor alleles of *rs10455872* and of *rs3798220* were greater (*P*<0·001 each, **Table 1**). Notably, the number of copies of the minor allele for each *LPA* SNP was strongly associated with higher median Lp(a) plasma levels (*P*<0·001) in an almost linear fashion (**appendix page 23**). For each minor allele of the *LPA* SNPs carried, median Lp(a) was higher by 250 %.

Association with angiographic CHD

We next determined the association of Lp(a) plasma levels and *LPA* SNPs with angiographically documented CHD (**Figure 1A and appendix pages 6-7**). Compared to patients with low Lp(a) (i.e. tertile 1), patients with Lp(a) within tertile 3 had a significantly higher risk for angiographic CHD (HR 1·44, 95% CI 1·14 to 1·83). Similar results were obtained for carriers of *LPA* risk variants, in whom odds for angiographic CHD was also significantly higher (OR 1·88, 95% CI 1·40 to 2·53), suggesting that Lp(a) causally impacts the development of CHD.

We further examined the association between Lp(a) levels and *LPA* SNP carrier status with the Friesinger score as a measure for the severity of angiographic CHD (**Figure 1B**). Both, elevated Lp(a) plasma levels and *LPA* minor alleles were associated with higher Friesinger

scores (*P*<0·001 for tertile 3 of Lp(a) concentration and *P*<0·001 for *LPA* SNP carriers), indicating more severe CHD, which is in line with previous studies[21,22].

Association of Lp(a) levels with outcomes

Next, we analyzed the association of elevated Lp(a) levels with subsequent all-cause and cardiovascular mortality. During a median follow-up of 9·9 years, 995 participants (30·0 %) of the LURIC study died, 622 due to CVD (18·8 % of all participants). Tertiles of Lp(a) were neither associated with all-cause nor cardiovascular mortality (**Figure 2A and appendix, page 8**). Adjustment for potential confounders did not change this observation. In additional analyses, this association was not modified (i.e. interact with) either LDL-C or statin treatment (**appendix page 9**).

To validate these findings, we analyzed the association between Lp(a) plasma levels and subsequent cardiovascular mortality in five additional and independent cohorts (HCS, KAROLA, WENBIT/WECAC, PROSPER, ATHEROGENE) with 10,195 participants with prevalent CHD. Baseline characteristics of these studies are shown in **appendix pages 10-14**. Notably, in all five contemporary cohorts of patients with stable CHD, tertiles of Lp(a) did not show any association with the composite cardiovascular end-point (events HCS: 218 (42·4%), KAROLA: 263 (25·2%)) or cardiovascular mortality (events WENBIT/WECAC: 416 (10·0%), PROSPER: 130 (7·0%), ATHEROGENE 230 (8·8%)) during follow-up (**Figure 2B and appendix pages 15-19**).

Association of *LPA* genetic variants with outcomes

We next examined the association between *LPA* SNPs and mortality in LURIC. Notably, we did not observe a significant association between either *LPA* SNP and all-cause or cardiovascular mortality during follow-up (**Figure 2A and appendix page 20**).

To validate these findings still further we performed a meta-analysis of log hazard ratios and their standard errors in 24 studies from the recently formed GENIUS-CHD consortium comprising 106,353 participants with established CHD. Here we examined the association of both *LPA* risk variants and all-cause as well as cardiovascular mortality during follow-up. Baseline characteristics of the contributing studies of GENIUS-CHD are shown in **appendix pages 21-22**. Notably, both minor alleles of *LPA* (rs10455872 and of *rs3798220*) were not associated with increased all-cause mortality (**Figure 3A+B**) or cardiovascular mortality (**Figure 3C+D**).

Discussion

In this study of patients with confirmed or suspected CHD, the concentration of Lp(a) at the time of recruitment and the number of minor alleles at two bi-allelic SNPs at the *LPA* locus were positively related to the presence and burden of CHD[14,21,22]. In contrast, we found that neither Lp(a) plasma concentrations nor *LPA* SNPs showed any association with cardiovascular or all-cause mortality during long-term follow-up in patients with established CHD, a finding we validated in 29 studies comprising 116,548 participants.

