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Cohort profile: role of lipoproteins in cardiovascular disease—the LipidCardio study

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ABSTRACT

Purpose The LipidCardio Study was established for in-depth analyses of cardiovascular risk factors, providing well-defined cardiovascular and metabolic phenotypes. In particular, the role of lipoproteins in the pathobiological process and treatment of cardiovascular disease (CVD) will be a main focus.

Participants 1005 individuals aged 21 years and older undergoing cardiac catheterisation during 17 months at a tertiary academic cardiology centre were enrolled (troponin-positive acute coronary syndrome was exclusion criterion). The baseline data not only contain detailed phenotyping, broad biochemical parameters, genetic data, but also standardised personal and family history, a screening test for cognitive impairment, pulse wave analysis and measurements of hand grip strength, among others. Blood samples were stored in a biobank for future analyses.

Findings to date The mean age of the participants at enrolment was 70.9±11.1 years (70% male). Coronary angiography provided evidence of obstructive coronary artery disease (CAD) in 69.9% of participants. Those with evidence of CAD were significantly more likely to be male, inactive, diabetic and with a family history of CVD than participants without CAD.

About 20% of patients had lipoprotein(a) (Lp(a)) concentrations above 106.9 nmol/L (fifth quintile). These patients had significantly increased odds of obstructive CAD compared with participants in quintiles 1–4 (crude OR 1.70, 95% CI 1.17 to 2.48, p=0.005). There was reasonable evidence that with increasing severity of CAD the odds of having elevated Lp(a) increased. We were able to replicate the established strong association between specified single nucleotide polymorphisms (SNPs) in the *LPA* gene (rs10455872, rs3798220 and rs186696265) and the *APOE* gene (rs7412), and the concentration of Lp(a), validating our phenotype database and biobank.

Future plans Mortality information will be obtained in 2 year intervals. Follow-up phone interviews will be conducted at 3 and 6 years after enrolment. We seek to cooperate with other researchers, for example, by sharing data and biobank samples.

Strengths and limitations of this study

- This cohort has up-to-date coronary angiographic information on all included subjects. While the majority of participants has confirmed obstructive coronary artery disease (CAD), there is a sufficiently large internal comparison group which is evidentially free from any detectable CAD.
- In addition, we are able to differentiate a group with non-obstructive CAD, constituting an interesting intermediate group. This differentiation is particularly important in terms of working with distinct phenotypes.
- In addition to comprehensive clinical information, we assessed functional status, lifestyle factors and genetics.
- A high quality biobank was established.
- A potential weakness is that patients were only recruited from one tertiary care hospital. Therefore, the results may not be readily generalised to other patients with CAD.

INTRODUCTION

Ischaemic heart disease accounts for >20% of all deaths in Europe.[1] Although age-adjusted mortality rates from coronary artery disease (CAD) have declined substantially in the past decades throughout Europe and the USA, the CAD burden remains high.[1–3]

Traditional modifiable risk factors for CAD perform well in predicting the risk of developing CAD and targeting them decreases cardiovascular risk in a dose-dependent manner.[4]

Still, about half of patients with prevalent CAD remain at very high residual risk of recurrent events despite optimally controlled risk factors.[5] Identification of additional modifiable risk factors to reduce—residual—cardiovascular risk is essential. Novel biomarkers and assessment of the individual genetic profile bear the potential of improving risk assessment and management in both primary and secondary prevention.

In this regard, lipoprotein(a) (Lp(a)) has emerged as a novel independent risk factor for CAD.[6] Lp(a), whose serum level is largely genetically determined, is still a subject of controversy.[6 7] For example, the underlying

physiological function of this lipoprotein is still unknown. There is reasonable evidence that Lp(a) is causally associated with CAD,[8] positively associated with coronary lesion severity and an independent risk factor for major adverse cardiovascular events, that is, the progression of CAD in patients with stable CAD who received optimal medical therapy.[7 9]

Screening for elevated Lp(a) presently is recommended in those at intermediate or high CV risk, in particular as an additional risk indicator.[7 10 11] To note, Lp(a) has also been suggested as a potential therapeutic target,[12] and an antisense oligonucleotide specific to apolipoprotein (a) has been recently shown to lead to dose-dependent reductions in average Lp(a) levels of >80%.[13]

Obviously, patients with prevalent CAD are a very heterogeneous group. Therefore, discrimination is likely to be advantageous over a one fits all disease management strategy. Further improvements in the management of CAD will presuppose careful characterisation of different phenotypes and subsequent joint application of genetics, epigenetics and metabolomics. For this purpose, we established the LipidCardio Study in 2016. We sought to implement detailed phenotyping and follow-up of patients with different severity of CAD and also without obstructive CAD to examine factors associated with the pathophysiological process and progression of cardiovascular disease (CVD). There will be a strong focus on lipoproteins and genetics. In particular, we seek to gain further insight into the role of Lp(a) in cardiovascular pathogenesis and to investigate the implications of a screening for Lp(a) in a high risk cohort of patients undergoing coronary angiography. Combining phenotype factors with genetic factors, we desire to elaborate the particular cardiovascular risk profile of patients with high Lp(a).

As another integral part of this study, we have collected ample blood specimens to hold high-quality, well-characterised biomaterials along with their clinical, genetic and demographic information for future biomedical research projects in store in a high-quality biobank.

Cohort description

Patients aged 18 years and older undergoing cardiac catheterisation at a single large academic centre (Department of Cardiology, Campus Benjamin Franklin, Charité-Universitätsmedizin Berlin), except those with troponin-positive acute coronary syndromes (ACS), were eligible for inclusion. Participation rate was particularly high (>95%). Between October 2016 and March 2018, 1005 consecutive patients were enrolled. All participants gave written informed consent at the time of enrolment. Patients unable to provide informed consent were excluded from the study.

The main study variables are shown in online supplementary table 1. A comprehensive data collection was performed, with a strong focus on cardiovascular health. Blood specimens were collected at the time of cardiac catheterisation (after administration of heparin), either as arterial blood sample directly from the radial or femoral artery sheath or as a venous blood sample from peripheral intravenous access. At enrolment, patients were interviewed to collect information on demographic characteristics, over-the-counter medication usage, health behaviours (alcohol/drug use, smoking and physical activity), a detailed standardised family history was obtained, and a screening test for cognitive impairment, the mini-mental state examination (MMSE), was performed. Information on regular prescription medications were obtained from the patients' medication plan. In addition, electronic medical records were reviewed by study personnel to obtain previous diagnoses of chronic conditions, as well as to document previous angiographic findings and coronary revascularisation history.

Specimens

Portions of the blood specimens were used to determine a basic panel of laboratory tests essential to this study. Lp(a) was determined using a turbidimetric assay (Roche Diagnostics GmbH, Mannheim). Lp(a) is given in nmol/L, correctly reflecting the number of Lp(a) particles.[14] A range of other parameters were taken over from the hospital information system, provided that they were ordered as part of the clinical routine. Importantly, all tests were done in one central, accredited laboratory.

EDTA blood samples were frozen immediately following collection at −80°C until DNA was isolated using the sbeadex livestock kit (LGC Genomics GmbH, Germany). Selected single nucleotide polymorphisms (SNPs) were genotyped using KASP chemistry (LGC, Hoddesdon, UK). We have also determined the two biomarkers, relative leukocyte telomere length and DNA methylation age (epigenetic clock), which was described elsewhere in detail.[15]

Additional blood samples were drawn and stored in the Central Biomaterial Bank Charité (ZeBanC),[16] providing the opportunity for additional measurements at a later date.

Coronary angiography

Cardiac catheterisation and coronary angiography were performed according to the standard protocols of the Interventional Cardiology Unit and by discretion of the interventional cardiologist. The interventional cardiologist routinely documented diagnostic findings. Comprehensive angiographic results at the time of enrolment were recorded in the study database.

Echocardiography, blood pressure measurement and pulse wave analysis

Echocardiography was performed as a part of the clinical routine and selected parameters were taken over into the study database.

Blood pressure was measured once on each arm, in a sitting position and at rest with a Boso Medicus Uno device with an adequate cuff size.

Central blood pressure, pulse wave reflection and pulse wave velocity were measured with the Mobil-O-Graph

Table 1 Baseline characteristics of the LipidCardio Study, total and according to presence or absence of elevated lipoprotein(a) (≥107 nmol/L).

	Total	Lp(a)<107 nmol/L	Lp(a)≥107 nmol/L
Sex, male	701 (69.8)	554 (71.5)	126 (65.3)
Age, years	70.9±11.1	70.7±11.4	71.7±9.9
Caucasian ancestry	981 (97.6)	756 (97.6)	188 (97.4)
Previous diagnosis of CAD	509 (50.7)	374 (48.3)	115 (59.6)
Previous bypass surgery	77 (7.7)	51 (6.6)	24 (12.4)
Previous myocardial infarction	310 (30.9)	227 (29.3)	61 (36.8)
Total obstructive CAD	701 (69.9)	526 (67.9)	151 (78.2)
One vessel	156 (15.5)	122 (15.7)	27 (14.0)
Two vessel	234 (23.3)	174 (22.5)	53 (27.5)
Three vessel	311 (31.0)	230 (29.7)	71 (36.8)
Non-obstructive CAD	113 (11.2)	94 (12.1)	14 (7.3)
No apparent CAD	170 (16.9)	155(20)	28 (14.5)
Aortic valve stenosis	100 (12.2)	71 (11.2)	26 (16.4)
Previous stroke	98 (9.8)	71 (9.2)	24 (12.4)
Atrial fibrillation	273 (27.2)	214 (27.6)	49 (25.4)
Diabetes mellitus type 2	270 (26.9)	220 (28.4)	43 (22.3)
Hypertension	813 (81.0)	627 (80.9)	156 (80.8)
Dyslipidaemia	598 (59.6)	455 (58.7)	121 (62.7)
Cancer	181 (18.0)	136 (17.6)	42 (21.8)
PAD	91 (9.1)	64 (8.3)	23 (11.9)
CKD	164 (16.3)	121 (15.6)	35 (18.1)
COPD	109 (10.8)	87 (11.2)	17 (8.8)
LDL-C (mg/dL)	99.1±40.6	97.1±39.8	106.4±41.9
ApoA1 (g/L)	1.28±0.28	1.27±0.28	1.32±0.27
ApoB (g/L)	0.85±0.27	0.83±0.27	0.93±0.28
WC (cm)	101.7±14.1	102.1±14.4	100.6±13.6
Systolic blood pressure (mm Hg)	134.0±21.3	134.0±21.5	134.3±21.1
Statin therapy	608 (60.5)	459 (59.2)	129 (66.8)
eGFR CKD-EPI formula (mL/min/1.73 m^2)	70.0±19.7	70.4±19.7	69.2±19.6
eGFR <60 mL/min/1.73 m^2	290 (29.8)	218 (29.3)	59 (30.9)

Values are mean±SD and n(%) unless stated otherwise. Of n=1005 observations values were missing in Lp(a) (n=37), LDL-C (n=41), ApoA1 (n=50), ApoB (n=49), WC (n=153), systolic blood pressure (n=148) and eGFR (n=33).
AF, atrial fibrillation; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CAD, coronary artery disease; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease-epidemiology collaboration; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PAD, peripheral arterial disease; WC, waist circumference.

PWA device, according to the operating instructions of the manufacturer.

Other measurements

Waist circumference was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest. Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor. For both measurements, the subjects were standing and wore little clothing.[17]

Hand grip strength was measured with a Smedley Dynamometer (Saehan, Type SH5002).

Questionnaires

The Seattle Angina Questionnaire and the Rapid Assessment of Physical Activity questionnaire were administered. Folstein's MMSE for screening of cognitive impairment was administered in face-to-face interviews by trained study personnel.

