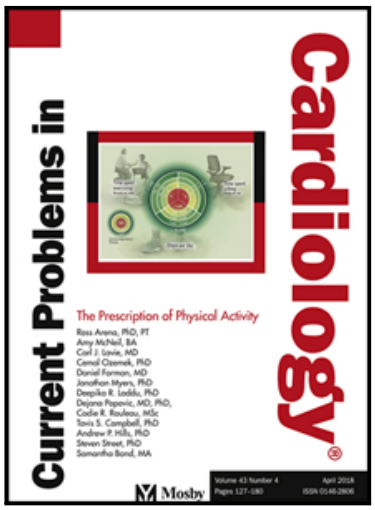

Serum lipoprotein(a) and 3-year outcomes in patients undergoing percutaneous coronary intervention

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Serum lipoprotein(a) and 3-year outcomes in patients undergoing percutaneous coronary intervention

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ABSTRACT

Background and aims: We aimed at addressing the association between serum lipoprotein (a) levels and clinical outcomes of consecutive patients undergoing PCI.

Methods: We used consecutive patients undergoing PCI at the Heart Center University of Freiburg, Bad Krozingen in Germany between January 2005 and November 2013. A total of 6679 patients [men (n = 5391) and women (n = 1288)] mean aged 67.5 (± 11.1) years were assessed at baseline and prospectively followed for 3 years. Lp(a) measurement were performed at hospital admission as a routine laboratory parameter.

Results: Approximately 30% of PCI patients show an elevated Lp(a) value of more than 50mg/dL. In total, 736 Patients died during the follow-up, thereof 189 (11.3%) in the first quartile, 186 (10.7%) in the second quartile, 183 (11.5%) in the third quartile and 178 (10.7%) in the last quartile (p value 0.843 from LogRank test). The MACE rate showed consistent results with 409 (24.4%), 385 (22.1%), 395 (24.7%) and 419 (25.3%) in the different respective quartiles (p value 0.125 from LogRank test).

Conclusion: In this large non-selected cohort of patients undergoing PCI followed by moderate intensity statin therapy, higher Lp(a) levels were not associated with worse clinical outcomes during a follow-up of 3 years.

Keywords

Lipoprotein (a), coronary artery disease, PCI, atherosclerosis, cardiovascular disease

INTRODUCTION

Coronary artery disease (CAD) is a multifactorial disease and remains the leading cause of death worldwide. Lipoprotein(a) [Lp(a)] was discovered in the early 1960s (1) and has been linked as an independent, possible causal, cardiovascular risk factor (2). It is a unique liver-derived low-density lipoprotein attached covalently via a disulphide bridge to apolipoprotein B-100 harbouring LDL cholesterol (1, 3). Its concentration is primarily genetically determined by single nucleotide variant at the LPA gene, with large interindividual variation in the general population (4) including substantial variability between different ethnic groups (5). Over the last two decades, evidence from Mendelian randomization and genome-wide association studies have linked elevated Lp(a) plasma level, defined as Lp(a) level of ≥120 nmol/L or approximately 50mg/dL, with an increased (6,

7)risk of atherosclerotic cardiovascular disease (ASCVD) and aortic stenosis (6-9), regardless of the reduction of LDL achieved by statins. In contrary, genetically determined low levels of Lp(a) (<75 nmol/L; <30 mg/dL are associated with a lower risk of cardiovascular disease(10). While coronary heart disease remains word-wide the leading cause of morbidity and mortality, pharmacological therapies that specifically target Lp(a) with promising results are in development but not currently available (11). How are the effects of increased serum Lp(a) level on clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) has been mainly evaluated in cohorts of Asian patients, with mixed results. While some studies suggested an increased risk for adverse clinical outcomes associated with elevated Lp(a) levels (12-15), other studies failed to detect such an association (16, 17). In the present study, we thus aimed to evaluate the clinical impact of Lp(a) in a large cohort of German patients undergoing percutaneous coronary intervention (PCI) with three-years of follow-up.

