ESC
European Society
of Cardiology

ORIGINAL PAPER

Lipoprotein(a) is associated with a larger systemic burden of arterial calcification

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Aims	Lipoprotein(a) [Lp(a)] is a genetically determined risk factor for cardiovascular disease. However, population-based evidence on the link between Lp(a) and subclinical arteriosclerosis is lacking. We assessed associations of Lp(a) concentrations with arteriosclerosis in multiple arteries.
Methods and results	From the population-based Rotterdam study, 2354 participants (mean age: 69.5 years, 52.3% women) underwent non-contrast computed tomography to assess arterial calcification as a hallmark of arteriosclerosis. We quantified the volume of coronary artery calcification (CAC), aortic arch calcification (AAC), extracranial (ECAC), and intracranial carotid artery calcification (ICAC). All participants underwent blood sampling, from which plasma Lp(a) concentrations were derived. The association of plasma Lp(a) levels was assessed with calcification volumes and with severe calcification (upper quartile of calcification volume) using sex-stratified multivariable linear and logistic regression models. Higher Lp(a) levels were associated with larger ln-transformed volumes of CAC [fully adjusted beta 95% confidence interval (CI) per 1 standard deviation (SD) in women: 0.09, 95% CI 0.04–0.14, men: 0.09, 95% CI 0.03–0.14], AAC (women: 0.06, 95% CI 0.01–0.11, men: 0.09, 95% CI 0.03–0.14), ECAC (women: 0.07, 95% CI 0.02–0.13, men: 0.08, 95% CI 0.03–0.14), and ICAC (women: 0.09, 95% CI 0.03–0.14, men: 0.05, 95% CI −0.02 to 0.11]. In the highest Lp(a) percentile, severe ICAC was most prevalent in women [fully adjusted odds ratio (OR) 2.41, 95% CI 1.25–4.63] and severe AAC in men (fully adjusted OR 3.29, 95% CI 1.67–6.49).
Conclusion	Higher Lp(a) was consistently associated with a larger calcification burden in all major arteries. The findings of this study indicate that Lp(a) is a systemic risk factor for arteriosclerosis and thus potentially an effective target for treatment. Lp(a)-reducing therapies may reduce the burden from arteriosclerotic events throughout the arterial system.
Translational perspective	In 2354 participants from the Rotterdam study, we assessed the link between Lp(a) concentrations and arterial calcifications, as proxy for arteriosclerosis, in major arteries. We found that higher Lp(a) levels were consistently associated with larger volumes of calcification in the coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries. The findings of our study indicate that Lp(a) is a systemic risk factor for arteriosclerosis, suggesting that the systemic burden of arteriosclerosis throughout the arterial system could be reduced by targeting Lp(a).

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Graphical Abstract

Calcification volumes across percentiles of Lp(a)
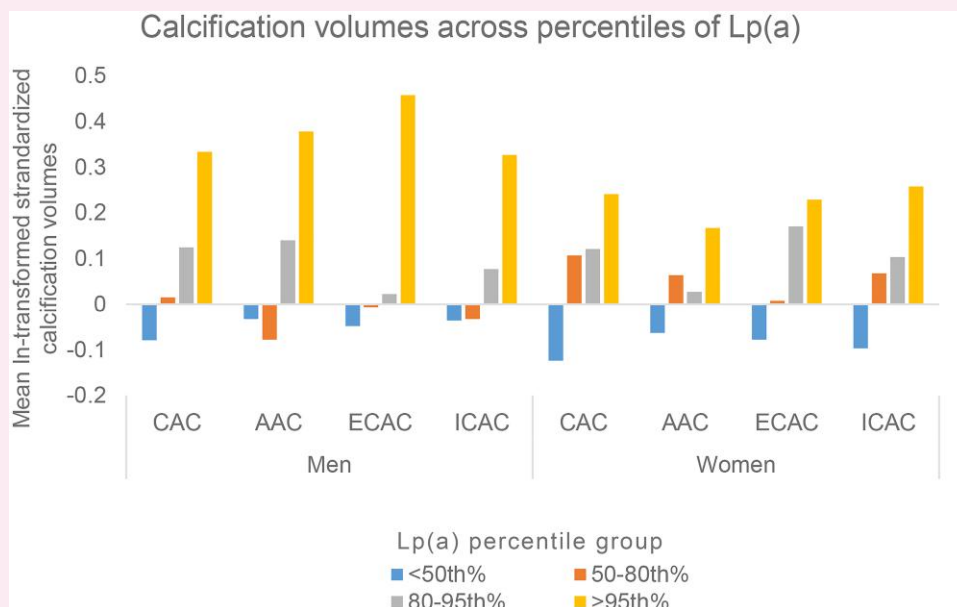
Calcification volumes across the percentile groups of Lp(a). Provided are mean ln-transformed calcification volumes [Ln(calcification volume + 1 mm3)] standardized after stratification by sex, across percentile groups of Lp(a). Lp(a), lipoprotein(a).