Table 2 Baseline characteristics by CAD status at baseline.

	No apparent CAD	Obstructive CAD		Non-obstructive CAD
		Prior	Newly diagnosed	
	187 (18.6%)	509 (50.8%)	200 (19.9%)	107 (10.7%)
Age (years)	66.2±12.9	72.0±10.7	71.9±9.8	72.3±9.2
Sex (female)	107 (57.2)	95 (18.7)	58 (29.0)	42 (39.3)
Diabetes mellitus 2	38 (20.3)	157 (30.8)	52 (26.0)	23 (21.5)
Dyslipidaemia	80 (42.8)	354 (69.8)	107 (53.5)	56 (52.3)
Smoking (current)	33 (20.8)	82 (17.9)	40 (22.2)	15(15)
Smoking (former)	61 (48.4)	247 (65.7)	81 (57.9)	44 (51.8)
LDL-C (mg/dL)	115.00±37.60	85.20±35.13	117.75±44.40	104.38±37.53
HDL-C (mg/dL)	56.76±17.76	47.84±15.34	50.91±15.19	55.82±18.30
Triglycerides (mg/dL)	112 (88–156)	120 (89–174)	124 (89–185)	119 (89–158)
Lp(a) (nmol/L)	17.4 (7.2–60.3)	20.5 (5.0–99.8)	22.3 (7.2–71.4)	15.30 (5.0–44.4)
Lp(a)>106.9 nmol/L	28 (15.5)	115 (23.5)	37 (19.0)	13 (12.6)
Glucose (mg/dL)	115.0±37.3	123.1±47.1	125.7±47.7	121.9±44.6
HbA1c (%)	5.70±0.70	6.00±0.84	5.99±0.89	5.78±0.81
ApoB (g/L)	0.93±0.24	0.77±0.25	0.95±0.30	0.89±0.27
Chronic kidney disease	36 (20.3)	175 (34.9)	55 (29.1)	23 (22.3)
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	75.4±20.4	68.3±19.4	70.1±21.0	69.5±15.1
ApoA1 (g/L)	1.39±0.31	1.23±0.26	1.30±0.25	1.33±0.27
Body mass index (kg/m^2)	27.89±5.05	27.83±4.70	27.58±5.03	27.75±5.40
C reactive protein (mg/L)	2.15 (1.1–9.1)	2.0 (0.9–6.9)	2.8 (1.1–7.6)	2.30 (0.8–7.0)
Systolic blood pressure (mm Hg)	131.96±20.40	133.3±21.5	138.3±20.8	132.48±20.37
Diastolic blood pressure (mm Hg)	80.6±13.0	76.5±13.8	80.5±14.1	76.1±10.9

Values are mean±SD and n(%), or median (25th–75th percentile) unless stated otherwise. Of 1003 observations, values were missing in DBP (n=148), SBP (n=148), CRP (n=300), BMI (n=111), ApoA1 (n=48), smoking current (n=105), smoking former (n=276), LDL-C (n=41), HDL-C (n=46), triglycerides (n=289), Lp(a) (n=35), glucose (n=250), HbA1c (n=22), ApoB (n=47), chronic kidney disease (n=33) and $eGFR_{CKD-EPI}$ (n=33). ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CAD, coronary artery disease; CKD-EPI, chronic kidney disease-epidemiology collaboration; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Planned follow-up measures

Mortality information will be obtained from the obligatory registry office in 2 year intervals. Follow-up phone interviews will be conducted by trained study personnel, and the calls are planned to be made at 3 and 6 years after initial enrolment. Adverse CVD events, including non-fatal myocardial infarction, ACS, heart failure, hospitalisations, cardiac procedures (eg, revascularisation), strokes and peripheral arterial disease events will be recorded. Additional information will be collected on follow-up coronary angiogram data, development of comorbidities (hypertension, diabetes, cardiac arrhythmia, valvular