METHODS

Patient population

This single-center retrospective observational study reports clinical outcomes of consecutive patients after PCI. All consecutive patients undergoing PCI at the Division of Cardiology and Angiology II, Heart Center University of Freiburg, Bad Krozingen, Germany, between January 2005 and November 2013 were prospectively entered into the hospital database. The study was approved by the ethics committee of the Albert-Ludwigs-Universität Freiburg, Germany, (number: EK-Freiburg 21-1072) on 04 March 2021 and is in accordance with the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 1983. There were no formal exclusion criteria. In agreement with existing European guidelines (18), the recommended DAPT duration was 12 months for all acute respectively 6 months for chronic coronary syndrome patients, unless an indication for

oral anticoagulation or high bleeding risk features were present. Glomerular filtration rate (GFR) classes were defined according to Chronic Kidney Disease – EPIdemiology (CKD-EPI) (19). Lp(a) measurement were performed at hospital admission as a routine laboratory parameter using an immunoturbidimetric assay (Tina-quant®, Roche, Bale, Switzerland) on a Hitachi Modular system.

Collection of data

As part of the quality management program of our institution, baseline demographic, clinical, angiographic and procedural data as well as outcome data are entered into the hospital database. Follow-up of patients undergoing PCI is routinely performed 30 days, 1 year, and 3 years after PCI and documented in the hospital database.

Definition of outcomes

As primary endpoint of this study, the difference in all-cause mortality rate after PCI between the different baseline Lp(a) quartiles at three years was evaluated. Major adverse cardiac events (MACE) defined as a composite of all-cause death, myocardial infarction and target vessel revascularisation within three years after the index procedure was defined as secondary outcome. In order to allow a comparison with previously published studies (2, 20, 21), a second analysis stratifying patients according to Lp(a) levels on the basis of percentiles of the distribution (1st–50th, 51st–80th, 81st–90th, 91st–95th, and 96th–100th percentiles) was performed.

Statistical analysis

Baseline characteristics are shown with means and standard deviations or counts with percentage (compared using Pearson's chi-square test or Fisher's exact test). Event-free survival rates among groups were estimated by the Kaplan–Meier method and compared by the log-rank test. Multivariable analyses were calculated at baseline for prediction of all-cause death by using Cox regression including variables with significant differences between the strata. No backward or forward elimination was performed. Adjusted variables were tested for collinearity using the VIF test. A p value of <0.05 was considered statistically significant, and all p values were 2-sided. As previously described (22), cholesterol assays capture cholesterol both in LDL and lipoprotein(a) particles. We therefore corrected LDL cholesterol values for lipoprotein(a) cholesterol. Lipoprotein(a) mass is composed of about 30–45% cholesterol (23). We used a conservative measurement of the content of lipoprotein(a) cholesterol by multiplying lipoprotein(a) mass (mg/dL) by 0.3 in order to derive lipoprotein(a) cholesterol, then we subtracted this value from the measured LDL cholesterol to obtain LDL cholesterol corrected for lipoprotein(a) cholesterol (LDL-corr) (23). All analyses were carried out using SPSS software (version 25.0; SPSS, Chicago, IL, USA).

Role of the funding source

There was no industry involvement in the design, analysis or funding of this study. This study was funded by institutional support of Division of Cardiology and Angiology II, Heart Center University of Freiburg, Bad Krozingen, Germany, which had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Patient population

From January 2005 to November 2013, 6679 patients who underwent their first PCI in the department of Cardiology and Angiology II, University Heart Center of Freiburg • Bad Krozingen, Germany were consecutively enrolled. Median follow-up length was 1263 days (1111-2897); follow-up at 3 years was complete for 96.4% of the population. The mean age was 67.5 (± 11.1) years, 70% were men and the BMI was 27.6 (± 4.3) kg/m². 36.2% of the patients presented with an impaired left ventricular ejection fraction (LVEF < 53%). The distribution of Lp(a) was consistent with previous studies and showed a skewed distribution with a small amount of patients towards the highest levels (**Figure 1**) (15, 24). Upon stratification of the population in 4 quartiles, the quartile with highest Lp(a) levels showed significantly less male patients and lower BMI values. Of note, this group showed a lower rate of diabetes mellitus as well as higher LDL and HDL values and higher rate of positive family history of coronary artery disease. All patients characteristics are highlighted in **Table 1**.

