Stroke

CLINICAL AND POPULATION SCIENCES

Elevated Lp(a) (Lipoprotein[a]) Levels Increase Risk of 30-Day Major Adverse Cardiovascular Events in Patients Following Carotid Endarterectomy

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BACKGROUND AND PURPOSE: General population studies have shown that elevated Lp(a) (lipoprotein[a]) levels are an emerging risk factor for cardiovascular disease and subsequent cardiovascular events. The role of Lp(a) for the risk of secondary MACE in patients undergoing carotid endarterectomy (CEA) is unknown. Our objective is to assess the association of elevated Lp(a) levels with the risk of secondary MACE in patients undergoing CEA.

METHODS: Lp(a) concentrations were determined in preoperative blood samples of 944 consecutive patients with CEA included in the Athero-Express Biobank Study. During 3-year follow-up, major adverse cardiovascular events (MACE), consisting of myocardial infarction, stroke, and cardiovascular death, were documented.

RESULTS: After 3 years follow-up, Kaplan-Meier cumulative event rates for MACE were 15.4% in patients with high Lp(a) levels (>137 nmol/L; >80th cohort percentile) and 10.2% in patients with low Lp(a) levels (≤137 nmol/L; ≤80th cohort percentile; log-rank test: *P*=0.047). Cox regression analyses adjusted for conventional cardiovascular risk factors revealed a significant association between high Lp(a) levels and 3-year MACE with an adjusted hazard ratio of 1.69 (95% CI, 1.07–2.66). One-third of MACE occurred within 30 days after CEA, with an adjusted hazard ratio for the 30-day risk of MACE of 2.05 (95% CI, 1.01–4.17). Kaplan-Meier curves from time point 30 days to 3 years onward revealed no significant association between high Lp(a) levels and MACE. Lp(a) levels were not associated with histological carotid plaque characteristics.

CONCLUSIONS: High Lp(a) levels (>137 nmol/L; >80th cohort percentile) are associated with an increased risk of 30-day MACE after CEA. This identifies elevated Lp(a) levels as a new potential risk factor for secondary cardiovascular events in patients after carotid surgery. Future studies are required to investigate whether Lp(a) levels might be useful in guiding treatment algorithms for carotid intervention.

Key Words: cardiovascular disease ■ endarterectomy, carotid ■ lipoprotein(a) ■ myocardial infarction ■ risk factor

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Carotid endarterectomy (CEA), an established treatment for patients with moderate to severe carotid artery stenosis, reduces the recurrent risk of ipsilateral stroke. These patients, however, are characterized by extensive polyvascular disease, reflecting the systemic nature of atherogenesis.[1] This results in a high

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Nonstandard Abbreviations and Acronyms

CEA	carotid endarterectomy
CVE	cardiovascular events
HDL	high-density lipoprotein
LDL	low-density lipoprotein
LDL-c	LDL cholesterol
Lp(a)	lipoprotein(a)
MACE	major adverse cardiovascular events
SMC	smooth muscle cell

residual cardiovascular risk following CEA,[2] with 3-year major adverse cardiovascular event (MACE) incidence rates as high as 19% to 35%.[1,3]

Although aggressive secondary prevention strategies have contributed to reduction of secondary MACE, the residual risk is still markedly elevated and a high number of patients on active secondary prevention still develop cardiovascular events. This suggests that other modifiable risk factors may contribute to the risk of secondary cardiovascular events.[4,5]

Genetic and observational data have convincingly demonstrated that elevated Lp(a) (lipoprotein[a]) is a causal and highly prevalent risk factor for cardiovascular diseases.[4–6] Lp(a) is an LDL (low-density lipoprotein)-like particle characterized by covalently bound Apo(a) to Apo B_{100} (Apolipoprotein B100) of LDL. Lp(a), like LDL cholesterol, is able to accumulate in the subendothelial space, leading to progressive atherosclerosis. It has also been shown to exert a plethora of signaling effects exacerbating its atherogenic capacity. Lp(a) induces a systemic proinflammatory state, but in addition has prothrombotic as well as pro-oxidant effects.[4,6,7]

To date, available evidence on Lp(a) and the risk for cardiovascular events is based on studies on individuals in primary prevention setting. Evidence on whether Lp(a) is associated with risk of recurrent cardiovascular events remain scarce[8] and only include patients with established coronary artery disease.[9–11] To date, the association between Lp(a) and recurrent cardiovascular events in patients with CEA is unknown. This association is important in weighing up treatment strategies, including add-on medical therapy or an endovascular approach for carotid revascularization. Hence, in the present study, we set out to address the impact of elevated Lp(a) levels and the risk of MACE in a large cohort of 944 patients with CEA.