Table 3 Associations of *LPA*-single nucleotide polymorphisms (*LPA*-SNPs) and lipoprotein(a) (Lp(a)) serum levels: linear regression analysis on Lp(a) serum levels (log10-transformed), adjusted for age and sex

SNP	Location (GRCh37.p13)	A1/A2 (call rate, %)	MAF	N^1	β	SE	P value	N^2
rs10455872	6:160589086	A/G (99.6)	0.0736	950	0.794	0.049	5.10×10^{-52}	933
rs3798220	6:160540105	C/T(99.9)	0.0236	953	0.865	0.092	3.93×10^{-20}	936
rs186696265	6:160690668	C/T (99.8)	0.0170	952	0.993	0.106	7.60×10^{-20}	935
rs429358	19:44908684	C/T(95.4)	0.1307	910	0.035	0.043	0.407	893
rs7412	19:44908822	C/T(99.9)	0.0692	953	0.150	0.057	0.008	936

A1/A2, allele 1/allele 2; Lp(a) association, genotype and Lp(a) level available; MAF, allele frequency of the minor allele in LipidCardio; N^1, number of genotyped samples; N^2, number analysed with respect to.

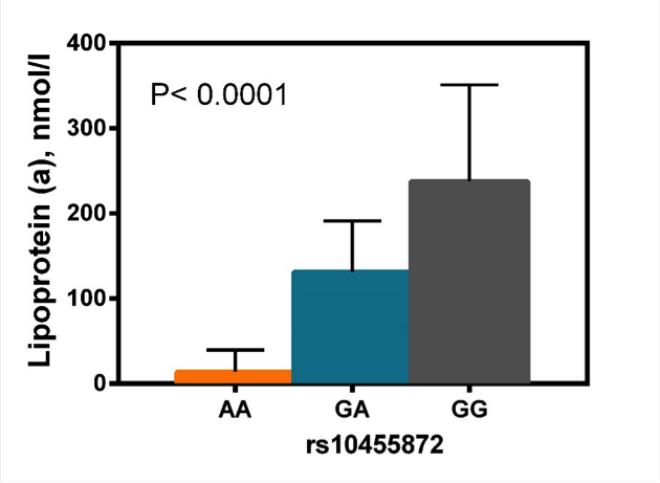

Figure 1 Association between single nucleotide polymorphism rs10455872 and lipoprotein(a) (Lp(a)) in the LipidCardio sample. rs10455872 genotype was significantly associated with median Lp(a) values (interquartile ranges are indicated, n=933). The p value was determined using the Kruskal-Wallis test.

heart disease, obstructive sleep apnoea and cancer) and changes in medications.

Patient and public involvement

Patients and public were not involved in the design or conduct of this study. Lp(a) plasma levels were disclosed to the participants.

Findings to date

The cohort

Baseline characteristics of the 1005 patients are shown in tables 1 and 2. The mean age at enrolment was 70.9±11.1 years. Approximately 70% of the participants were male and 97.6% were of white Caucasian ancestry. Coronary angiography provided evidence of obstructive CAD (defined as >50% luminal narrowing in a major epicardial vessel) in 69.9% of participants at enrolment, 11.2% had non-obstructive CAD and 18.8% had normal coronary angiograms without evidence of atherosclerosis (no apparent CAD). In 509 patients (50.6%) obstructive CAD had been previously known, and angiography was performed for evaluation of disease progression or planned intervention of residual stenosis.

Those with evidence of obstructive CAD were significantly more likely to have a positive family history of CVD (OR 1.48, 95% CI 1.06 to 2.06, p=0.019), compared with participants with no apparent CAD. Likewise, participants with obstructive CAD were significantly more likely to be physically inactive (OR 1.50, 95% CI 1.09 to 2.16, p=0.014).

Lipoprotein(a): clinical and genetic associations

The median serum concentration of Lp(a) at baseline was 19.3 nmol/L (IQR<7.0–77.1 nmol/L). Lp(a) levels were positively associated with age among women, whereas in men Lp(a) levels were consistent across the age spectrum. Referring to this, whereas overall there was no evidence of a significant sex difference in Lp(a) levels, in patients aged over 60 years the median Lp(a) concentration was significantly higher in women (26.4; IQR 8.2–109.6) than in men (18.2; IQR <7.0–71.4, p=0.038).

Accounting for the right-skewed distribution of Lp(a) in the general population and also in cardiovascular high-risk populations, it has become current practice to examine the distribution of Lp(a) by quintiles, particularly individuals in the fifth quintile being at increased risk of CV disease. Also, the commonly referenced threshold of 100–125 nmol/L (equals 50 mg/dL), usually corresponds approximately to the cut-off point defining the fifth quintile.[6 18] Of total 968 patients with available Lp(a) measurements, 193 patients (19.9%) had Lp(a) values above 106.9 nmol/L (fifth quintile).

Participants in the highest quintile of Lp(a) (≥107 nmol/L) had significantly increased odds of obstructive CAD compared with participants in the lowest quintile (OR 1.58, 1.02 to 2.45, p=0.039) or in quintiles 1–4 (OR 1.7, 95% CI 1.17 to 2.48, p=0.005), respectively. Moreover, there was reasonable evidence that with increasing severity of CAD (non obstructive CAD, 1-vessel, 2-vessel and 3-vessel obstructive CAD) the odds of having a significantly elevated Lp(a) increased (test for trend p=0.015).

Genetic associations

In order to assess if our cohort data are suitable for genetic association analyses, we genotyped and examined *LPA*-SNPs rs10455872, rs3798220 and rs186696265, which have been previously reported to be strongly associated with Lp(a) serum levels.[19–22] Overall, 179 patients (18.8%) were carriers of at least one minor allele. All three SNPs were significantly associated with Lp(a) levels in the LipidCardio cohort (table 3). The strongest evidence of an association with Lp(a) serum levels was found for rs10455872 (β=0.794; $p=5.1\times10^{-52}$, table 3 and figure 1). Our data were compatible with an overall positive association (OR 1.35; 95% CI 0.93 to 1.99, p=0.118) between carrying a minor *LPA* variant and CAD; even though the evidence was week. However, when stratified by sex there was reasonable evidence to suggest an association between the *LPA*-SNPs tested and obstructive CAD in women (OR 1.85, 95% CI 1.02 to 3.35, p=0.04), while in men there was no evidence for such an association. The association in women was stable even after adjusting for age, type 2 diabetes, LDL-C and statin therapy.

Furthermore, we genotyped the two SNPs rs429358 and rs7412 constituting the three isoforms of apolipoprotein E (APOE) apoE2, apoE3 and apoE4. Rs7412 was recently confirmed in a large genome-wide association meta-analysis to be associated with Lp(a) serum levels with genome wide significance.[19] Indeed, we found rs7412 to be significantly associated with Lp(a) concentration (β=0.15; p=0.008), that is, we could replicate the previous finding. Similar to the earlier study, there was no evidence that rs429358 was also associated with Lp(a) serum levels in

the LipidCardio cohort (data not shown), while there was reasonable evidence of an association between the inferred APOE isoforms (online supplementary table 2) and Lp(a) serum levels (β=0.015; p=0.006, n=893) (see online supplementary table 2).

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Contributors Conceived and designed the study: ID, MK, UL and ES-T. Recruitment of participants: UL, DL, MK and DS. Providing routine clinical data: UL and DL. Collected study specific data: MK, SJ, DS and ID. Analysed the data: MK and ID. Wrote the manuscript: MK and ID. All authors revised and approved the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the ethics committee at Charité-Universitätsmedizin Berlin (approval number: EA1/135/16).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement We are interested to share data and biobank samples with other researchers in joint collaborative projects, for example, for replication of phenotypic and/or genetic findings or meta-analyses of study results. Interested groups should contact the study coordinating PI Ilja Demuth at ilja.demuth@charite.de for the data-sharing application form. Each application will be reviewed by the LipidCardio PIs (currently ID, UL and ES-T) and the decision communicated to the applicants usually within 6 weeks of submission.

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