At discharge, statin therapy of moderate intensity (intensity as described by the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults (25)) was recommended to 89.1% of the patients. The majority of patients received clopidogrel after PCI.

Clinical outcomes according to strata of Lp(a) levels

After three years of follow-up, a total of 736 patients died, thereof 189 (11.3%) in the first quartile, 186 (10.7%) in the second quartile, 183 (11.5%) in the third quartile and 178 (10.7%) in the last quartile (p value 0.843 from LogRank test). The MACE rate showed consistent results with 409 (24.4%), 385 (22.1%), 395 (24.7%) and 419 (25.3%) in the different respective quartiles (p value 0.125 from LogRank test). After adjustment for covariates with significant differences, no significant differences were seen for death of any causes (p = 0.593), death or myocardial infarction (p = 0.730) or MACE (p = 0.118) in Cox proportional hazard models. Similar results were obtained when patients were stratified according to previous studies (15, 26) comparing high (> 85 mg/dl and < 120 mg/dl) and very high levels (≥ 120 mg/dl, 95th percentiles) of Lp(a) to Lp(a) levels below 30 mg/dl (**supplemental figure 1a-c**).

Lp(a) level compared to other predictors of adverse clinical outcomes

In multivariate Cox regression analysis, Lp(a) levels in categories of 10 mg/dl were not associated with an increased risk of all-cause death, all-cause death or myocardial infarction or MACE (Figure 3). Of note, clinical characteristics such as initial presentation with acute coronary syndrome, higher age, presence of diabetes mellitus or a higher GFR classes were predictive for adverse clinical outcomes.

DISCUSSION

We aimed to evaluate a possible association between Lp(a) levels and clinical outcomes of patients undergoing PCI. Our findings can be summarized as follows:

1. Approximately 30% of PCI patients show an elevated Lp(a) value of more than 50mg/dL.
2. Patients with a higher Lp(a) level at baseline do not experience a higher rate of all-cause death, all-cause death or myocardial infarction or MACE within three years of follow-up.
3. After extensive multivariate adjustment for differences in baseline variables, there was no significant interaction between Lp(a) values and clinical outcomes.

Cardiovascular disease remains the most common cause of death in industrialized countries and Lp(a) has been found in several studies to be a genetically determined risk factor (27). As already described in a small sample study, (28) we found in our PCI cohort a rate of approximately 30% of elevated Lp(a) >50mg/dL, which is higher than the 20% found in the general population (29).

Despite recent data showing that Lp(a) is an independent risk factor, we didn't find any significant impact on clinical outcomes. Compared to the to date largest analysis evaluating the association of Lp(a) levels and clinical outcomes with patient-level data from statin outcome trials (22), our study displays several similarities but also distinct differences. Regarding similarities, the patients receiving statin therapy in the meta-analysis of Willeit et al (n=14'536, 50.0%) were also treated with moderate intensity statins, as recommended by guidelines during the enrolment period of the included studies. The percentage of men is in similar range and the average follow-up is likewise 3.0 years.

In contrast to these similarities, there are also important differences between our study and this meta-analysis (22). Indeed, our PCI population has a median age of 67.5 years which is more than 5 years older that the cohort of Willeit (29.069 patients, median age 62 years). Of note, the meta-analysis from Willeit and colleagues demonstrated a correlation between the age and the cardiovascular risk in patients receiving statin therapy with Lp(a) values ≥50mg/dL, with the cohort aged over 70 years showing no significant increase in risk. Second, the overall prevalence of elevated Lp(a) levels ≥50mg/dL was lower in the meta-analysis of Willeit et al., with 14% as compared to 28.3% in our study. This finding and the high percentage of patients presenting with acute coronary syndrome (34.6% of patients) suggests that our study represents a higher-risk cohort as compared to the meta-analysis by Willeit et al.