For many years, Lp(a) has been known to be associated with risk for CHD, independent of traditional cardiovascular risk factors[4-6,23-25]. These findings mainly derive from studies on apparently healthy persons in the general population[4-6,25] rather than from investigations of patients with established CHD. Genetic diversity at the *LPA* locus including *rs10455872* and *rs3798220* has been associated with the Lp(a) concentration in the plasma and with incident cardiovascular disease[6,14]. A recent study has shown that *LPA* KIV2 repeats as well as Lp(a) serum levels were associated with CHD prevalence[26]. A causal link between Lp(a) and atherosclerosis development is therefore likely and the current findings are completely in line with those reported previously.

However, in the LURIC study and in the five independent validation cohorts of patients with established CHD and in 24 studies from the GENIUS-CHD consortium, we did not find any clear association of Lp(a) concentrations or *LPA* variants and subsequent long-term mortality. These findings at least raise the possibility that the association of Lp(a) with risk in patients with CHD is weaker than in healthy persons, which may be due to competing risks commonly prevalent in this patient population. In one of the earlier meta-analyses[4], the risk ratio for CHD in general population based studies was 1.7 (95% CI 1·4 to 1·9) when the top tertile was compared with the lowest tertile of Lp(a), but only 1.3 (95 % CI 1·1 to 1·6) in nine studies of patients with pre-existing comorbidities (two studies in dialysis patients, one in diabetes mellitus, six in CHD). The latter was mainly driven by the contribution of the Scandinavian Simvastatin Survival Study (4S), which had recruited patients with severe hypercholesterolemia not representative of all CHD and accounted for three fourth of this evidence. Notably in 4S, total cholesterol was between 212 and 309 mg/dL, which is considerably higher than in LURIC or the studies of GENIUS-CHD, limiting generalization of the findings to cohorts with lower total cholesterol. Only one of the eight remaining studies reported a significant association between Lp(a) and incident CHD[4]. Another, more recent publication examining Lp(a) in established CHD has also indicated a modest, non-significant

relationship between Lp(a) and future events in studies with mean LDL-C below 130 mg/dL at baseline, and a stronger association in patients with LDL-C greater than 130 mg/dL[17].

Taken together, the association between Lp(a) and cardiovascular events may therefore be modified by LDL-C, and, beyond this, also by the high levels of statin use. While we were not able to detect such interactions in the present analyses, it is worth noting that baseline LDL-C in LURIC was 117±34 mg/dL and on average 130±38 mg/dL in the studies of the GENIUS-CHD consortium and as such we were unable to examine the association of Lp(a) with outcomes at very high levels of LDL-C. Adjustments for other potential confounders investigated at baseline also did not modify our findings, although we were unable to account for other factors that may have changed during follow-up such as LDL-C. However, considering the poor adherence with statins in Germany, we suspect the impact of time dependent changes of LDL-C is unlikely, at least in German cohorts contributing to our analysis[27].

There are other limitations that need consideration. Firstly, Lp(a) plasma levels in LURIC and in the validation cohorts have been measured using different methods. To exclude biases caused by different calibrations of these assays, all risk estimates were calculated for tertiles of Lp(a) calculated within each cohort. Nevertheless, we cannot entirely exclude the possibility that Lp(a) plasma levels were altered by the initial cardiovascular event itself or by changes during follow-up. Secondly, the current study has focused only on all-cause and cardiovascular mortality, while others have combined a range of fatal and non-fatal cardiovascular events[4-6,17]. We have preferred this strategy because it is arguably robust against differences between studies and changes over time in the definition and adjudication of non-fatal events[28]. This could have reduced our statistical power due to fewer events and meant we missed potentially very small effect sizes. The possibility of a type 2 error remains although with the sample size afforded by our multiple replication cohorts we anticipate this risk is minimal. Although we did not find evidence for an effect of Lp(a) above 50 mg/dL (not shown) beyond which the recent ESC and EAS guideline considers risk significant[29], we cannot rule out that extreme concentrations would still have an impact. Finally, we cannot currently exclude the impact of Lp(a) levels or genetic variants on risk of subsequent non-fatal events in contrast to fatal events given that such differences have been described for other risk factors[30]. Ischemic and/or thrombotic events, fatal and non-fatal, might be more specifically related to Lp(a) than the totality of CVD deaths. These will require further study as outcome data emerges, particularly since Lp(a) levels appeared to associate similarly with fatal CHD and non-fatal MI in prior analyses in patients without CHD[6].