METHODS

Study Population

From the Athero-Express Biobank, all patients undergoing CEA between 2002 and 2016 with available lipid profile measurements were included in the current study. Patients undergoing CEA for restenosis were excluded (Figure 1). The Athero-Express started in 2002 and is a prospective ongoing biobank study, including all consecutive patients scheduled for CEA in 2 referral hospitals in the Netherlands (the St. Antonius Hospital Nieuwegein and University Medical Center Utrecht). The study design has been described previously in more detail.[12] In short, preoperative blood and atherosclerotic plaque specimens of all patients undergoing CEA are collected. Indications for CEA were reviewed by a multidisciplinary vascular team and experienced surgeons performed the surgery in accordance with local and international guideline.[2,13–16] Standardized preoperative questionnaires and hospital medical records were used to obtain baseline patient characteristics. Perioperative assessment was structurally done by a neurologist or vascular surgeon. Hospital medical records were reviewed for perioperative events. All patients received questionnaires annually for the first 3 consecutive years after CEA to collect follow-up data on cardiovascular events or hospital admissions. If an outcome event occurred, medical records were checked and relevant documentation was acquired by contacting the general practitioner or hospital. If patients did not respond to the follow-up questionnaire, the general practitioner was contacted for follow-up information. The medical ethics board of both hospitals approved the study, and all study participants provided written informed consent. The study is conducted in accordance with the declaration of Helsinki. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Laboratory Measurements

All venous blood samples were collected during hospital admission before surgery and stored at −80°C until further use. Patients with available lipid profile measurements (assessed as part of routine care) were selected for Lp(a) measurements. Lp(a) concentrations were measured with a latex-enhanced particle immunoturbidimetric assay in serum samples using the Cobas c702 (Roche) and the LPA2 Tina-quant Lp(a) Gen.2 kit from Cobas (LPA2: CAN 8723). In short, Lp(a) was measured in nanomoles per liter by means of a particle enhanced immunoturbidimetric assay, where Lp(a) agglutinates with latex particles coated with anti-Lp(a) antibodies. The precipitate is determined turbidimetrically at 800/660 nm. The measuring rage of this assay is between 7 and 240 nmol/L. More information regarding specific performance data, the repeatability, and intermediate precision can be found in the manufacturers' instructions.

Atherosclerotic Plaque Assessment

Histological assessment of the atherosclerotic plaques was performed according to a standardized protocol on sections of the culprit segment and has previously been described in detail.[17] In short, plaques were stained with alpha-actin for smooth muscle cells (SMC), CD68 for macrophages, CD34 for microvessels, picrosirius red for collagen and lipid content, hematoxylin-eosin for general overview including calcifications, and hematoxylin-eosin and fibrin for intraplaque hemorrhage. All stainings were semiquantitatively scored by 2 independent observers. SMCs, macrophages, collagen content, presence of calcifications, were scored either as no/minor (0) or moderate/heavy (1) staining. Microvessel density was determined by the average number of

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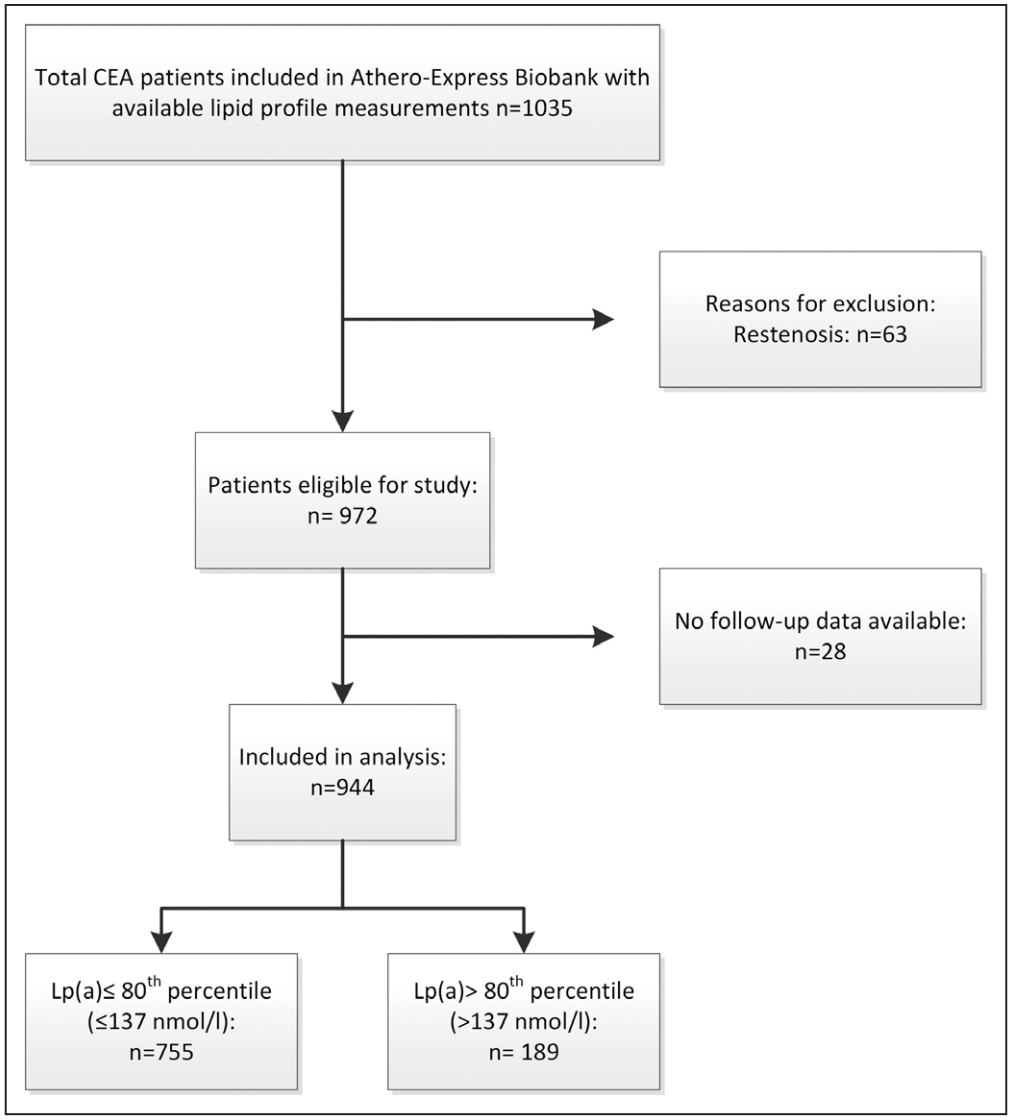