More recently, a similar study was published by Yoon et al. (30) showing a significant association between elevated levels of Lp(a) >30mg/dl with the recurrent ischemic events (composite of cardiovascular death, spontaneous myocardial infarction and ischaemic stroke) in 12064 patients who underwent PCI over a median follow-up of 7.4 years. In this cohort, 3747 (31.1%) patients had high Lp(a) defined as >30mg/dL. This cut-off is much lower than the 50mg/dl cut-off used in our study and that of Willeit et al. Extrapolating from the distribution curve presented, the 50mg/dl cut-

off is approximately at the 80th percentile, indicating that the distribution of Lp(a) in a Asian population undergoing PCI is very different than in a European one. Moreover, human Lp(a) has a heterogeneity according to the patients characteristics making any extrapolation of the data impossible. Beyond this ethnical variation, there are several notable differences between the two studies. Firstly, our cohort is much older (mean age 67.5 versus 62 years). Secondly, their cohort contains 47% of patients presenting with ACS compared to 34.6% in ours. Thirdly, no information about the statin intensity at discharge is given. This study also failed to show a significant difference regarding individual endpoints like cardiovascular death, death from any cause, spontaneous myocardial infarction or stroke.

In contrast to the primary prophylaxis setting, the clinical implication of Lp(a) in a secondary prevention setting is unclear and the various studies present conflicting results (30-34). Our findings call again into question whether treatment specifically aimed at reducing Lp(a) levels can thus reduce the risk of ischaemic cardiovascular events by patients already diagnosed with coronary artery disease. Future trials that evaluate whether lowering Lp(a) levels will reduce cardiovascular events are needed to better stratify the patients who are most likely to benefit from a medical therapy lowering Lp(a) levels.

To this end, the results of the ongoing Horizon-Lp(a) will give further insight as to whether lowering the Lp(a) in higher-risk populations is associated with a clinical benefit.

Strengths and limitations

To our knowledge, this is the first study evaluating outcomes in a European PCI cohort stratified by Lp(a) level. We were able to provide a uniform lipoproteins assay as measurement technique and were consistent in the time point at which Lp(a) was measured. Our study has several limitations. Firstly, the results are from a large retrospective single-center cohort and, as such, may not be generalizable to other cohorts. Secondly, our study population with documented coronary artery disease has a higher Lp(a) value than the general German population. The intensity of statin therapy is not in line with current recommendations, which recommend a much more aggressive drug therapy than at the time of enrolment. Lastly, it needs to be pointed out that our study did not measure the incidence of stroke, as compared to some of the studies included in the meta-analysis of Willeit et al. However, stroke has been a rare clinical event in all included outcome trials and often presented as composite endpoint and not as single endpoint. Not having included this endpoint in our study is therefore unlikely to account for the lack of association between Lp(a) levels and clinical outcomes.

FUNDING

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CONTRIBUTION

N.C: conception and design, analysis and interpretation of data, drafted the article; T.N: conception and design, acquisition of data, analysis and interpretation of data, revised the article; W.H: conception and design, acquisition of data and interpretation, revised the article; C.M.V, M.F, N.L, D.W and F-J.N: acquisition of data and interpretation, revised the article

CONFLICTS OF INTEREST

F.-J.N. received institutional research grants, consultancy fees and speaker honoraria from Daiichi-Sankyo, Astra Zeneca, Sanofi-Aventis, Bayer, The Medicines Company, Bristol, Novartis, Roche, Boston Scientific, Biotronik, Medtronic and Edwards. W.H. received institutional grants and lecture fees from Bayer Vital, Boehringer Ingelheim, Bristol-MyersSquibb, Daiichi Sankyo, Novartis, AstraZeneca and The Medicines Company. M.F. reports speaker honoraria from Boston Scientific, Biotronik, Medtronic, and Teleflex. D.W reported personal fees from AstraZeneca, Bayer, Novartis, and Medtronic The other authors declare no conflicts of interest.