Keywords   lipoprotein(a) • Lp(a) • arterial calcification • arteriosclerosis • risk factors

Introduction

In recent years, lipoprotein(a) [Lp(a)] has rapidly gained attention as a causal risk factor for cardiovascular events.[1–4] The pathophysiological mechanism through which Lp(a) increases the risk of cardiovascular disease has not been fully understood. Lp(a) is a low-density lipoprotein (LDL) particle, to which a unique apolipoprotein a [Apo(a)] is attached.[2–6] Lp(a) appears to stimulate the initiation and accumulation of arteriosclerosis, as was demonstrated in animal models.[7,8] Subsequent studies conducted in patients at a high risk of cardiovascular disease showed that elevated Lp(a) levels were associated with a larger burden of arteriosclerosis.[9–11] Studies in asymptomatic individuals remain scarce.

Prior studies on the link between Lp(a) and arteriosclerosis focused on the coronary arteries. Over the years, it has become increasingly clear that the burden of arteriosclerosis, despite its systemic nature, considerably differs across arteries within the same individual.[12] This may partly be explained by cardiovascular risk factors that contribute distinctly to the development of arteriosclerosis across arteries.[12,13] Given its potential role in the initiation of arteriosclerosis,[7] it could be hypothesized that Lp(a) is a systemic risk factor for arteriosclerosis, affecting the burden of arteriosclerosis similarly across arteries. If Lp(a) is an important systemic risk factor for arteriosclerosis, it would be of major clinical relevance, bearing in mind that Lp(a)-lowering therapies are available. Moreover, previous work suggested a differential contribution of Lp(a) to cardiovascular disease risk between men and women.[14] The sex-specific association of Lp(a) with arteriosclerosis at different sites has not been addressed. Information on the sex-specific role of Lp(a) on the burden of arteriosclerosis in different arteries could ultimately lead to better preventive strategies for cardiovascular disease risk reduction.

Studying the association between Lp(a) and arteriosclerosis is an essential first step in investigating whether the upcoming Lp(a)-reducing therapies[15] may potentially reduce the burden of arteriosclerosis in men and women. Within the population-based Rotterdam study, we assessed the sex-specific association of Lp(a) plasma levels with the amount of arterial calcification, as a proxy for arteriosclerosis, in the coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries.

Methods

Setting

This study is embedded within the Rotterdam study, a large prospective population-based cohort that investigates determinants and occurrence of chronic diseases among adults and the elderly. The design of the Rotterdam study has been described in detail previously.[16] Briefly, all participants are interviewed at study entry and undergo examinations including laboratory assessments and imaging during two visits to the research centre. Follow-up examinations take place every 3–5 years. The Rotterdam study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam study has been entered into The Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study allowing to obtain their information from treating physicians.

Population for analyses

Between 2003 and 2006, all participants who visited the research centre of the RS were invited to undergo a non-contrast multidetector computed tomography (MDCT) scan to quantify arterial calcification, as a proxy of arteriosclerosis, in the following arteries: coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries. In total, 2524 participants were scanned (response rate, 78%). Out of 2524 scans, 111 were not gradable for arterial calcification at any of the arteries because of the presence of a coronary stent, pacemaker, or image artefacts, leaving a total of 2413 complete examinations with information calcification in different arteries. Blood samples were collected in the same time period as the CT examination, and were immediately stored in −80°C freezers. Lp(a) levels were measured in the year 2020, in blood samples that had not been defrosted previously. Out of 2413 participants with a complete CT examination, 59 were excluded due to missing Lp(a) levels, resulting in 2354 participants for the analyses.

Assessment of Lp(a)

Fasting blood samples were collected during a visit to the research centre. Plasma was isolated and immediately put on dry ice and stored in −80°C freezers. Lp(a) levels were measured in the year 2020, in samples that had not been defrosted, using the Kringle IV Type 2 number-independent Randox immunoassay on a Cobas c501 Chemistry Analyzer, with a range of 0–350 mg/dL.[14]

Assessment of arterial calcification

We used 16-slice or 64-slice MDCT scanners (Somatom Sensation 16 or 64; Siemens, Forchheim, Germany) to obtain non-contrast CT images. We performed a cardiac scan and a scan that ranged from the aortic root to the Circle of Willis. On these scans, we assessed calcification in the coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries. Coronary artery calcification (CAC), aortic arch calcification (AAC), and extracranial carotid artery calcification (ECAC) were quantified using dedicated software (Syngo Calcium Scoring; Siemens, Forchheim, Germany). Intracranial carotid artery calcification (ICAC) was quantified using a semiautomatic scoring method involving manual segmentations of calcification in each consecutive CT slice. The calcification volume was computed using the pixel size and the increment.[17,18] A detailed description of the evaluation methods is provided elsewhere.[18,19]

Assessment of cardiovascular risk factors

Information on cardiovascular risk factors was obtained through standardized home interviews, physical examination, and blood sampling.[16] Body mass index (BMI) was calculated as weight (kg)/height (m^2). Systolic and diastolic blood pressure were measured twice at the right arm in sitting position using a random-zero sphygmomanometer, and the average of the measurements was used. Mean arterial pressure (MAP) was calculated using the following formula: $2 \times$ diastolic pressure + systolic pressure/3. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were assessed using an automatic enzymatic procedure (Hitachi 911, Roche CHOD PAP). We used a non-HDL-corrected variable in the analyses, which was derived by subtracting the HDL and Lp(a) compound from the total cholesterol value.[20] Trained interviewers obtained the information on antidiabetic medication, blood pressure- and lipid-lowering medication use, and smoking behaviour. Diabetes mellitus was defined as the use of antidiabetic medication, fasting serum glucose level ≥7.1 mmol/L, or random serum glucose level ≥11.1 mmol/L.[21] Smoking behaviour was categorized as 'current smoking' and 'non-smoking'. We defined history of cardiovascular disease as a history of myocardial infarction (MI), stroke, percutaneous transluminal coronary angioplasty [percutaneous coronary intervention (PCI)], and/or coronary artery bypass graft (CABG). Information on MI, stroke, PCI, and CABG was obtained at baseline and during follow-up visits as described previously.[22–24]

Statistical analysis

We created the following sex-specific percentiles of the Lp(a) concentrations based on commonly used clinical cut-offs: <50th percentile, 50–80th percentile, 80–95th percentile, and >95th percentile.[25] For each percentile group, median Lp(a) levels were presented. To investigate the link between Lp(a) and arterial calcifications, we used the following strategy. First, we analysed the association between Lp(a) and calcification volume. Considering the skewed distribution of the calcification volumes, we performed a natural log-transformation and added 1 mm^3 to each non-transformed volume to deal with calcium scores of 0 [Ln (calcification volume + 1 mm^3)]. Subsequently, these values were standardized to compare results across the arteries. We used linear regression models to examine the association of Lp(a) [per 1 SD increase and Lp(a) percentile group] with calcification volumes in different arteries. Model 1 was adjusted for age. Model 2 was adjusted for age, non-HDL-corrected, BMI, smoking, diabetes, MAP, antihypertensive medication, and prevalent cardiovascular disease, and Model 3 was additionally adjusted for lipid-lowering medication use. Second, the outcome was dichotomized. We computed sex-specific quartiles of the calcification volumes and defined the upper quartile as 'severe' calcification. Accordingly, we used logistic regression to investigate the association of Lp(a) [per 1 SD increase and per Lp(a) percentile group] with severe calcification and adjusted in Models 1, 2, and 3. All analyses were sex stratified based on literature.[14] Also, we formally tested interaction by adding multiplicative interaction terms of Lp(a) with sex to the model.

Additionally, we investigated the association of Lp(a) per 1 SD increase with each quartile of calcification, with the first quartile as reference group, using multinomial regression analyses while adjusting for all three models. In addition, we repeated the continuous analyses in participants without a history of cardiovascular disease, adjusting for age, non-HDL-corrected, BMI, smoking, diabetes, MAP, and antihypertensive medication. Furthermore, we repeated the analyses in participants who use lipid-lowering medication and in those who do not use lipid-lowering medication. To account for missing information of covariables (maximum amount of missingness was 2.6%), we used multiple imputation by chained equations.[26] Analyses were performed using SPSS Statistics 24 (IBM, Chicago, IL, USA; www.spss.com), R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/), and RStudio 3.4.4 (Boston, MA, USA; http://www.rstudio.org/).

Results

Baseline characteristics of the study population are shown in *Table 1*. The mean age was 69.5 years (SD ± 6.7), and 52.3% were women. In all arteries, calcification volumes were larger in men than women. Notably, the Lp(a) level was higher in women than in men (median Lp(a) in women 13.6 mg/dL and in men 11.2 mg/dL). *Figure 1* shows the Lp(a) level per percentile group. For each percentile group, the Lp(a) level was higher in women than men.

In both women and men, a higher level of Lp(a) was associated with larger volumes of CAC (Model 3 adjusted beta 95% CI per 1 SD in women: 0.09, 95% CI 0.04–0.14, men: 0.09, 95% CI 0.03–0.14), AAC (women: 0.06, 95% CI 0.01–0.11, men: 0.09, 95% CI 0.03–0.14), ECAC (women: 0.07, 95% CI 0.02–0.13, men: 0.08, 95% CI 0.03–0.14), and ICAC (women: 0.09, 95% CI 0.03–0.14, men: 0.05, 95% CI −0.02 to 0.11) albeit the latter not statistically significant among men. The effect estimates for the association between Lp(a) and calcification volumes in all arteries were largest in the highest compared with the other percentile groups of Lp(a). Only in women, the >95th percentile of Lp(a) was less prominently associated with ECAC than the 80–95th percentile (*Figure 2*).

When investigating the presence of severe calcification in women, we found that an overall higher Lp(a) level was most strongly associated with severe ICAC [Model 3 adjusted odds ratio (OR), for the fourth quartile compared with the lowest three quartiles of ICAC: 1.23, 95% CI 1.07–1.42]. Specifically for women within the upper percentile of

Table 1 Study population characteristics

Characteristics	Men (n = 1122)	Women (n = 1232)
Age, years, mean (SD)	69.57 (6.56)	69.45 (6.86)
Body mass index, kg/m^2, mean (SD)	27.47 (3.37)	27.82 (4.41)
Systolic blood pressure, mmHg, mean (SD)	146.01 (19.55)	147.15 (20.45)
Diastolic blood pressure, mmHg, mean (SD)	81.35 (10.77)	79.21 (10.52)
MAP, mmHg, mean (SD)	102.92 (11.89)	101.86 (12.01)
Total cholesterol, mmol/L, mean (SD)	5.42 (0.94)	5.93 (0.95)
Total cholesterol corrected, mmol/L, mean (SD)	5.23 (0.96)	5.69 (0.99)
HDL, mmol/L, mean (SD)	1.31 (0.34)	1.57 (0.40)
Non-HDL cholesterol, mmol/L, mean (SD)	4.11 (0.93)	4.36 (0.97)
Non-HDL cholesterol corrected, mmol/L, mean[a] (SD)	3.92 (0.95)	4.12 (1.01)
Hypertension, n (%)	834 (74)	907 (74)
Diabetes, n (%)	162 (14)	139 (11)
History of cardiovascular disease, n (%)	160 (14)	70 (6)
Lipid-lowering medication, n (%)	257 (23)	280 (23)
Antihypertensive medication, n (%)	463 (41)	476 (39)
Smoking, n (%)	110 (10)	160 (13)
Lp(a), mg/dL, median (IQR)	11.2 (4.70–32.0)	13.6 (5.80–41.20)
Lp(a), mg/dL, mean (SD)	24.0 (29.76)	30.84 (39.41)
Lp(a) percentile group, n		
<50th	561 (50)	619 (50)
50–80th	337 (30)	367 (30)
80–95th	167 (15)	185 (15)
>95th	57 (5)	61 (5)
Coronary artery calcification, mm^{3}[b]	127.4 (18.3–480.25)	15.95 (0.00–117.85)
Aortic arch calcification, mm^{3}[b]	283.1 (51.2–942.33)	216.7 (38.43–784.70)
Extracranial carotid artery calcification, mm^{3}[b]	41.1 (1.7–153.55)	11.65 (0.00–74.88)
Intracranial carotid artery calcification, mm^{3}[b]	50.3 (9.17–174.90)	34.81 (5.24–114.99)

IQR, interquartile range; HDL, high-density lipoprotein; Lp(a), lipoprotein(a); MAP, mean arterial pressure; SD, standard deviation.
[a]HDL minus the Lp(a) compound from the total cholesterol value.
[b]Median volumes.

Lp(a) in particular, i.e. >95th percentile, the association with severe ICAC was strongest (Model 3 adjusted OR 2.41, 95% CI 1.25–4.63; Table 2). In men, the most pronounced association was observed for the upper percentile of Lp(a) with severe AAC (Model 3 adjusted OR for the fourth vs. the lowest three quartiles of AAC among men within >95th percentile of Lp(a): 3.29, 95% CI 1.67–6.49; Table 2). Supplementary data online, Table S1 provides the associations of Lp(a) per 1 SD increase with each quartile of calcification. Overall, a higher Lp(a) level was most strongly associated with the fourth quartile of calcification compared with the first quartile of calcification. Interactions of Lp(a) with sex were tested and did not reach statistical significance (P > 0.05).

Repeating the analyses in participants without a history of cardiovascular disease revealed similar results (see Supplementary data online, Table S2). Overall, repeating the analyses in individuals with and without using lipid-lowering medication did not materially change the interpretation of the results though statistical power was limited (Supplementary data online, Tables S3 and S4). In women, the >95th percentile Lp(a) was associated with severe AAC only among those using lipid-lowering medication (OR 3.49, 95% CI 1.11–10.63). In contrast, in men, the >95th percentile of Lp(a) was associated with severe

AAC (OR 3.75, 95% CI 1.40–10.04), ECAC (OR 2.75, 95% CI 1.16–6.55), and ICAC (OR 2.98, 95% CI 1.24–7.15) among those not using lipid-lowering medication, whereas these associations did not reach statistical significance among those using lipid-lowering medication.

Discussion

In this population-based sample, we found that higher Lp(a) levels were associated with a larger burden of arterial calcification, with similar patterns across the different arteries. Individuals within the highest percentile (>95th percentile) of Lp(a) concentrations had the largest calcification volumes, independent of other cardiovascular risk factors. Focusing on individuals in the upper percentile of Lp(a) and the highest quartile of calcification, women within the upper percentile of Lp(a) level had the most severe ICAC, while men within the upper percentile had the most severe AAC.

Several mechanisms have been proposed through which Lp(a) may promote arteriosclerosis. Oxidized phospholipids colocalize with Lp(a), promoting inflammation and osteogenic differentiation leading to the accumulation of cholesterol and calcification.[27,28]
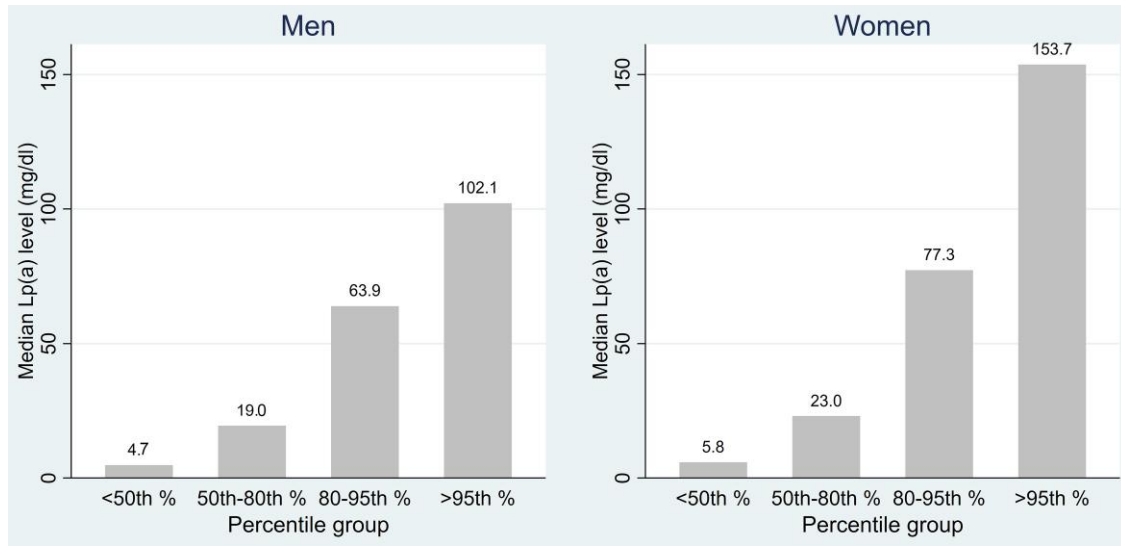
Figure 1 Lp(a) levels per percentile group. Presented are median Lp(a) levels in mg/dL across the percentile groups. Lp(a), lipoprotein(a).
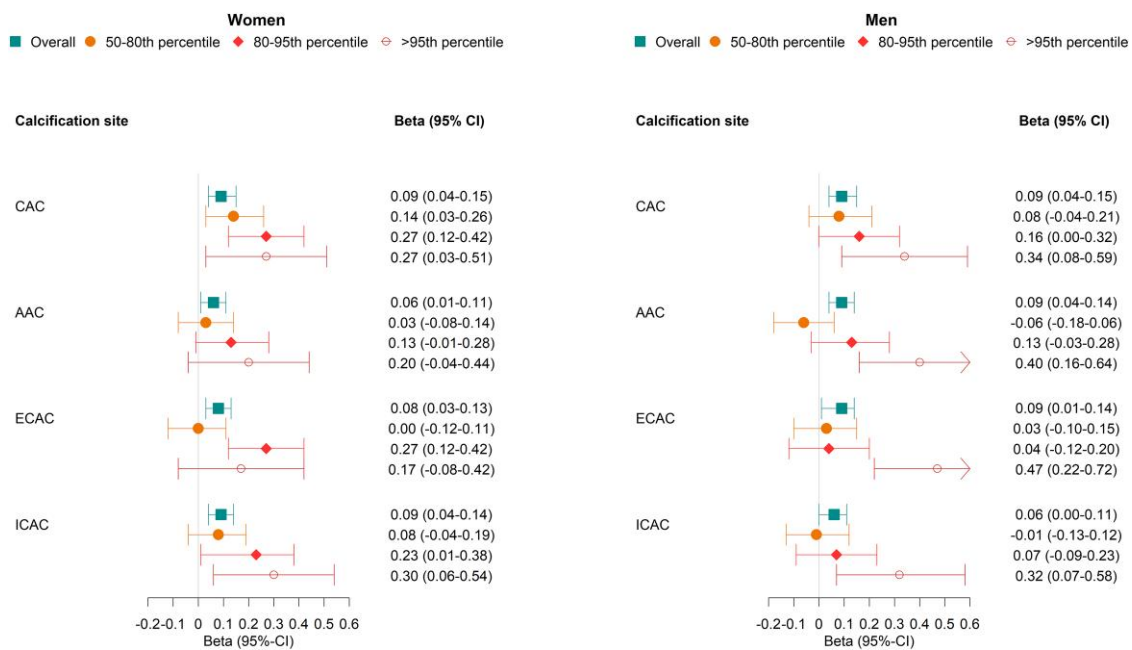
Figure 2 Association of Lp(a) with calcification volumes. Values represent standardized ln-transformed calcification volumes per 1 SD increase in Lp(a), and per Lp(a) percentile group. Figure is adjusted for age, non-HDL-corrected, BMI, smoking, diabetes, MAP, antihypertensive medication, prevalent CVD, and lipid-lowering medication use. AAC, aortic arch calcification; CAC, coronary artery calcification; CVD, cardiovascular disease; ECAC, extracranial carotid artery calcification; HDL, high-density lipoprotein; ICAC, intracranial carotid artery calcification; Lp(a), lipoprotein(a); MAP, mean arterial pressure.

Furthermore, although the underlying pathways are incompletely understood, Lp(a) and Apo(a) influence the function of smooth muscle cells and endothelial cells.[29] Accordingly, endothelial and smooth muscle cell dysfunction and their interaction affect the homeostasis of blood vessels and could promote atherogenesis. In the current study, we found that the associations between Lp(a) and arterial calcification were particularly prominent among individuals in the upper percentile of Lp(a) concentration, whereas the lower concentrations of Lp(a) were not robustly associated with larger calcification volumes. This is in line with current knowledge of the pathophysiological roles of Lp(a).[28] It has been suggested that low Lp(a) concentrations have beneficial effects on tissue repair and vascular remodelling. In contrast, high Lp(a) concentrations could induce harmful pathophysiological pathways promoting arteriosclerosis.[28]

Table 2 Association of Lp(a) with severe calcification, i.e. the upper quartile of arterial calcification volumes

			CAC	AAC	ECAC	ICAC
Women	Lp(a), overall	Model 1	1.20 (1.06–1.37)	1.16 (1.01–1.33)	1.18 (1.04–1.35)	1.28 (1.13–1.46)
	Lp(a), percentiles					
	<50th		Ref.	Ref.	Ref.	Ref.
	50–80th		1.44 (1.05–1.96)	1.18 (0.85–1.63)	1.10 (0.80–1.50)	1.20 (0.87–1.66)
	80–95th		1.35 (0.91–2.01)	1.17 (0.77–1.77)	1.62 (1.10–2.34)	1.52 (1.02–2.28)
	>95th		2.21 (1.22–4.03)	1.76 (0.94–3.36)	1.58 (0.85–2.92)	2.93 (1.60–5.38)
	Lp(a), overall	Model 2	1.17 (1.02–1.35)	1.15 (1.00–1.34)	1.14 (0.99–1.31)	1.23 (1.07–1.42)
	Lp(a), percentiles					
	<50th		Ref.	Ref.	Ref.	Ref.
	50–80th		1.38 (1.00–1.91)	1.13 (0.81–1.58)	1.02 (0.74–1.42)	1.14 (0.82–1.59)
	80–95th		1.41 (0.93–2.14)	1.23 (0.80–1.90)	1.68 (1.13–2.50)	1.52 (1.00–2.31)
	>95th		1.86 (0.97–3.55)	1.66 (0.83–3.30)	1.25 (0.65–2.42)	2.42 (1.26–4.64)
	Lp(a), overall	Model 3	1.16 (1.01–1.34)	1.15 (0.99–1.33)	1.14 (0.99–1.30)	1.23 (1.07–1.42)
	Lp(a), percentiles					
	<50th		Ref.	Ref.	Ref.	Ref.
	50–80th		1.40 (1.02–1.94)	1.14 (0.81–1.59)	1.03 (0.74–1.43)	1.14 (0.82–1.60)
	80–95th		1.38 (0.90–2.10)	1.21 (0.78–1.87)	1.65 (1.10–2.47)	1.50 (0.99–2.29)
	>95th		1.85 (0.96–3.55)	1.65 (0.83–3.29)	1.25 (0.64–2.42)	2.41 (1.25–4.63)
Men	Lp(a), overall	Model 1	1.12 (0.98–1.28)	1.19 (1.04–1.37)	1.20 (1.05–1.36)	1.08 (0.95–1.24)
	Lp(a), percentiles					
	<50th		Ref.	Ref.	Ref.	Ref.
	50–80th		0.99 (0.71–1.36)	1.12 (0.80–1.58)	1.04 (0.75–1.45)	1.18 (0.85–1.63)
	80–95th		1.12 (0.75–1.68)	0.73 (0.46–1.16)	0.86 (0.56–1.31)	0.74 (0.47–1.16)
	>95th		1.60 (0.88–2.90)	3.50 (1.90–6.44)	3.10 (1.74–5.53)	2.33 (1.28–4.23)
	Lp(a), overall	Model 2	1.07 (0.92–1.23)	1.17 (1.01–1.36)	1.15 (1.00–1.33)	1.06 (0.91–1.22)
	Lp(a), percentiles					
	<50th		Ref.	Ref.	Ref.	Ref.
	50–80th		0.93 (0.66–1.31)	1.08 (0.75–1.54)	0.97 (0.69–1.37)	1.14 (0.81–1.60)
	80–95th		1.06 (0.69–1.63)	0.74 (0.46–1.18)	0.83 (0.53–1.28)	0.73 (0.47–1.16)
	>95th		1.17 (0.60–2.29)	3.39 (1.72–6.66)	2.70 (1.45–5.05)	2.10 (1.11–3.98)
	Lp(a), overall	Model 3	1.06 (0.91–1.23)	1.18 (1.01–1.36)	1.15 (1.00–1.33)	1.05 (0.91–1.22)
	Lp(a), percentiles					
	<50th		Ref.	Ref.	Ref.	Ref.
	50–80th		0.93 (0.66–1.32)	1.08 (0.75–1.55)	0.97 (0.69–1.37)	1.15 (0.82–1.61)
	80–95th		1.05 (0.68–1.61)	0.73 (0.46–1.18)	0.83 (0.53–1.28)	0.73 (0.46–1.15)
	>95th		1.10 (0.56–2.15)	3.29 (1.67–6.49)	2.67 (1.43–5.00)	2.01 (1.06–3.82)

Values represent odds ratios and 95% confidence interval for severe CAC, AAC, ECAC, and ICAC (upper quartile of calcification volume vs. lowest three quartiles), and per percentile group. Model 1 is adjusted for age. Model 2 is adjusted for age, non-HDL corrected, BMI, smoking, diabetes, MAP, antihypertensive medication, and prevalent cardiovascular disease, and Model 3 is additionally adjusted for lipid-lowering medication use.
AAC, aortic arch calcification; CAC, coronary artery calcification; ECAC, extracranial carotid artery calcification; HDL, high-density lipoprotein; ICAC, intracranial carotid artery calcification; Lp(a), lipoprotein(a); MAP, mean arterial pressure.

Despite the systemic nature, the correlation of arteriosclerosis between arteries is only weak to moderate.[19] This could partly be the result of differences in underlying cardiovascular risk factors.[30–33] Our findings indicate that Lp(a) affects the whole arterial system and thus increases the systemic burden of arteriosclerosis. In this regard, Lp(a) is a unique risk factor because, to our knowledge, it is the first risk factor that shows very similar, consistent associations with arteriosclerosis in the different arteries of the heart–brain axis. However, when focusing only on individuals within the highest Lp(a) percentile and the most severe amount of calcification, we did find sex differences albeit statistically insignificant. Women within the upper Lp(a) percentile had the most severe ICAC, and men within the upper Lp(a) percentile had

the most severe AAC. One could argue that AAC reflects more of the systemic burden of arteriosclerosis in men, whereas ICAC may be a better proxy for the systemic burden in women. The differences between women and men may also partly be explained by a potential influence of unmeasured shared risk factors.[34] Our findings point at important Lp(a) effects and utmost relevance in the light that Lp(a) lowering therapies are available, implicating Lp(a) could be one of the first systemic targets to reduce arteriosclerosis in multiple major vessels, thereby carrying a potential to reduce cardiovascular disease.

Our study has several strengths and limitations. The strengths of the present study include the homogeneous population–based setting combined with extensive imaging-based data on arteriosclerosis at

multiple sites. In addition, we used an Lp(a) immunoassay that is highly correlated (correlation coefficient 0.99) with the gold standard for measuring Lp(a).[35,36] Nevertheless, several methodological considerations need to be mentioned. First, we performed cross-sectional analyses, and we, therefore, cannot draw conclusions about the temporal relationship between Lp(a) and arteriosclerosis. Although Lp(a) likely influences the burden of arterial calcification, we cannot rule out the possibility of associations in the opposite directions. For example, changes in haemodynamic forces may promote the initiation and accumulation of arterial calcification. In turn, the accumulation of arterial calcification is accompanied by changes in the arterial wall. Biochemical stresses may—as a vicious circle—lead to endothelial injury and disturbed blood flow, which could endorse the accumulation of plasma lipoproteins. Second, we used arterial calcification as a proxy for arteriosclerosis. We were unable to elaborate on non-calcified plaques because those were not visualized. Nevertheless, the burden of arterial calcification correlates highly with the total plaque burden.[37] In addition, Lp(a) may play a role in the initiation of calcification in particular.[7,38] Third, while our results are highly generalizable to a homogeneous population of elderly persons of European descent, our findings are less generalizable to younger individuals and other ethnicities. Lastly, we lacked information on triglycerides and LDL cholesterol levels. Accordingly, we adjusted for non-HDL cholesterol levels in our analyses, although it remains challenging to eliminate residual confounding fully.

Conclusion

A high Lp(a) level was consistently associated with a large burden of calcification in different arteries among men and women from a population-based cohort. Our findings indicate a potential to lower the systemic burden of arteriosclerosis throughout the arterial system by targeting Lp(a).

Supplementary data

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

Acknowledgement

Funding

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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