To the best of our knowledge, this is the largest study in which the association of Lp(a) levels and SNPs at the *LPA* locus with outcomes in patients with established CHD has been examined simultaneously. Our results, and others show that Lp(a) levels and *LPA* SNPs promote early development of atherosclerosis and associate with greater angiographic severity of CHD. Further, it has been shown that patients with established CHD who carry Lp(a) increasing SNPs are more likely to have earlier CHD onset and have greater susceptibility to atherosclerotic manifestations outside of the coronary tree[21], supporting a role of Lp(a) in atherosclerosis progression. The lack of association of Lp(a) with CVD fatality in established CHD is thus a surprising finding that we do not have a final explanation for. Among the possible explanations would be index event or survival biases. These cannot be fully excluded, but are unlikely to have impacted our findings significantly as the minor allele frequencies of the *LPA* SNPs were identical to those reported in the control populations including the PROCARDIS cohort and other cohorts[14] and given the lack of imbalances of patients characteristics across genotypes. It is important to note that although Lp(a) concentrations would not be useful for predicting mortality, CHD patients with high Lp(a) could still benefit from Lp(a) lowering, as it might attenuate disease progression.

Screening for elevated Lp(a) has been recommended in persons at intermediate or high risk of CVD or CHD according to conventional criteria[3]. Given the broad evidence in favor of Lp(a) as a marker of risk in clinically healthy persons[3,24] , our data would indicate that it might be more rewarding to integrate Lp(a) into risk stratification in primary rather than in secondary prevention. We acknowledge, however, that markedly increased Lp(a) plasma concentrations in patients with established CHD may be helpful to trigger an intensive screening of family members to improve early preventive measures for the carriers.

Importantly, interventions to lower Lp(a) are scarce. While drug therapies may eventually be used for lowering Lp(a), it has to be determined to which extent Lp(a) lowering by PCSK9 inhibiting antibodies affects cardiovascular outcomes besides their strong effect on lowering of LDL-C[16]. More specific therapies targeting Lp(a) directly such as anti-sense oligonucleotides are in development and testing stages and will shed further light on the value of reducing Lp(a) in the future[31].

In conclusion, we found that while plasma Lp(a) levels and genetic variants that strongly determine Lp(a) levels are associated with CHD burden and severity, however, neither predict risk of future subsequent cardiovascular or total mortality among participants with established CHD. While the discrepancy with findings in general populations where Lp(a) increases risk of a first CHD event requires further investigation, these data suggest that use

of Lp(a) as a risk marker may be more useful in predicting first CHD event onset rather than progression to death after a CHD event.

Research in context

Evidence before this study

Plasma Lp(a) is a recognized emerging risk factor for coronary heart disease (CHD). We performed a systematic search in MEDLINE using the terms 'lipoprotein(a)' or 'lp(a)' to identify studies reporting on the association between Lp(a) and cardiovascular risk. Last search has been performed on May 15, 2016. Several studies show a clear association between elevated Lp(a) plasma levels and an increased risk for atherosclerotic CVD in general populations. However, such an association is weak or absent in fewer and underpowered studies of patients with established CHD. Given that Lp(a) plasma levels are genetically determined by two SNPs in *LPA* loci (*rs10455872* and *rs3798220*), larger epidemiologic and genetic association studies are now feasible to explore the role of Lp(a) in patients with CHD. Importantly, therapies for reducing Lp(a) are also emerging. Thus, a greater understanding of the role of Lp(a) in patients with established CHD would aid its use as a risk stratification biomarker and treatment target in this population.

Added value of this study

Our study examined the association between Lp(a) concentrations and two common variants at the *LPA* locus with (1) the prevalence and severity of CHD and (2) mortality during long-term follow-up in patients with established CHD. In 29 independent cohorts consisting of 116,548 participants during long-term follow-up, neither Lp(a) concentrations nor *LPA* genetic variants were associated with cardiovascular or all-cause mortality during follow-up.

Implications of all the available evidence

While the observational data for measuring Lp(a) for risk stratification in general populations is robust, our findings raise questions about the value of doing this in patients with established CHD. The reasons for the discrepancy require further detailed study. Importantly, therapies to reduce Lp(a) are emerging such as PCSK9 inhibitors and antisense agents.

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Figure legends

Figure 1: (A) Association between tertiles of Lp(a) or carrier status of *LPA* SNPs, respectively, and coronary heart disease as determined by logistic regression analyses. Multivariate analyses were adjusted for age, sex, diabetes, systolic blood pressure, body mass index, smoking status, estimated glomerular filtration rate, LDL-C, and lipid-lowering therapy. (B) Marginal means (95 % CI) of the severity of coronary disease (Friesinger score) according to tertiles of Lp(a) or *LPA* SNP carrier status. Analyses were adjusted for age, sex, diabetes, systolic blood pressure, body mass index, smoking status, estimated glomerular filtration rate, LDL-C, and lipid-lowering therapy.

Figure 2: (A) Association between tertiles of Lp(a) as well as *LPA* SNP carrier status and all-cause as wells as cardiovascular mortality in participants of the LURIC study as determined by Cox regression analyses adjusted for age, sex, diabetes, systolic blood pressure, body mass index, smoking status, estimated glomerular filtration rate, LDL-C, and lipid-lowering therapy. (B) Association between tertiles of Lp(a) and composite cardiovascular end-point (HCS and KAROLA) and cardiovascular mortality (WENBIT/WECAC, PROSPER and ATHEROGENE) as determined by Cox regression analyses. Multivariate analyses were adjusted for age, sex, diabetes, systolic blood pressure, body mass index, smoking status, estimated glomerular filtration rate, and LDL-C.

Figure 3: Forest plot of risk ratios for all-cause (A) and (B) as well as cardiovascular mortality (C) and (D) according to *LPA* SNPs rs3798220 (A) and (C) as well as rs10455872 (B) and (D) in studies of GENIUS-CHD consortium. Markers represent point estimates of risk ratios; marker size represents study weight in random-effect meta-analysis. Horizontal bars indicate 95% confidence intervals.

Table 1
Baseline characteristics of the LURIC cohort, overall and stratified according to tertiles of Lp(a)

	Overall (n=3313)	Lp(a) Tertile 1 ≤ 10·0 mg/dL (n=1146)	Lp(a) Tertile 2 10·1-26·0 mg/dL (n=1065)	Lp(a) Tertile 3 >26·0 mg/dL (n=1102)	P*
Age	62·7±10·6	62·8±10·7	62·8±10·7	62·4±10·4	0·445
Sex					
Male	2308 (69·7%)	842 (73·5%)	735 (69·0%)	731 (66·3%)	0·001
Female	1005 (30·3%)	304 (26·5%)	330 (31·0%)	371 (33·7%)	0·001
BMI (kg/m²)	27·5±4·1	27·5±4·1	27·7±4·2	27·2±3·9	0·066
Systolic blood pressure (mmHg)	141±24	142±23	140±24	141±24	0·184
Lp(a) (mg/dL)	16·0 (31·0)	5·0 (6·4)	16·0 (7·1)	58·0 (44·7)	<0·001
Any *LPA* SNP minor allele&	524 (15·9%)	73 (6·4%)	81 (7·7%)	370 (34·0%)	<0·001
***LPA* SNP rs10455872$ A/G**	399 (13·1%)	56 (5·2%)	63 (6·4%)	280 (27·8%)	<0·001
***LPA* SNP rs10455872$ G/G**	10 (0·3%)	0	1 (0·1%)	9 (0·9%)	<0·001
***LPA* SNP rs3798220§ T/C**	124 (3·8%)	17 (1·5%)	19 (1·8%)	88 (8·1%)	<0·001
***LPA* SNP rs3798220§ C/C**	1 (<0·1%)	0	0	1 (0·1%)	<0·001
Total cholesterol (mg/dL)	192±39	189±39	191±38	197±40	<0·001
Triglycerides (mg/dL)	173±118	179±136	173±115	167±99	0·089
HDL-C (mg/dL)	39±11	38±11	39±11	39±10	0·037
LDL-C (mg/dL)	117±34	112±34	116±33	122±36	<0·001
VLDL-C (mg/dL)	37±26	39±30	36±26	36±24	0·002
Apolipoprotein B (mg/dL)	104±25	103±24	103±24	107±25	<0·001
Glycated hemoglobin (%)	6·3±1·2	6·3±1·4	6·3±1·2	6·3±1·2	0·203
eGFR CKD-EPI (ml/min/1·73m²)	81·7±20·1	82·1±20·7	81·5±20·1	81·4±19·6	0·602
hsCRP (mg/L)	3·4 (7·3)	3·6 (8·4)	3·4 (7·1)	3·2 (6·3)	0·037
IL-6 (ng/L)	3·2 (4·3)	3·3 (4·8)	3·2 (4·2)	3·2 (4·1)	0·235
Fibrinogen (mg/dL)	377 (132)	370 (142)	380 (128)	381 (124)	0·619
Friesinger Score	5·4±3·9	5·1±3·9	5·2±4·0	5·9±3·8	<0·001
Coronary artery disease	2580 (77·9%)	867 (75·7%)	810 (76·1%)	903 (81·9%)	<0·001
Previous myocardial infarction	1365 (41·2%)	446 (38·9%)	448 (42·1%)	471 (42·7%)	0·144
Diabetes mellitus	1322 (39·9%)	467 (40·8%)	440 (41·3%)	415 (37·7%)	0·170

Lipid lowering therapy	1607 (48·5%)	489 (42·7%)	529 (49·7%)	589 (53·4%)	<0·001
Smoking	2120 (64·0%)	741 (64·7%)	681 (63·9%)	698 (63·3%)	0·808
Hypertension	2409 (72·7%)	826 (72·1%)	762 (71·5%)	821 (74·5%)	0·255
Total deaths (all-cause)	994 (30·0%)	361 (31·5%)	322 (30·2%)	311 (28·2%)	0·233
Cardiovascular deaths	621 (18·9%)	232 (20·4%)	186 (17·6%)	203 (18·5%)	0·129

Values are presented as mean (SD), median (IQR) or number (%). BMI=body mass index. HDL=high-density lipoprotein. LDL=low-density lipoprotein. VLDL=very low-density lipoprotein. Lp(a)=lipoprotein(a). IL-6=interleukin-6. eGFR=estimated glomerular filtration rate. hsCRP=high sensitivity C-reactive protein.

5   * Comparison between tertiles of Lp(a). $p < 0·05$ was considered significant. $ *LPA* SNP rs10455872 data were available in 3058 participants. § *LPA* SNP rs3798220 data were available in 3286 participants. & Ten participants carried a minor allele in *LPA* SNP rs10455872 and rs3798220. Any *LPA* SNP minor allele information is available in 3287 participants. In 23 participants, no information on *LPA* SNPs is available.

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