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Figure 1. Distribution of Lipoprotein(a) in the study population

Figure 2. Kaplan-Meier curves of cardiovascular outcomes according to lipoprotein(a) quartiles. Lp(a)-Value (mg/dL): 1st quartile = 3 - 9; 2nd quartile = 10 - 22; 3rd quartile = 23 - 56; 4th quartile = 57 – 319 A. The cumulative survival rate analysis according to quartiles B. The cumulative

event-free (death and myocardial infarction) analysis according to quartiles C. The cumulative event-free (death, myocardial infarction and target vessel revascularisation) analysis according to quartiles

Figure 3. Forest-Plot – association of measured lipoprotein(a) with cardiovascular events in the study population **GFR** = estimated glomerular filtration rate; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **MACE** = death, myocardial infarction and target vessel revascularisation

Table 1. Patient characteristics according to lipoprotein(a) quartiles

	All patients	**1st quartile**	**2nd quartile**	**3rd quartile**	**4th quartile**	**p-value**
	N = 6679	N = 1677	N = 1746	N = 1598	N = 1658	
Baseline characteristics						
Age (years)	67.5 ± 11.2	67.2 ± 11.3	68.4 ± 10.9	66.7 ± 11.1	66.7 ± 11.6	<0.001
Male sex (%)	70.0%	74.8%	69.9%	71.0%	64.3%	<0.001
BMI (kg/m²)	27.6 ± 4.3	27.7 ± 4.1	27.5 ± 4.3	27.6 ± 4.3	27.0 ± 4.3	<0.001
Current smoker (%)	19.2%	20.1%	18.8%	17.9%	19.8%	0.374
Hypertension (%)	80.9%	82.2%	79.7%	81.8%	79.8%	0.144
Diabetes mellitus (%)	25.1%	27.9%	24.4%	25.6%	22.7%	0.006
Family history of coronary artery disease (%)	36.0%	34.3%	34.0%	35.9%	39.9%	0.002
Clinical presentation						
Acute coronary syndrome (%)	34.6%	33.9%	35.7%	36.5%	32.1%	0.033

LVEF (%)						0.865
≥51%	63.8%	63.4%	65.3%	62.4%	63.9%	
<51%	36.2%	36.6%	34.7%	37.6%	36.1%	
41 - 51%	21.0%	21.1%	20.6%	21.6%	20.8%	
30 - 40%	10.0%	10.5%	9.5%	10.0%	9.8%	
0 - 29%	5.2%	4.9%	4.6%	5.9%	5.5%	
NYHA Class						0.188
0	27.9%	29.1%	28.9%	26.4%	26.9%	
I	17.2%	17.4%	18.6%	16.4%	16.3%	
II	33.1%	33.0%	31.8%	34.1%	33.5%	
III	16.6%	15.5%	15.8%	17.0%	18.1%	
IV	5.3%	4.9%	4.8%	6.2%	5.1%	
CCS						0.154
0	7.8%	8.9%	7.2%	6.8%	8.1%	0
1	4.5%	4.3%	4.5%	4.5%	4.7%	1
2	23.7%	23.1%	23.4%	22.6%	25.8%	2
3	16.9%	16.8%	16.0%	18.1%	16.6%	3
4	38.4%	38.0%	40.7%	39.2%	35.4%	4
5	6.2%	6.6%	5.6%	5.9%	6.6%	5
6	2.5%	2.0%	2.6%	2.8%	2.7%	6
Laboratory						
eGFR, ml/min/1.73 m²	76.7	77.8	75.9	75.6	77.1	0.009
LDL cholesterol (mg/dl)	130.2±41.4	124.8±39.8	130.2±41.9	131.3±40.8	134.7±42.6	<0.001