Figure 1. Flowchart of study population.
A total of 1035 carotid endarterectomy (CEA) patients with available lipid profile measurements were included in the Athero-Express Biobank. Following exclusion of patients with restenosis (n=63) and no available follow-up data (n=28), 944 patients were eligible for this study. Patients were classified in low Lp(a) (lipoprotein[a]; ≤80th cohort percentile, ≤137 nmol/L) n=755 and high Lp(a) (>80th cohort percentile, >137nmol/L) n=189.

vessels of 3 hotspots within every plaque. Lipid content was estimated as a percentage of total plaque area and stratified into <10%/40% and higher than 10%/40%. Intraplaque hemorrhage was rated as absent or present. Intraobserver and interobserver variability were examined previously and showed good reproducibility (κ, 0.6–0.9).[18] In addition, macrophage and SMCs content were scored quantitatively using computerized analysis software AnalySIS 3.2 (Soft Imaging Systems GmbH, Münster, Germany) and reported as percentage positive staining per plaque area.

Outcomes

The primary outcome, MACE, was a composite encompassing myocardial infarction, stroke, or cardiovascular death. Cardiovascular death was defined as fatal myocardial infarction, fatal stroke (bleeding or ischemic), fatal ruptured abdominal aneurysm, fatal heart failure, or sudden death. Patients who reached multiple end points during follow-up only the first manifestation of a cardiovascular event was used for analysis. End point criteria have been described previously[12]; all were adjudicated by 2 members of an outcome assessment committee.

Statistical Analyses

Based on the thresholds proposed in previous studies and guidelines[4,19,20] for Lp(a), Lp(a) levels were stratified in high and low based on the 80th cohort percentile as cutoff. Continuous variables are presented as mean (±SD) or as median (interquartile range) when appropriate. Discrete data are presented as frequencies and percentages. To compare baseline characteristics and plaque composition of patients across high and low Lp(a) groups, Pearson χ^2 test was used for categorical data, Student *t* test for continuous data, and Mann-Whitney *U* test for non-normally distributed variables. The MACE-free survival after 30 days and 3

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years of follow-up of patients in high and low Lp(a) categories was estimated with Kaplan-Meier survival analysis. Survival was compared by performing the log-rank test. Cox proportional hazard regression was used to calculate the hazard ratio (HR) with 95% CI for the association between Lp(a) and the occurrence of MACE during follow-up. Based on literature age, sex, smoking status, systolic blood pressure, diabetes mellitus, LDL, HDL (high-density lipoprotein), history of peripheral artery disease or coronary artery disease, and presence of contralateral carotid stenosis were identified as potential confounders.[1,4,6,21] LDL cholesterol was corrected for the Lp(a) contribution by subtracting 30% of total Lp(a) mass (corresponding to the cholesterol content in Lp[a]) from LDL cholesterol. Across the selected confounders, the proportion of missing values was analyzed (Table 1). Missing values were imputed using a multiple imputation procedure.[22,23] The selected confounders were included in a multivariable Cox proportional hazards model. All *P* values were 2-tailed, with a value <0.05 considered to indicate statistical significance. Statistical analyses were performed with R Studio Version 1.1.456 (R Foundation for Statistical Computing, Vienna, Austria).[24]

RESULTS

Patient Population and Baseline Characteristics

Nine hundred forty-four patients who underwent CEA with available lipid profile measurements were identified

Table 1. Baseline Characteristics of Study Population

	Total	Lipoprotein(a), nmol/L		*P* Value	Missing Values
		≤137	>137		
	n=944	n=755	n=189		n (%)
Age, y	69.7 (9)	69.7 (9)	69.4 (10)	0.63	0 (0)
Sex (women)	293 (31)	212 (28)	81 (43)	<0.01*	0 (0)
BMI, kg/m^2	26.2 (4)	26.2 (4)	26.3 (4)	0.85	24 (2.5)
Hypertension	668 (73)	536 (73)	132 (70)	0.51	27 (2.9)
Systolic BP, mm Hg	151 (25)	152 (25)	148 (26)	0.08	115 (12.2)
Diastolic BP, mm Hg	80 (13)	81 (13)	79 (14)	0.25	116 (12.3)
eGFR, mL/(min·1.73 m^2)	74 [60–88]	74 [60–88]	76 [62–89]	0.46	71 (7.5)
Current smoker	321 (34)	265 (35)	56 (30)	0.17	9 (1.0)
Diabetes mellitus	209 (22)	174 (23)	35 (18)	0.2	0 (0)
Insulin use	59 (6)	54 (7)	5 (3)	0.02*	1 (0.1)
Oral glucose inhibitor use	149 (16)	125 (17)	24 (13)	0.22	1 (0.1)
Hypercholesterolemia	591 (71)	455 (68)	136 (81)	<0.01*	113 (12.0)
Triglycerides, mg/dL	1.5 [1.1–2.0]	1.5 [1.1–2.0]	1.5 [1.1–2.0]	0.61	4 (0.42)
LDL, mmol/L	2.0 [1.5–2.6]	2.1 [1.5–2.6]	1.8 [1.3–2.4]	<0.01*	4 (0.42)
HDL, mg/dL	1.1 (0.3)	1.0 (0.3)	1.1 (0.3)	<0.01*	4 (0.42)
Total cholesterol, mg/dL	4.1 (1.1)	4.1 (1.1)	4.4 (1.0)	<0.01*	4 (0.42)
Anticoagulant use	92 (10)	78 (10)	14 (7)	0.27	1 (0.1)
Antiplatelet use	833 (88)	663 (88)	170 (90)	0.71	3 (0.3)
Statin use	753 (80)	594 (79)	159 (84)	0.16	1 (0.1)
History of CAD	268 (28)	207 (28)	61 (32)	0.24	1 (0.1)
History of stroke	314 (33)	254 (34)	60 (32)	0.65	0 (0)
History of PAD	182 (19)	146 (19)	36 (19)	0.98	1 (0.1)
Preprocedural neurological symptoms				0.87	12 (1.3)
Asymptomatic	119 (13)	94 (13)	25 (13)		
Ocular	267 (29)	218 (29)	49 (26)		
TIA	160 (17)	126 (17)	34 (18)		
Stroke	387 (42)	308 (41)	79 (42)		
Contralateral stenosis				0.14	122 (12.9)
0%–50%	465 (57)	378 (58)	87 (51)		
50%–100%	358 (44)	275 (42)	83 (49)		
Days between last event and surgery	23.0 [12.0–50.8]	24 [12.0,50.0]	22.5 [11.7–51.0]	0.87	175 (18.5)

Data are presented as n (%), mean±SD, or median [IQR]. BMI indicates body mass index; BP blood pressure; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; PAD, peripheral artery disease; and TIA, transient ischemic attack.

*Statistically significant with a $P<0.05$.

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for the current study (Figure 1). Baseline characteristics of the study population are presented in Table 1. The mean age of all patients was 69.7 years (±9), and 31% (n=293) were women. Based on the 80th percentile as cutoff, patients were stratified in to high >137 nmol/L (n=190) and low ≤137 nmol/L (n=755) Lp(a) levels. The number of women was higher in the high Lp(a) group (43% versus 28%, $P<0.001$) compared with the low Lp(a) group. The mean follow-up time was 2.57 (±0.85) years, during which 102 out of 944 (10.8%) patients reached the end point MACE. MACE consisted of 27 myocardial infarction, 63 strokes, and 12 cardiovascular-related deaths.

Elevated Lp(a) Levels Are Associated With MACE in 30 Days Follow-Up

Kaplan-Meier cumulative event rates for MACE after 3 years follow-up were 15.4% in patients with high Lp(a) levels and 10.2% in patients with low Lp(a) levels ($P=0.047$; Figure 2). High Lp(a) levels (above 80th percentile; >137 nmol/L) were significantly associated with 3-year MACE with an HR of 1.54 (95% CI, 1.00–2.39), compared with patients with low Lp(a) levels (below 80th percentile; <137 nmol/L). Adjustment for risk factors led to a more pronounced association with an HR of 1.69 (95% CI, 1.07–2.66) for patients with high Lp(a) levels compared to patients with low Lp(a) levels (Figure 3).

However, out of the 102 patients who reached the end point MACE, one-third of the patients (35 patients) had MACE within 30 days postsurgery. We, therefore, further analyzed the relation of elevated Lp(a) and the number of MACE that occurred during this 30-day perioperative period. In the subgroup of patients that had perioperative MACE, 6 patients underwent CEA for asymptomatic carotid stenosis and the remaining for symptomatic carotid stenosis. Presenting symptoms that were the reason for CEA were 10 ocular symptoms (Amaurosis Fugax, ocular ischemic symptoms), 11 transient ischemic attack, 7 stroke, and 1 was unclear to localize. Median time from event to intervention was 23 days [interquartile range, 12.5–46.5]. Thirty-day MACE consisted of 28 strokes, 6 myocardial infarction. and 1 cardiovascular-related death. Kaplan-Meier analysis for 30-day MACE revealed a significant difference in MACE-free survival between patients with high and low Lp(a) levels ($P=0.032$; Figure 4A). After adjustment for sex and age, a strong association was found between high Lp(a) levels and the risk of 30-day MACE, with an HR of 2.05 (95% CI, 1.01–4.17; Figure 3). Because the association with 30-day MACE seemed much stronger compared with 3-year MACE, Kaplan-Meier curves were plotted excluding the cases within the first 30 days postsurgery. This revealed no significant association between high Lp(a) levels and MACE from time point 30 days to 3 years onward (Figure 4B).

Elevated Lp(a) Levels Are Not Associated With Plaque Characteristics

To investigate whether high Lp(a) levels result in more MACE due to its association with more vulnerable plaque characteristics, we related plaque characteristics to Lp(a) levels. Using semiquantitative analysis, plaque characteristics (such as calcification, collagen, lipid core, intraplaque hemorrhage, macrophage, and SMC) were compared between patients with low and high levels of Lp(a). Quantitative measurement was done for vessel density, number of microvessels, macrophage staining, and SMC staining. For both semiquantitative as quantitative analysis, no significant differences were found in plaque histology between both groups (Table 2).

DISCUSSION

In the present study, we show that elevated Lp(a) levels (>137 nmol/L; >80th cohort percentile) are associated with high risk of postoperative MACE, extending the impact of Lp(a) on overall cardiovascular diseases risk from primary to secondary cardiovascular patients. Strikingly, the association between high Lp(a) and 3-year risk of MACE was completely driven by the events in the first 30 days after CEA.

Observational studies[4–6,25] have established the association of Lp(a) with cardiovascular disease risk. The evidence on recurrent cardiovascular events and Lp(a), however, is limited. A general population study on individuals with preexisting cardiovascular disease revealed that high concentrations of Lp(a) were associated with a high risk of recurrent cardiovascular events.[8] This association was also found in a cohort of patients with established coronary artery disease.[10] Patients with CEA, however, were not included in both studies. Accordingly, we measured Lp(a) levels in a large cohort of 944 consecutive patients with CEA. In this large cohort, more women were present in the high Lp(a) group, which is likely ascribed to the inclusion of older postmenopausal women (mean age total high Lp[a] group 69.4 years). This is in line with previous results from a cohort study among patients without ischemic stroke at baseline.[21] Earlier studies in carotid atherosclerosis have shown that high Lp(a) plasma levels are associated with the presence or progression of carotid atherosclerotic plaque visualized by different imaging modalities in patients without a cardiovascular history.[26–29] In contrast, in other studies in young adults without cardiovascular risk factors,[30,31] in statin-treated familial hypercholesterolemia patients,[32] and in a cohort of patients with premature coronary artery disease,[33] no association was found between high Lp(a) levels and atherosclerotic changes in the carotid artery. We now show for the first time that elevated Lp(a) levels are associated with MACE 30 days after CEA.

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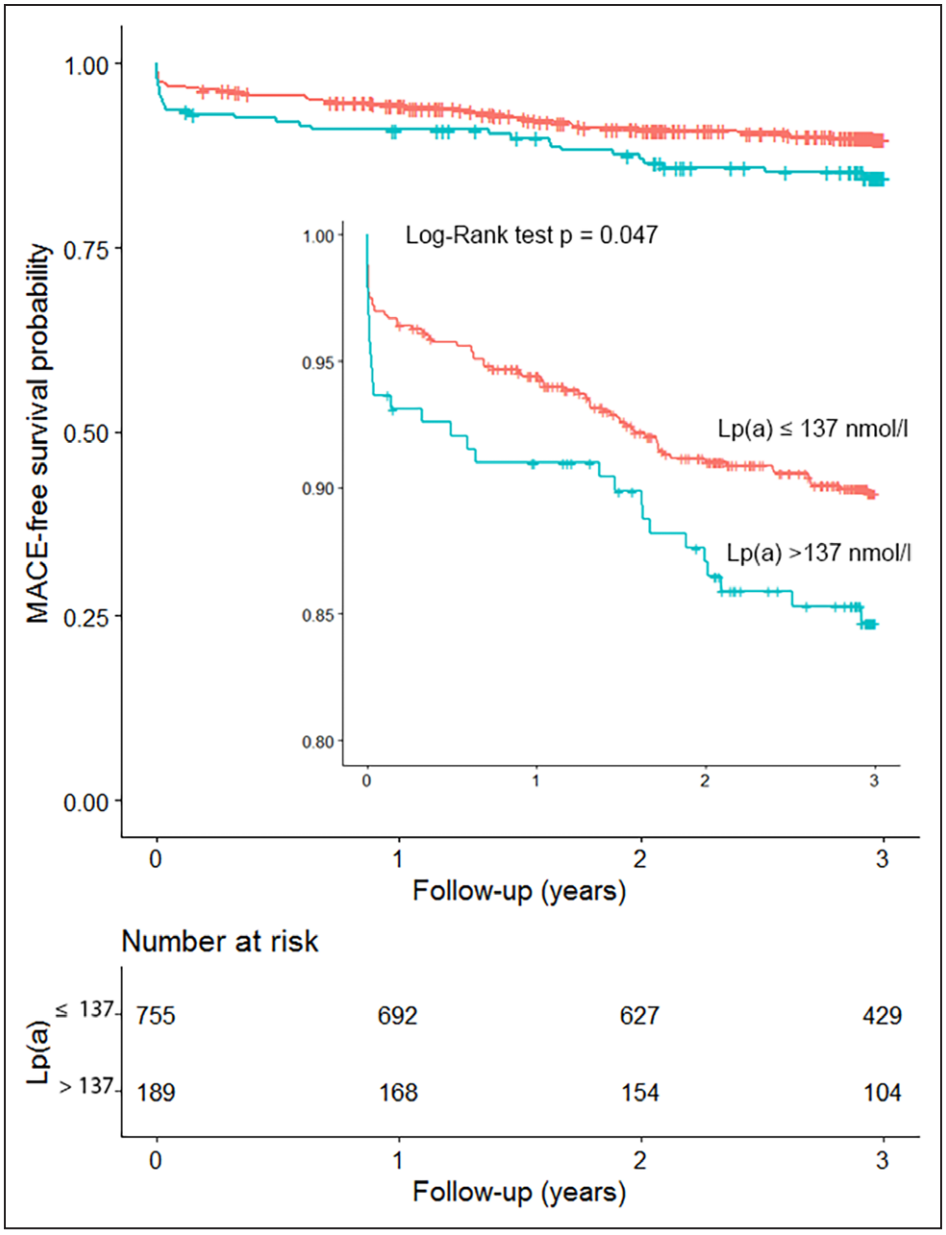

Figure 2. Kaplan-Meier curves according to high and low Lp(a) (lipoprotein[a]) levels for the end point 3 y major adverse cardiovascular events (MACE).

Low Lp(a) corresponds to the value of ≤137 nmol/L (≤80th cohort percentile), high Lp(a) corresponds to the value of >137 nmol/L (>80th cohort percentile). *P* value of log-rank test. The inset shows the same data on an enlarged *y* axis.

Adjustment for cardiovascular risk factors resulted in an even stronger association between high Lp(a) levels and 3-year MACE, indicating that Lp(a) promotes atherosclerosis in the presence of other risk factors.[30] Evidence supporting this arises from imaging studies that demonstrate an increase in intima-media thickness in patients with elevated Lp(a) levels, in a cohort of dialysis patients,[34] and patients with concurrent severe hypercholesterolemia[35] or diabetes mellitus.[36] This is also supported by studies performed in young adults[30,31] or in populations without risk factors,[32] where no association between Lp(a) levels and presence of atherosclerotic changes in the carotid artery were found.

The threshold to define Lp(a) elevation is a matter of debate. The cutoff in current study was based on the 80th percentile, as proposed in several previous studies and guidelines.[4,7,19,20] For patients with established coronary heart disease, a noncontinuous relation with Lp(a) levels and secondary cardiovascular events has recently been reported wherein patients in the highest quintile had an increased risk.[10] Furthermore, Lp(a) has a skewed concentration distribution with a tail toward extremely high levels. We think Lp(a) measurements in patients with extreme levels have the potential to substantially improve risk prediction. This is supported by other study groups[8,21,37–39] and underscored by our additional results

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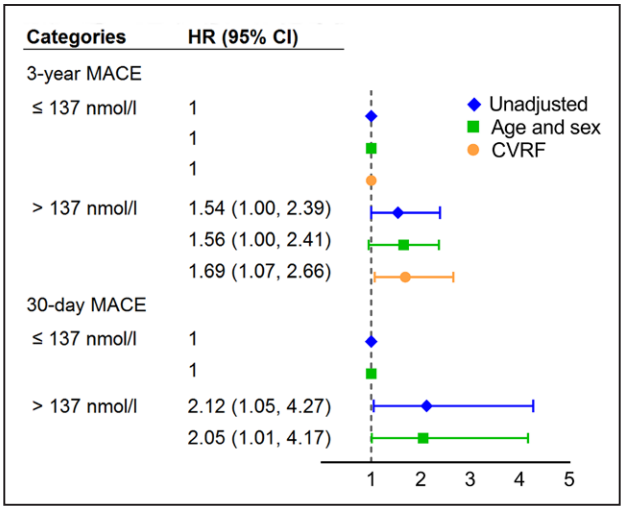

Figure 3. Cox regression analysis according to high Lp(a) (lipoprotein[a]; >137 nmol/L, >80th cohort percentile) and low Lp(a) (≤137 nmol/L, ≤80th cohort percentile) for the end point 3-y major adverse cardiovascular events (MACE) and 30-d MACE.

Unadjusted hazard ratios (HR; blue rhombus), adjusted hazard ratios for age and sex (green square) and cardiovascular risk factors (CVRF; orange circle) age, sex, systolic blood pressure, smoking status, diabetes mellitus, LDL (low-density lipoprotein), HDL (high-density lipoprotein), history of peripheral artery disease or CAD and presence of contralateral carotid stenosis.

for extreme Lp(a) levels (Figure I and Table I in the Data Supplement).

In this study, further analysis for 30-day risk of MACE revealed that the 3-year risk of MACE was driven by the events in the first 30 days. Furthermore, the association with elevated Lp(a) levels was much stronger compared with 3-year MACE. The main outcome, 3-year MACE, was mostly determined by stroke (63 out of 102); of these, 28 were within 30 days postsurgery. Periprocedural stroke is an important complication of CEA and severely limits the absolute benefit of the procedure.[40,41] When excluding the cases within the first 30 days postsurgery, no significant association was found between high Lp(a) levels and MACE from 30 days to 3 years onward. These data imply that the association of elevated Lp(a) levels and MACE is driven by 30-day stroke outcome. To validate these important findings, studies in larger cohorts are warranted because the number of perioperative events was low. In literature, the vast majority of studies report an increased risk of primary ischemic stroke in patients with elevated Lp(a) levels,[6,21,42–44] while only a small number of studies report contrasting results.[45,46] However, the reported association in these studies is weaker compared to the risk associated with coronary heart disease. In the present study, a much stronger association between elevated Lp(a) levels and the composite end point MACE is observed, with HR, 2.05 (95% CI, 1.01–4.17) for 30-day risk of MACE (Figure 3). Nevertheless, our findings extend to recurrent events because patients included in the Athero-Express biobank all have an indication for CEA and thus already had their primary event. Furthermore, the risk of early recurrent stroke is related to the underlying pathology, where patients with large artery cerebrovascular disease have a higher early risk of recurrent stroke compared with etiologic subgroups, such as small-vessel strokes.[47] A higher risk of recurrent vascular events in patients with elevated Lp(a) levels (>30 mg/dL), after first ischemic stroke, has been reported in a previous study, with an adjusted HR of 2.60 (95% CI, 1.19–5.67).[48] We, therefore, extend the results from the previous study and highlight the importance of Lp(a) in patients with cerebrovascular symptoms caused by carotid stenosis.

Several pathophysiological mechanisms through which Lp(a) is able to mediate atherogenesis have been proposed. First, as with LDL, Lp(a) was shown to accumulate both in progressive lesions and in ruptured plaques,[49] suggesting that high levels of Lp(a) in plaque are associated with rupture-prone plaque phenotype. Second, a large body of evidence shows that Lp(a) exerts its proinflammatory properties by the oxidized phospholipids bound to Apo(a) (apolipoprotein(a)).[7] Recent studies have shown that oxidized phospholipids bound to Lp(a) are able to elicit an inflammatory response in the endothelium, a process fueled by increased endothelial glycolysis and which are corroborated in patients from the Athero-Express biobank.[50]

Finally, the structural homology of Apo(a) with plasminogen can reduce fibrinolytic activity, resulting in reduced thrombus degradation plaque rupture and subsequently larger number of ischemic events. It is proposed that high Lp(a) levels might promote cardiovascular events by its prothrombotic properties.[30,51] For this, we also assessed the association between high Lp(a) and plaque phenotype (Table 2). Specific plaque characteristics, such as large lipid core, inflammation, thin fibrous cap, and intraplaque hemorrhage are associated with plaque rupture.[17,52–57] However, no statistically significant association between plaque phenotype and Lp(a) levels was found (Table 2), although high Lp(a) levels were associated with MACE. In corroboration, the association between plaque characteristics and the outcome 3-year MACE did not show differences between both groups (Table II in the Data Supplement). These results suggest that with this dichotomization, Lp(a) does not appear to affect plaque modification but may play a role in enhancing a prothrombotic state. A mouse model of ischemic stroke showed that reduced blood plasminogen levels increase infarct size.[58] In humans, it was shown that blood tissue-type plasminogen activator and plasminogen activator inhibitor-1 levels are higher in stroke patients versus controls, suggesting an altered fibrinolytic system in stroke patients.[59] Also, the amount of plasminogen bound and plasmin formed at the surface of fibrin are directly related to in vivo variations in

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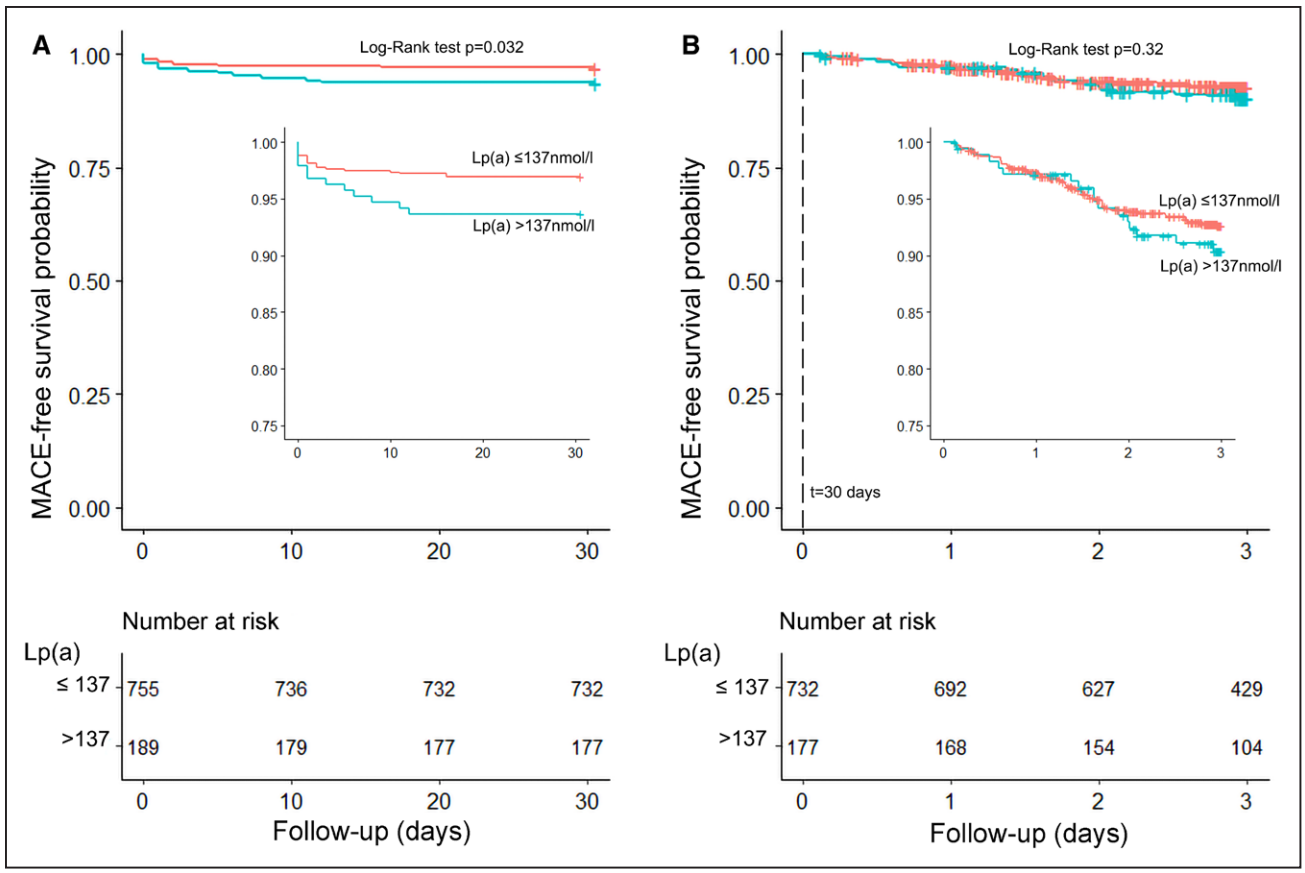

Figure 4. Kaplan-Meier curves according to high and low Lp(a) levels for both 30-d and 30-d to 3-y major adverse cardiovascular events (MACE).

Kaplan-Meier curves according to (A) high and low Lp(a) levels for the end point 30-d MACE and (B) 3-y MACE from timepoint 30 d to 3 y. Low Lp(a) corresponds to the value of ≤137 nmol/L (≤80th cohort percentile), high Lp(a) corresponds to the value of >137 nmol/L (>80th cohort percentile). *P* value of log-rank test. The inset shows the same data on an enlarged *y* axis.

the circulating concentration of Lp(a).[60] More studies are warranted to investigate if the role of elevated Lp(a) in modulating fibrinolytic activity leads to a higher risk of stroke within 30 days of surgery in patients with CEA. In particular, during this time period, these patients are prone for carotid embolization: (1) as a consequence of manipulation of the carotid plaque during surgery, (2) the endarterectomized surface that can form emboli or (3) emboli that can originate from a loose intimal flap.[40]

If elevated Lp(a) levels are related to the risk of secondary MACE, this could have impact on clinical decision making. Preoperatively, Lp(a) could be used as part of multiscale treatment algorithms to facilitate patient-specific treatment. For instance, patients with high Lp(a) levels in combination with other determinants, could be assigned to CEA as treatment strategy, over carotid stenting, CEA is associated with a lower risk of perioperative stroke compared to carotid stenting. However, in order for this to be implemented, future studies in stented carotid stenosis populations are warranted. In addition, this will also have marked consequences for secondary prevention. A recent study investigated whether lipid-lowering treatment with evolocumab, an anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibody, alters arterial wall inflammation in patients with elevated Lp(a). Therapy with Evolocumab leads to potent LDL-c (LDL cholesterol) reduction (−60%) and a modest Lp(a) reduction (−14%). Interestingly, this did not reduce arterial wall inflammation, possibly attributable to the residually elevated Lp(a) levels. Hence, Lp(a) lowering therapy, for example, using Apo(a) antisense oligonucleotides, is strongly advised[61] because only lowering the classical modifiable risk factors will leave a high residual risk of MACE in patient with elevated Lp(a) levels.[62]

Strengths and Limitations

For proper interpretation of the study results, some limitations need to be considered. Although the continuity of the Athero-Express is unparalleled, it should be noted that over the broad inclusion period, improvements in treatment options, in-hospital care, and timing of the surgery have occurred. However, the distribution of MACE and Lp(a) levels show no evident relationship with surgery year over time (Table III and Figure II in the Data Supplement).

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Table 2. Semiquantitative and Continuous Plaque Characteristics Stratified by High and Low Lp(a) Levels

	Lp(a), nmol/L		
	≤137	>137	
	n=755	n=189	*P* Value
Semiquantitative Plaque Characteristics			
Moderate/heavy calcification, %	264 (42)	66 (48)	0.32
Moderate/heavy collagen staining, %	481 (78)	108 (77)	0.91
Presence of lipid core ≥10%, %	438 (70)	98 (70)	0.91
Presence of intraplaque hemorrhage, %	337 (54)	80 (57)	0.60
Moderate/heavy macrophage infiltration, %	312 (51)	72 (53)	0.76
Moderate or heavy smooth muscle staining, %	403 (65)	101 (72)	0.16
Vessel density ≥median, %	245 (48)	63 (55)	0.18
Continuous quantified plaque characteristics			
Median number of microvessels per hotspot (median [IQR])	6.30 [3.00–11.00]	7.00 [3.67–13.00]	0.10
% of positive macrophage staining per plaque (median [IQR])	0.22 [0.05–0.76]	0.25 [0.07–0.71]	0.66
% of positive smooth muscle staining per plaque (median [IQR])	1.23 [0.48–2.44]	1.13 [0.50–2.71]	0.75

IQR indicates interquartile range; and Lp(a), lipoprotein(a).

Next, the changes in lipid levels or lipid-lowering treatments during the 3 years of follow-up could not be taken into account. As for the end points, we could not determine the proportion of strokes caused by thromboembolic events attributable to atrial fibrillation. However, all end points were prespecified and assessed by 2 outcome assessors, ensuring clear differentiation of the outcomes. Although the number of stroke events was limited and stroke-specific analysis could not be performed, this study provides evidence for future studies to investigate the association of Lp(a) and 30-day risk of stroke as this will be important in determining the indication for CEA or carotid stenting. Finally, it has to be noted that this study population consisted of whites, making these findings difficult to extrapolate to other ethnicities because race is a modifying variable in Lp(a) related risk.[27] A strength of this study is that we are the first to show a strong association between elevated Lp(a) levels and secondary MACE in patients with CEA with available plaque histology in a large biobank that is unique.

Conclusions

In a CEA population, we demonstrated that elevated Lp(a) levels (>137 nmol/L; >80th cohort percentile) are associated with an increased risk of 30-day MACE mainly composed of perioperative stroke. This study identifies elevated Lp(a) levels as a new and additional risk factor for secondary cardiovascular events, potentially identifying patients at highest preoperative risk.

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Disclosures

None.

Supplemental Materials

Figures I–II
Tables I–III

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