LDLcorr (mg/dl)	118.4±42.4	123.0±39.8	125.7±41.9	120.2±41.0	104.2±43.5	<0.001
HDL cholesterol (mg/dl)	51.8±14.8	50.5±14.4	51.5±15.0	51.6±14.8	53.6±14.8	<0.001
Triglycerides (mg/dl)	162.7±120.5	169.4±133.9	159.4±123.7	156.4±106.8	150.0±94.5	0.018
Lp(a) (mg/dl)	39.5±43.2	6.0±1.9	15.0±3.7	36.9±9.9	101.6±42.2	<0.001
HbA1c (%)	6.88%±1.25%	6.99%±1.23%	6.86%±1.37%	6.89%±1.30%	6.72%±1.09%	0.052
Hemoglobin (g/dl)	14.17±1.63	14.28±1.57	14.18±1.64	14.17±1.67	14.05±1.65	0.001
Statin intensity at discharge						0.064
1	3.0%	3.9%	2.9%	2.7%	2.4%	
2	89.1%	88.6%	89.5%	90.1%	88.1%	
3	7.9%	7.5%	7.6%	7.2%	9.5%	

Values are provided as mean (standard deviation) or as percentage. Statin intensity as defined in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (1=Low-Intensity Statin, 2=Moderate-Intensity Statin, 3=High-Intensity Statin) (25)

Lp(a)-Value (mg/dL): 1st quartile = 3 - 9; 2nd quartile = 10 - 22; 3rd quartile = 23 - 56; 4th quartile = 57 - 319

BMI = body mass index; **CCS** = canadian cardiovascular society; **eGFR** = estimated glomerular filtration rate; **HbA1c** = glycated hemoglobin; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **LDLcorr** = low-density lipoprotein corrected; **Lp(a)** = lipoprotein(a); **LVEF** = left ventricular ejection fraction; **NYHA** = New-York heart association

Figure 1

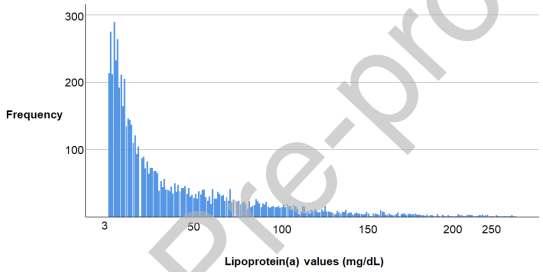

Figure 2A

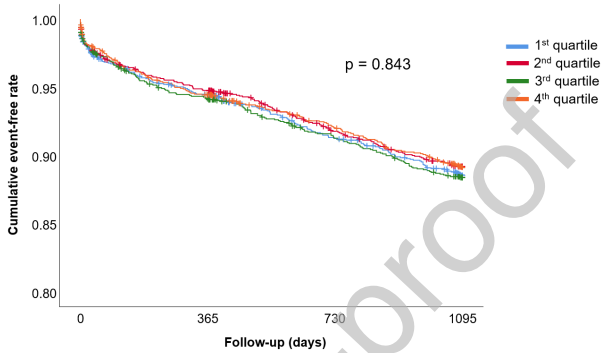

Figure 2B

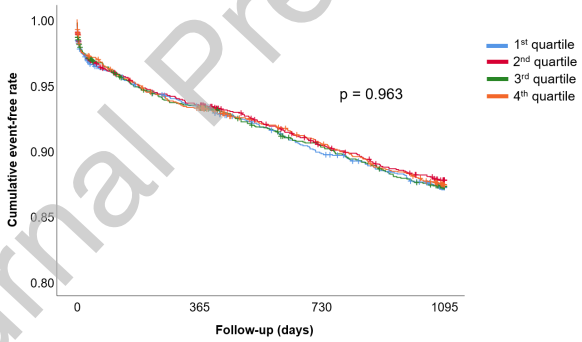

Figure 2C

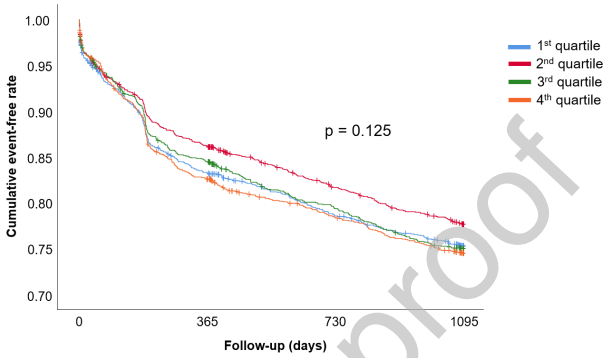

Figure 3: