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ORIGINAL ARTICLE

Lipoprotein(a) Does Not Correlate with Hypertensive Mediated Organ Damage and Subsequent Cardiovascular Events in a Primary Prevention Cohort

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Abstract

Introduction Elevated lipoprotein(a) [Lp(a)] levels have been strongly related to cardiovascular (CV) risk. However, its association with Hypertension Mediated Organ Damage (HMOD) and CV events in the primary prevention setting remains unclear.

Aim To evaluate in these patients, the correlation between Lp(a) levels and: (i) heart, vessels and kidney HMOD and; (ii) CV events and all-cause mortality in a primary prevention setting.

Methods 747 low CV risk subjects were recruited between 2009 and 2014. HMOD was assessed through Pulse Wave Velocity, carotid Intima-Media Thickness (IMT), presence of carotid plaques, Left Ventricular Hypertrophy (LVH) and Ejection Fraction and glomerular filtration rate. All-cause mortality and CV events up to 2021 were retrieved by electronic health records, for a median follow-up time of 10 years (I–III quartiles 9.6–11.1).

Results Mean age was 50.8 ± 13.0 years and 63.5% of the subjects were men. The prevalence of hypertension was 37.9%, dyslipidemia 67.2%, smoking 17.8%, and diabetes mellitus 8.7%. Median Lp(a) value was 17 mg/dL (5.9–56.0), and 26.5% of patients had values above 50 mg/dL. Regarding HMOD, 10.3% subjects had arterial stiffness, 7.2% increased IMT, 19.8% carotid plaques while only 0.7% had LVH. No significant correlation was found between Lp(a) levels and indices of subclinical HMOD. Furthermore, no relationship was found between CV events and all-cause mortality and Lp(a) levels.

Conclusions In this primary prevention cohort, elevated Lp(a) levels were not associated with significant structural damage to the heart, carotid arteries, or increased aortic stiffness and were not associated with CV events and all-cause mortality.

Keywords Lipoprotein(a) · Pulse wave velocity · Left ventricular hypertrophy · Intima-media thickness · Carotid plaque · Cardiovascular events

1 Introduction

Traditional cardiovascular (CV) risk factors (age, sex, genetic predisposition, dyslipidemia, diabetes, hypertension, smoking, obesity, and physical inactivity) could explain only a part of the risk of developing CV events [1]. Novel biomarkers contributing to increased CV risk have been identified, including elevated lipoprotein(a) [Lp(a)]. Structurally, Lp(a) is an atherogenic lipoprotein consisting of apolipoprotein(a) covalently bound to a Low-Density Lipoprotein (LDL) [2]. Its values are predominantly determined by genetic factors and the prevalence of high Lp(a) values (>50 mg/dL) is estimated to be around 20% of the population, making it the most frequent heritable CV risk factor [3]. Lp(a) values have been strongly and consistently linked to an increased likelihood of subsequent CV events

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[4–8]. However, only few papers investigate its relationship with heart, vessels and kidney Hypertension Mediated Organ Damage (HMOD) focusing on Pulse Wave Velocity (PWV) [9–12], Intima-Media Thickness (IMT) [11, 13–15], carotid plaques [13, 16], Left Ventricular Hypertrophy (LVH) [17, 18], Ejection Fraction (EF) [19] and Glomerular Filtration Rate (GFR) [20]. Furthermore, results were heterogeneous, probably depending on the CV risk of enrolled populations (children, adolescents, healthy individual, hypertensives).

The present study evaluates a primary prevention cohort aiming at assessing: (i) the prevalence of elevated Lp(a) values; (ii) its relationship with HMOD and (iii) its association with subsequent all-cause mortality and CV events. HMOD was evaluated at multiple levels, i.e. aortic (PWV), carotid (IMT and carotid plaque), cardiac (LVH and EF) and renal (GFR).

2 Methods

2.1 Study population

Between September 2009 and February 2014, a total of 1500 individuals aged 18 to 88 were recruited at the primary prevention unit of the S. Gerardo Hospital (Monza, Italy). Patients were both enrolled from the arterial hypertension outpatient services and from the blood donor list of the same hospital.

Exclusion criteria were: age below 18, pregnancy or lactation, previous acute cerebrovascular and cardiac events (myocardial infarction, angina pectoris, heart failure, stroke, transient ischemic attacks and claudication), medical conditions that would modify the reliability of heart and vessels HMOD evaluation (atrial fibrillation, very frequent ventricular or supraventricular extrasystoles and previous stent placement at carotid, aortic or femoral levels), chronic obstructive pulmonary disease, substance dependency and malignancies.

Three patients that were not resident in the catchment area of the ATS of Milan or Brianza and were excluded due to the impossibility of collect follow-up data.

Finally, Lp(a) measurements were available in 747 patients on which we conduct the present analysis. There were some significant differences between patients with available Lp(a) and patients without it as shown in Supplementary Table 1. Briefly, the first ones presented lower PWV values (8.0 ± 1.8 vs 8.3 ± 1.9 m/s, p=0.001) and a lower prevalence of vascular HMOD (10.3% vs 13.5%, p=0.047) while showing higher IMT values (0.66 ± 0.19 vs 0.63 ± 0.18 mm, p<0.001) but similar prevalence of IMT HMOD (7.2% vs 6.8%, p=0.768). Carotid plaques were more frequent in patients with available Lp(a) (19.8% vs 14.8%, p=0.005).

Despite these differences at baseline, no differences were seen regarding follow-up CV events and mortality between these two groups. Patients with available Lp(a) experienced 71 CV events (9.5%) while the ones without Lp(a) experienced 53 events (7.0%), without significant differences among them (log-rank test p=0.371 to account for different follow-up). For mortality, included patients experienced 34 events (4.6%), while the ones without Lp(a) had 44 events (5.8%, log-rank test p=0.107). Finally, regarding the composite event, included patients experienced 93 events (12.4%), while the ones without Lp(a) experienced 84 events (11.2%, log-rank test p=0.928).

At baseline a comprehensive medical history was obtained, and physical examinations were conducted for all participants. Blood Pressure (BP) was measured using a semi-automated device (OMRON Healthcare Europe, Hoofddorp, Netherlands) following a five-minute seated rest with the arm positioned at heart level; the mean of two readings was utilized for the analysis. Subjects were then placed in the supine position and CV HMOD assessment began. The within-operator and between-operator intra-session coefficient of variability, as well as the inter-session one, of all the HMOD evaluated were reported in Supplementary Table 2.

Body Mass Index (BMI) was calculated using measured height and weight, while Waist Circumference (WC) was recorded at the midpoint between the lower ribs and iliac crest.

We measured fasting serum glucose, serum total cholesterol, High-Density Lipoprotein (HDL) cholesterol, LDL cholesterol, serum triglycerides and creatinine levels. Diabetes was defined as a fasting plasma glucose > 126 mg/L in two occasions or as the use of antidiabetic drugs while CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min. Class of antihypertensive drugs were recorded and uncontrolled hypertension was defined as values higher than 140/90 mmHg. Finally, dyslipidaemia was defined as an LDL cholesterol > 116 mg/dL or as the use of statins therapy.

The study protocol was approved by institutional ethics review committees of the institution involved and all participants provided informed written consent after being informed of its nature and purpose.

2.2 Laboratory methods

Biochemical analyses were conducted using an automated Modular Analytics SWA system (Roche Diagnostics), employing enzymatic colorimetric assays for glucose (GOD-PAP method), total cholesterol (CHOD-PAP

method), HDL cholesterol (third-generation enzymatic colorimetric method), triglycerides (GPO-PAP method). For patients with TG levels above 400 mg/dL, direct LDL cholesterol measurement was used; otherwise, Friedewald's formula was applied to calculate: Total cholesterol - [HDL cholesterol + (triglycerides/5)].

Creatinine levels were measured via the Jaffé kinetic colorimetric method, and GFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation. Renal HMOD was defined as a GFR < 60 mL/min.

Lp(a) concentrations were quantified using an immunoturbidimetric method on a Roche Cobas® 8000 c502 module (Roche Diagnostics GmbH, Mannheim, Germany), calibrated against the World Health Organization/International Federation of Clinical Chemistry reference material SRM 2B. The assay is isoform-insensitive, thus minimizing the size-related analytical bias due to variable numbers of kringle IV-2 repeats in the apolipoprotein(a) moiety. All samples were run in duplicate, and internal quality control materials at two levels (low and high) were analyzed daily in accordance with CLSI EP05-A3 and EP28-A3c guidelines. The limit of detection was 1.0 mg/dL, and the functional sensitivity was 3.5 mg/dL. Inter-assay and intra-assay coefficients of variation were <5%.

The performance of the method and its analytical imprecision were verified locally through validation runs prior to study initiation. All samples were measured in a single analytical batch to minimize inter-run variability.

2.3 Follow-up

Follow-up of all-cause mortality and CV events was performed through record linkage with administrative health data of the ATS of Milan and Brianza, were the patients live at baseline. The median follow-up was 10 years (I-III quartiles 9.6, 11.1). Vital status was updated to June 30th 2021 using the database of patients registered with the regional health system in each ATS (NAR: Nuova Anagrafe Regionale Assistiti). Patients emigrated outside the region were censored at emigration date. The following CV events were included and assessed using the database of hospital discharge records: acute myocardial infarction or equivalents (ICD-9-CM codes 411.X, 413.X, 414.X as principal diagnosis or 410.X, 423.0, 429.5, 429.6, 429.71, 429.79, 429.81 in any diagnostic filed), stroke (430.XX-437.XX in any diagnostic field), coronary revascularization (00.66, 36.03-36.07, 36.09-36.17, 36.19, 36.2, 36.31-36.34, 36.9 in any procedure field), carotid revascularization (00.61-00.65, 38.2, 38.10- 38.12, 38.31, 38.32, 38.41, 38.42, 39.72, 39.74 in any procedure field), and lower extremity revascularization (39.25, 39.29, 39.50, 39.90 in any procedure field). Furthermore, the following drugs were included and assessed using the database of drug prescriptions: prasugrel (ATC code B01AC22) and ticagrelor (B01AC24).

The evaluated endpoints were the time to: (i) first CV events, (ii) all-cause mortality and (iii) composite outcome (CV event or death).

2.4 Pulse wave velocity

Aortic stiffness was assessed by measuring PWV between the carotid and femoral arteries on the same side, with participants in a supine position. A validated automatic device (Complior, Colson; Alam Medical, Paris, France) was used to simultaneously capture arterial waveforms at both sites. The distance between measurement points was determined using a rigid ruler from the hip to the neck through a rigid ruler with sliding vertical extension has been used in order to overcome problem with obese patients. Vertical extensions have been placed on the carotid and femoral point of evaluation so that the distance can be measured without the encumbrance of the patient's belly or breast. The values were corrected by a 0.8 factor accordingly to the PWV measurement methods consensus documents. This correction factor has been introduced to adjust for the contemporary travel of the pulse wave to the carotid artery and to the femoral artery through the aortic arch. In fact, measuring the direct distance between the two points lead to an overestimation of the real path length traveled by the pulse wave [21]. Each subject underwent two measurements, and the mean value was used for statistical evaluation. A PWV higher than 10 m/s was considered suggestive of arterial stiffness (vascular HMOD).

2.5 Echocardiography

A trained cardiologist performed two-dimensional echocardiographic evaluations using a SONOS 5500 ultrasound system (Philips Healthcare, Andover, Massachusetts, USA) with a 2.5 MHz transducer. High-frame-rate grayscale loops were recorded from four-chamber, two-chamber, and three-chamber views at an average frame rate of 90 frames per second.

Left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness, and posterior wall thickness were measured. EF was assessed using the Simpson method, while left ventricular mass (LVM) was calculated using the Devereux formula [22]: LVM (g) = 0.8 x 1.04 x [(LVEDD (cm) + septal thickness + posterior wall thickness)^3 - LVEDD^3] + 0.6.

LVM was indexed to both body surface area (BSA) and to height$^{2.7}$ to yield the left ventricular mass indexed (LVMI). BSA was estimated using the DuBois formula: BSA (m^2) = 0.007184 x height (cm)^0.725 x weight (kg)^0.425.

LVH was defined when LVMI exceeded 115 g/m^2 for men and 95 g/m^2 for women when indexed to BSA and 50 g/h$^{2.7}$ for men and 47 g/h$^{2.7}$ for women when indexed to h$^{2.7}$.

2.6 Carotid ultrasound

Carotid ultrasonography was performed with participants in a supine position, with the neck slightly extended. A SONOS 5500 ultrasound system (Philips Healthcare) was used to examine the right carotid artery. The transducer was positioned perpendicularly to the arterial axis under B-mode guidance. Intima-media thickness (IMT) was measured on the posterior wall of the common carotid artery, 2 cm below the bifurcation, by identifying the hypoechoic and anechoic layers.

Two measurements per subject were recorded, and the mean value was used for statistical analysis. A pathological IMT was defined as >0.9 mm while carotid plaques were identified when IMT surpassed 1.2 mm.

2.7 Statistical analysis

The distribution of continuous variables was summarized using mean and Standard Deviation (± SD) (when normally distributed) or median and interquartile (IQR) (when skewed). Categorical variables were expressed as counts and percentages. T-test (or Mann-Whitney test for skewed variables) was used to compare continuous variables while Chi-square test was used to compare categorical variables between groups.

In particular, the association between Lp(a) and HMOD binary outcomes was assessed using Mann-Whitney test while Spearman correlation analyses was used for continuous outcomes. Multivariable logistic regression analysis adjusted by age, sex, diabetes, LDL cholesterol, statins, anti-hypertensive therapies and GFR was also performed for binary outcomes while linear regression was used for continuous outcomes.

The crude incidence of CV events was estimated using the Aalen-Johansen method considering death without CV event as a competing risk. The curves were compared between patients with Lp(a)>50 vs ≤50 using the Gray test. The cumulative incidence of death and of the composite outcome (CV event or death) was estimated using the Kaplan-Meier method and compared using the Log-rank test. Finally, unadjusted Cox models for CV events, death and the composite outcome were fitted using a restricted cubic spline function to model the Hazard Ratio (HR) of Lp(a). Multivariable Cox models adjusted by age, sex, diabetes, LDL cholesterol, statins, anti-hypertensive therapies and GFR were also fitted.

All statistical analyses were performed using R, with significance set at a two-tailed p-value < 0.05.

3 Results

3.1 Population characteristics

Table 1 shows the clinical characteristics of the 747 participants included in the analysis. Mean age was 50.8 ± 13.0 years and 63.5% were male. Regarding CV risk factors, dyslipidemia was the most frequent one (67.2%) followed by arterial hypertension (37.9%), smoking (17.8%) and diabetes mellitus (8.7%).

Participants were generally overweight, with mean WC 90.8 ± 12.4 cm and BMI 26.0 ± 3.9 kg/m^2. Mean systolic and diastolic BP were 130.4 ± 17.5 mmHg and 79.3 ± 13.6 mmHg, respectively.

Median fasting glucose was 88 mg/dL (IQR 81, 98), mean total cholesterol 195.6 ± 33.7 mg/dL, HDL 55.4 ± 14.0 mg/dL, LDL 120.6 ± 29.5 mg/dL and triglycerides 90 mg/dL (IQR 66, 127) while median Lp(a) value was 17.0 mg/dL (IQR 5.9, 56.0) and 26.5% of the subjects had a value higher than 50 mg/dL (Fig. 1).

Serum creatinine was 0.88 mg/dL (IQR 0.80, 1.00) corresponding to a mean GFR of 93.1 ± 17.5 mL/min and a prevalence of CKD of 2.4%.

Concerning drugs, medication used for hypertension were in 23.2% of cases angiotensin converting enzyme inhibitors, 18.9% angiotensin receptor blockers, 15.0% β-blockers, 16.6% calcium channel blockers, 7.1% α-blockers and 17.0% diuretics while 9.8% of the subjects took statins.

Finally, regarding HMOD evaluation, median PWV was 8.0 ± 1.8 m/s with 10.3% (95% Confidence Interval – CI - 8.2, 12.7) of individuals having values compatible with HMOD. Carotid ultrasonography revealed a mean IMT of 0.66 ± 0.19 mm corresponding to 7.2% (95% CI 5.4, 9.4) of the subjects having a value > 0.9 mm while plaques were identified in 19.8% (95% CI 17.0, 22.9) of the participants.

Cardiac assessment showed a mean EF of 63.2 ± 4.5% while LVMI was 55.7 ± 13.9 g/m^2 with LVH (BSA indexed) present only in 4 patients (0.7%, 95% CI 0.2, 1.7).

3.2 Lipoprotein(a) and HMOD

No correlations emerged between Lp(a) and continuous (PWV, IMT, LVMI, EF and GFR – Fig. 2) or categorical HMOD (PWV HMOD, IMT HMOD, carotid plaque, LVH and CKD – Fig. 3). LVH results were based on BSA-indexed LVMI, but findings were unchanged using height$^{2.7}$ indexing (p = 0.72). Negative results were confirmed also at multivariable logistic regression analysis adjusted by age, sex,

Table 1 Population characteristics.

Variables	N=747
Demography	
Male sex (%)	474 (63.5)
Age (years) (mean (SD))	50.8 (13.0)
Cardiovascular risk factors	
Hypertension, N (%)	283 (37.9)
Hypertension duration, years (median [I-III QUARTILES])	10 [5, 15]
Dyslipidaemia, N (%)	358 (67.2)
Smoking, N (%)	133 (17.8)
Diabetes mellitus, N (%)	65 (8.7)
Family history of CV events, N (%)	111 (14.9)
Chronic kidney disease, N (%)	14 (2.4)
Clinical parameters	
WC, mg/dL (mean (SD))	90.8 (12.4)
BMI, kg/m^2 (mean (SD))	26.0 (3.9)
SBP, mmHg (mean (SD))	130.4 (17.5)
DBP, mmHg (mean (SD))	79.3 (13.6)
HR, bpm (mean (SD))	65.8 (10.4)
Biochemical variables	
Total cholesterol, mg/dL (mean (SD))	195.6 (33.7)
HDL cholesterol, mg/dL (mean (SD))	55.4 (14.0)
LDL cholesterol, mg/dL (mean (SD))	120.6 (29.5)
Triglycerides, mg/dL (median [I–III QUARTILES])	90 [66, 127]
Glucose, mg/dL (median [I–III QUARTILES])	88 [81, 98]
Creatinine, mg/dL (median [I–III QUARTILES])	0.88 [0.80, 1]
GFR, mL/min (median [I–III QUARTILES])	93.1 (17.5)
Lp(a), mg/dL (median [I–III QUARTILES])	17.0 [5.9, 56.0]
Cardiovascular drug therapies	
ACE-I, N (%)	173 (23.2)
ARBs, N (%)	141 (18.9)
β-blockers, N (%)	112 (15.0)
Calcium channel blockers, N (%)	124 (16.6)
α-blockers, N (%)	53 (7.1)
Diuretics, N (%)	127 (17.0)
Statins, N (%)	73 (9.8)
Hypertension mediated organ damage	
PWV, m/s (median [I–III QUARTILES])	8.0 (1.8)
PWV HMOD, N (%)	77 (10.3)
IMT, mm (median [I–III QUARTILES])	0.66 (0.19)
IMT HMOD, N (%)	51 (7.2)
Carotid Plaque, N (%)	148 (19.8)
LVMI, g/m^2 (median [I–III QUARTILES])	55.7 (13.9)
LVH, N (%)	4 (0.7)
LVEF, % (median [I–III QUARTILES])	63.2 (4.5)

ACE-I Angiotensin-Converting Enzyme Inhibitors, *ARBs* Angiotensin Receptor Blockers, *WC* Waist Circumference, *BMI* Body Mass Index, *PWV* Pulse Wave Velocity, *HMOD* Hypertension Mediated Organ Damage, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HR* Heart Rate, *GFR* Glomerular Filtration Rate, *HDL* High-Density Lipoprotein, *LDL* Low-Density Lipoprotein, *IMT* Intima-Media Thickness, *LVMI* Left Ventricular Mass Index, *LVH* Left Ventricular Hypertrophy, *DecTime* Deceleration Time , *LVEF* Left Ventricular Ejection Fraction, *Lp(a)* Lipoprotein(a).

diabetes, LDL cholesterol, statins, anti-hypertensive therapies and GFR with IMT HMOD (OR for 10 mg/dL Lp(a) increase 0.89; 95% CI 0.79, 1.00; p=0.052), carotid plaque (OR 0.97; 95% CI 0.93, 1.01; p=0.157) and PWV HMOD (OR 0.99; 95% CI 0.93, 1.05; p=0.725). The analysis was not performed for LVH and CKD because the number of events observed was too small.

After stratifying for the presence of arterial hypertension, regarding continuous HMOD evaluation (Supplementary Figure 1), a significant association between Lp(a) and GFR (r=− 0.14, p=0.021) was found in hypertensive patients while, in normotensive patients, a border-line association was found with EF (r=− 0.097, p=0.049). Both associations persist at multivariable linear regression analysis adjusted by age, sex, diabetes and LDL cholesterol (mean difference in GFR for 10 mg/dL increase in Lp(a) among hypertensive patients -0.49 mL/min; 95% CI − 0.79, − 0.20; p=0.001, mean difference in EF for 10 mg/dL increase in Lp(a) among normotensive patients − 0.16%; 95% CI − 0.25, − 0.08; p<0.001).

Regarding categorical HMOD (Supplementary Figure 2, CKD and LVH boxplots in hypertensive subjects were not showed due to the fact that only 1 and 0 subjects respectively present it), in normotensive patients, significantly higher Lp(a) values were found in patients without IMT HMOD (median [IQR] 20.9 [6.5, 61.1] vs 11.5 [4.8–27.9] mg/dL, p=0.036). However, these association did not persist at multivariable logistic regression analysis adjusted by age, sex, diabetes, LDL cholesterol, and GFR (OR for 10 mg/dL increase in Lp(a) 0.88; 95% CI 0.76, 1.00; p=0.054).

Results were consistent after stratification by gender and statin treatment without any significant association between Lp(a) and HMOD.

3.3 Lipoprotein(a) and follow-up

Clinical follow-up data were available for 725 participants. During the follow-up a total of 71 CV events and 34 deaths were observed, with 93 individuals experiencing a composite outcome.

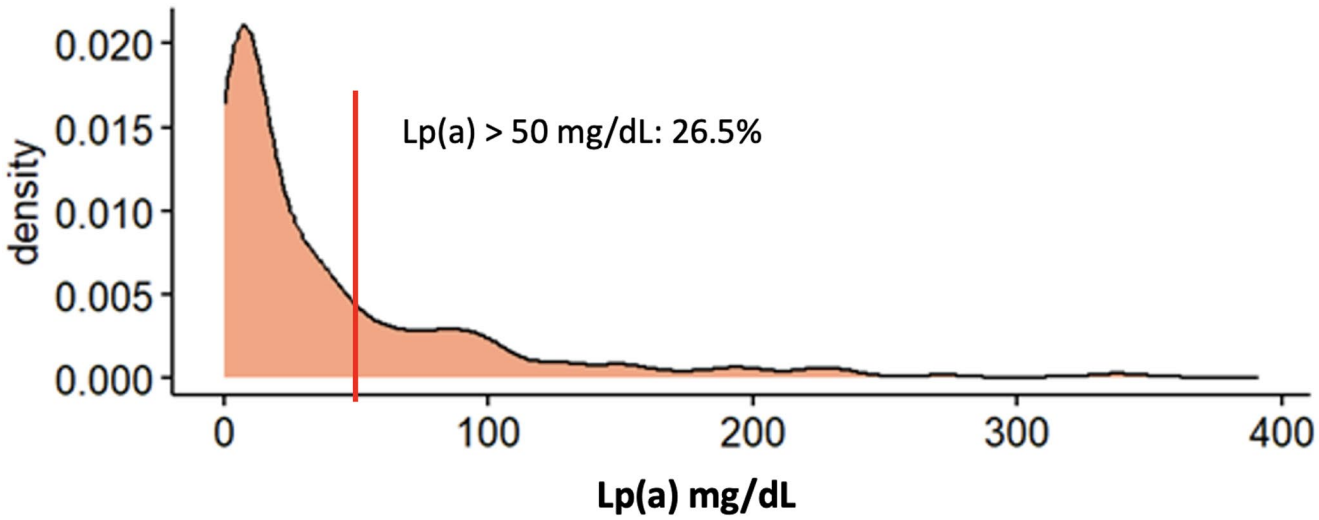


Fig. 1 Density plot showing the distribution of Lipoprotein(a) in the study sample. *Lp(a)* Lipoprotein(a).

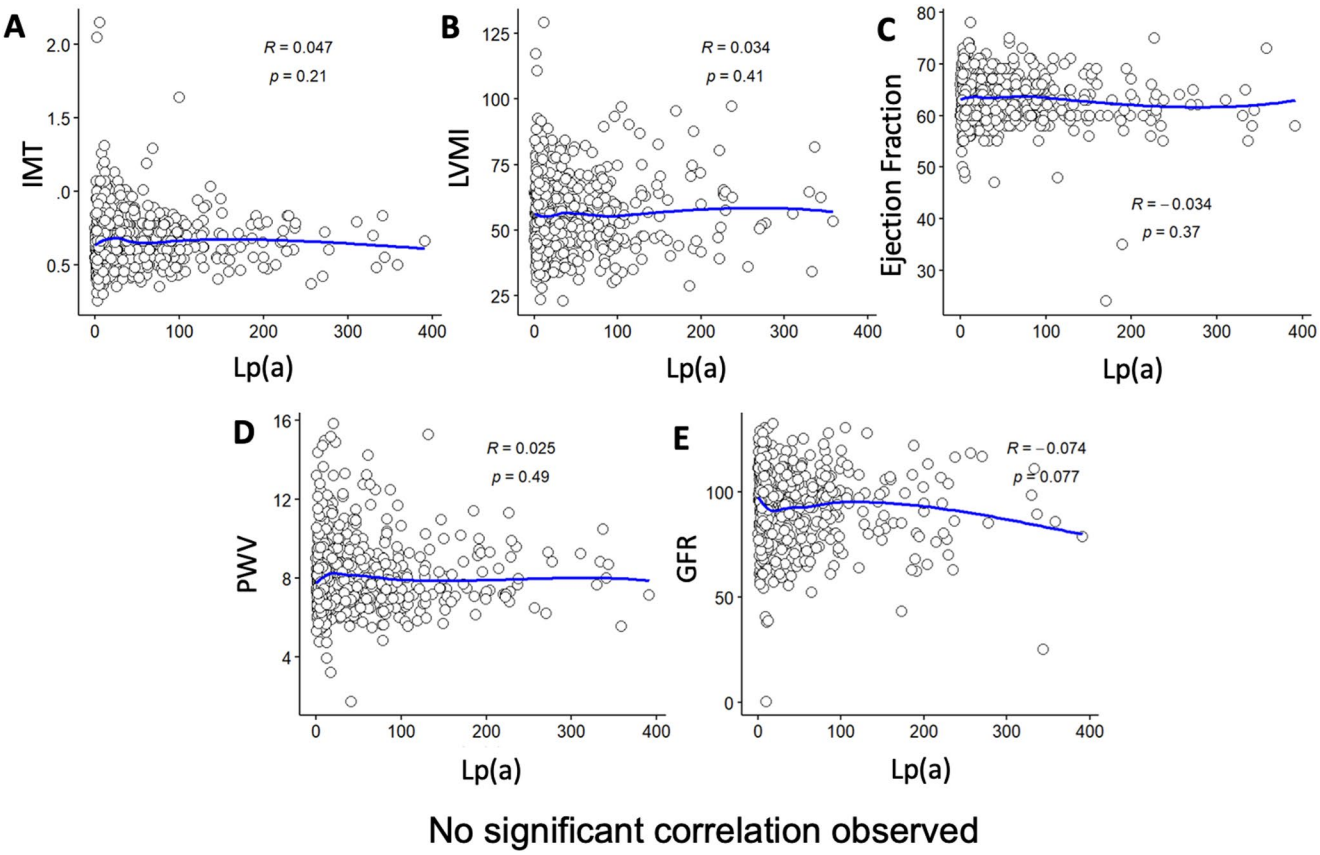


Fig. 2 Scatterplots with trend lines showing the relationship between Lipoprotein(a) and continuous hypertension-mediated organ damage variables. IMT (panel A), LVMI (panel B), Ejection fraction (panel C), PWV (panel D) and GFR (panel E). Spearman correlation index and *p*-value are shown. *Lp(a)* Lipoprotein(a), *IMT* Intima Media Thickness, *LVMI* Left Ventricular Mass Index, *PWV* Pulse Wave Velocity, *GFR* Glomerular Filtration Rate.

The relationships between Lp(a) and CV events, mortality, and the composite event were displayed by a Cox regression HR modeled using restricted cubic splines (Fig. 4) revealing a non-monotonic trend but with 95% confidence interval (CI) that consistently encompass the value of 1, thus without demonstrating an association. Without using splines, the Cox model HRs (95%CI, *p*-value) for Lp(a) for 10 mg/dL increase were 1.01 (0.97–1.05, *p*=0.636),

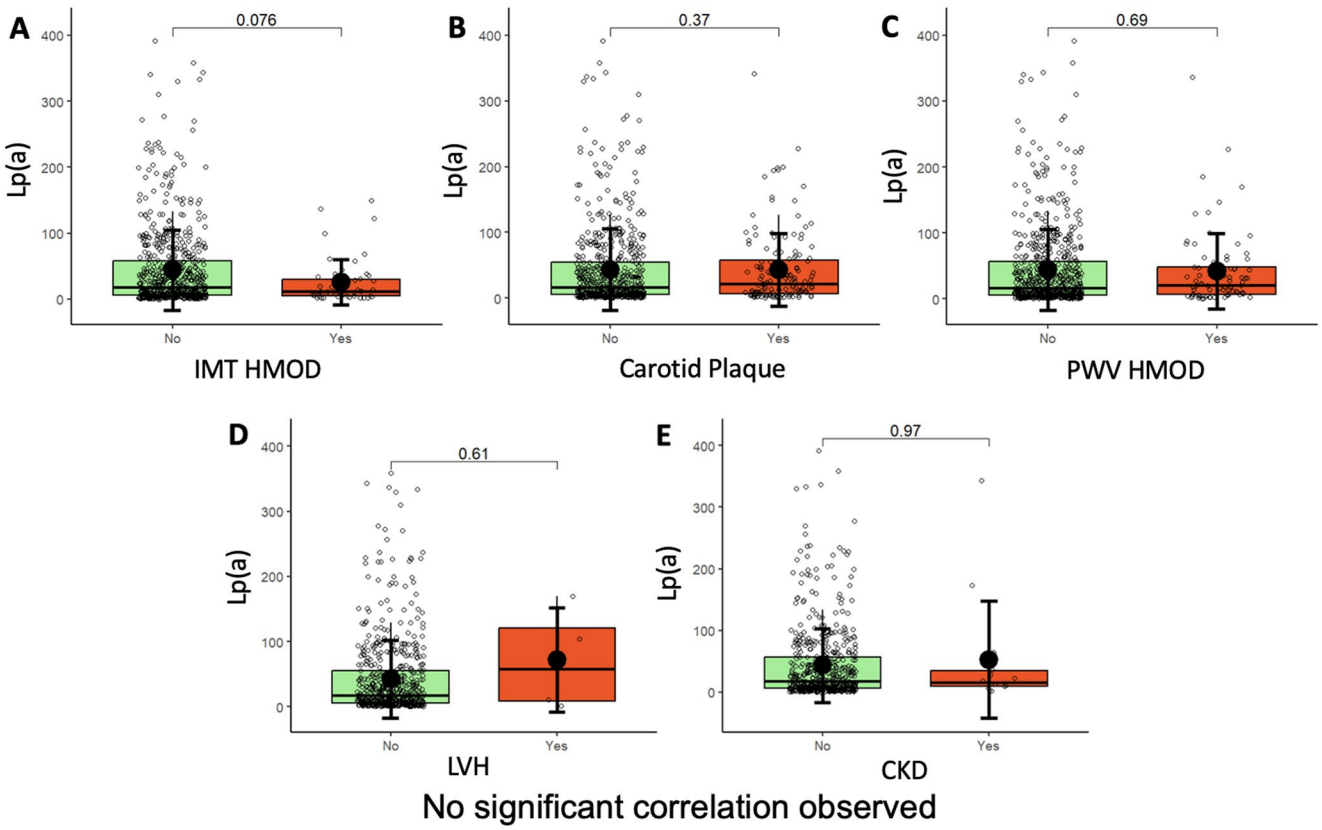


Fig. 3 Boxplots showing the distribution of Lipoprotein(a) levels according to categorical hypertension-mediated organ damage outcomes. IMT (panel A), carotid plaque (panel B) PWV (panel C), LVH (panel D) and CKD (panel E). Mann-Whitney test *p*-values are shown. Point and error bars represent mean ± SD. *Lp(a)* Lipoprotein(a), *IMT* Intima Media Thickness, *HMOD* Hypertension Mediated Organ Damage, *LVH* Left Ventricular Hypertrophy, *PWV* Pulse Wave Velocity, *CKD* Chronic Kidney Disease.

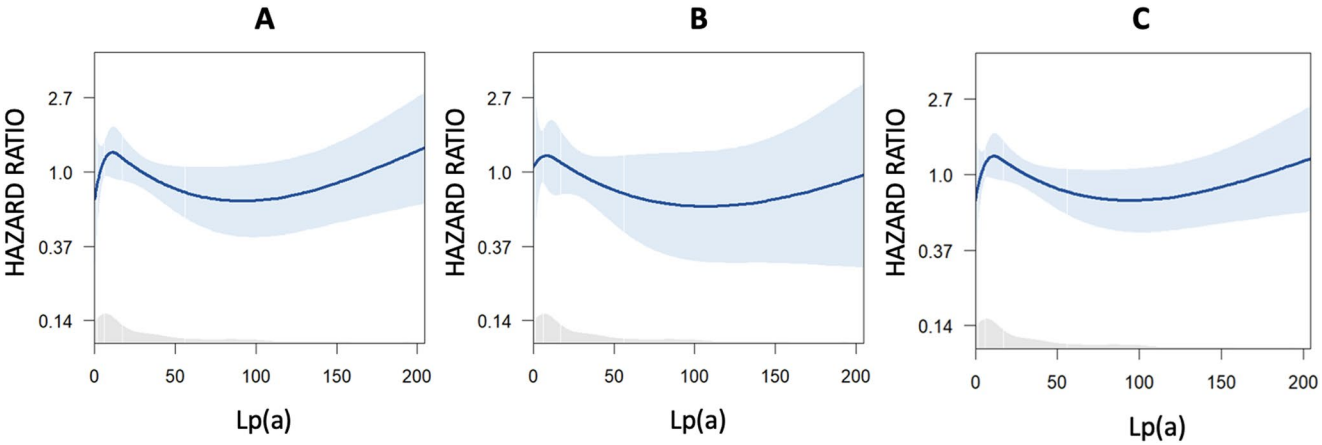


Fig. 4 Estimated hazard ratio of Lipoprotein(a) using Restricted Cubic Splines on CV events (panel A), mortality (panel B) and the composite outcome (panel C). The y-axis is log-transformed. Estimates are from unadjusted Cox models. Restricted Cubic Splines have five knots set on the minimum, first, second, third quartile and maximum value of Lipoprotein(a). *Lp(a)* Lipoprotein(a).

1.00 (0.94–1.05, *p*=0.871) and 1.00 (0.97–1.03, *p*=0.945), for the three outcomes respectively. Multivariable adjusted models (with age, sex, diabetes, LDL cholesterol, statins, anti-hypertensive therapies and GFR as covariates) yielded similar results: 1.01 (0.96, 1.05; *p*=0.819), 0.93 (0.81, 1.06; *p*=0.262) and 0.99 (0.95, 1.04; *p*=0.665), for the three outcomes respectively.

This was also confirmed when patients were divided in two groups based on the Lp(a) cut-off of 50 mg/dL and no difference was seen in cumulative incidence curves (Fig. 5).

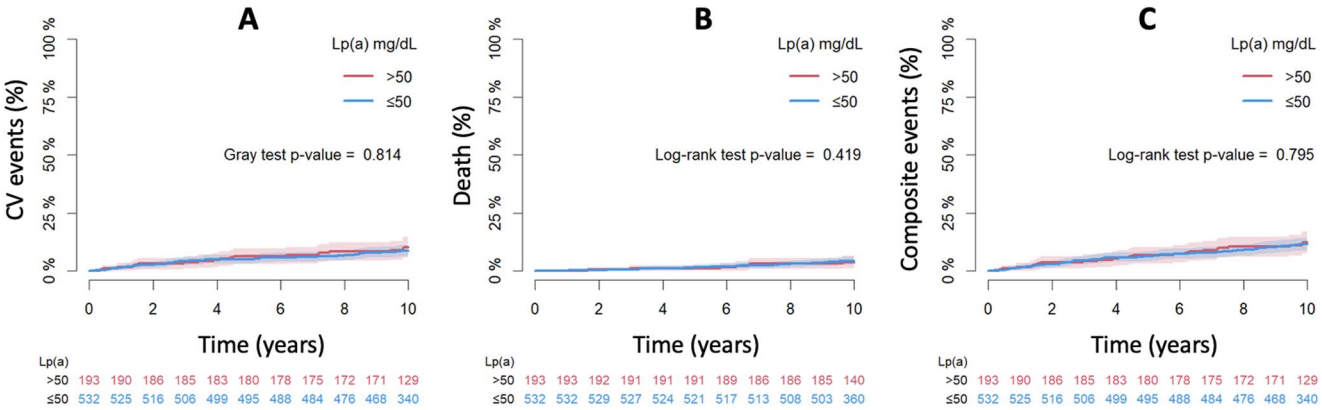


Fig. 5 Cumulative incidence of cardiovascular event (panel A), death (panel B) and composite event (panel C) stratified b Lipoprotein(a) < or ≥ 50 mg/dL. *Lp(a)* Lipoprotein(a), *CV* CardioVascular.

Supplementary Table 3 report the 5- and 10-years incidence values (with 95% CI) for Lp(a)>50 vs ≤50 for the three outcomes.

4 Discussion

Our primary prevention study shows three main findings: (i) high Lp(a) is a frequent risk factor, as 26.5% of enrolled subjects presents values higher than 50 mg/dL; (ii) Lp(a) is not a major determinant of early structural or functional changes in the vasculature, myocardium or kidney; and (ii) Lp(a) is not associated with mortality or future CV events.

Regarding prevalence, our results were consistent with previous findings in European-origin populations, where the prevalence of elevated Lp(a) ranges from 20 to 30% depending on the cutoff used and the assay standardization [23]. However, there prevalence seems to be lower in other ethnic groups (15% in a Chinese cohort [24] and only 6.1% in a Latin-American cohort [25]) while it is significantly higher (two- to threefold) in Black patients [24].

Obviously, a higher prevalence of Lp(a) elevated values was found in cohorts having a disease in whose pathogenesis Lp(a) is implicated. In fact, among patients with acute coronary syndrome 23–32% exhibit Lp(a) levels ≥ 30 mg/dL, particularly younger individuals or those with premature or familial coronary artery disease [25–27]. The prevalence of elevated Lp(a) is similar in patients with chronic coronary syndrome [28], aortic valve stenosis (28–33% [29, 30]), heart failure (58.5% [31] and stroke (35% [6, 32]).

Regarding the second main results of our study, several studies have investigated the relationship between Lp(a) levels and subclinical markers of HMOD, including arterial stiffness, IMT, carotid plaques, LVH and left ventricular and kidney function. However, the results are heterogeneous, particularly depending on the evaluated populations.

With respect to arterial stiffness most of the published studies present negative results such as we found. In 138 hypertensive patients (with age superimposable to our population, 51 ± 14 years), elevated Lp(a) have been independently associated with augmentation index (AIx) but not to carotid-femoral PWV [9]. Similarly, Vlachopoulos et al. evaluated 240 untreated hypertensive individuals and reported no significant association between Lp(a) levels and carotid-femoral PWV [33]. In a more recent investigation conducted in hypertensive patients, no significant association was found between serum Lp(a) levels and brachial-ankle PWV [34]. These results have also been confirmed by a recently published mendelian randomization study showing no association between Lp(a) and both carotid-femoral and brachial-ankle PWV [11]. The same also applies to local stiffness index such as carotid PW [35], that was not found to be associated with Lp(a) in young familial hypercholesterolemia patients [10].

Heterogeneity in the results increased when carotid atherosclerosis was evaluated with some studies reporting that elevated Lp(a) is associated with the presence of carotid plaques even in otherwise healthy individuals. In a study on 4,896 individuals an independent association between elevated Lp(a) and carotid plaque presence was identified [16]. On 200 familiar hypercholesterolemia children, higher Lp(a) concentrations were associated with IMT progression during a 20-year follow-up [36]. These findings have been reinforced by several recent studies. A large population-based cohort confirmed the independent association between elevated Lp(a) levels and the presence of carotid plaques in asymptomatic individuals [32]. Similarly, another study demonstrates a positive correlation between Lp(a) concentrations and both carotid IMT and plaque score in a Japanese adult cohort [37]. Furthermore, a Mendelian randomization study provided additional evidence supporting a causal role of Lp(a) in the development of carotid atherosclerosis [38]. However, other studies have yielded opposing results with

no correlation between Lp(a) and IMT [14, 15]. In a study on 317 normolipidemic subjects, individuals with Lp(a) >30 mg/dL had no difference in carotid IMT with a higher probability of carotid plaques but only at univariable analysis losing its significance at multivariable one [13].

In terms of cardiac structure, only one study (a large cross-sectional analysis of NHANES III data on 4,052 subjects) has evaluated the association between Lp(a) and LVH, using electrocardiographic criteria [39]. However, ECG-based detection of LVH is limited by modest sensitivity and specificity while our study is the first to assess this relationship using the more sensitive echocardiographic approach. No association was found, although LVH was rare in our population (4 subjects, 0.7%). Larger and more representative cohorts are needed to better understand this specific form of HMOD.

Moreover, higher baseline Lp(a) levels have been reported to be inversely associated with follow-up EF in patients who developed Heart Failure (HF) [19]. However, this finding comes from a selected population with clinical HF, and similar evidence in asymptomatic individuals is lacking. Again, elevated Lp(a) has been linked to incident HF, rather than isolated reductions in EF (without clinical symptoms of HF). For instance, in a cohort of chronic HF patients, higher Lp(a) predicted recurrent HF hospitalizations and CV death, but not EF values per se [40]. Similarly, in the ARIC and Jackson Heart Studies, Lp(a) was not independently associated with reduced EF but was more strongly related to incident HF with preserved EF, particularly among Black adults [41]. Altogether, these findings suggest that while Lp(a) may play a role in symptomatic HF risk, there is limited evidence supporting a direct association with echocardiographically measured EF in general populations.

The relationship between Lp(a) and renal function has also been explored, with conflicting evidence. An early NHANES III analysis found no association between Lp(a) and GFR overall [42]. However, more recent community-based data showed that higher Lp(a) levels were independently associated with mildly reduced GFR, particularly in older adults [43].

Interestingly, cardiovascular risk linked to Lp(a) appears more pronounced in individuals with reduced renal function. In fact, in a study on patients undergoing percutaneous coronary intervention, elevated Lp(a) predicted adverse events only when GFR was <60 mL/min/1.73 m^2 [44].

Our results regarding the relationship between Lp(a) and HMOD are mainly negative. However, when subjects were stratified accordingly to hypertension diagnosis some weak univariate associations (r index near 0.1) have been observed, i.e. between Lp(a) and GFR in hypertensive subjects and with EF in normotensive subjects. Both analyses were still significant after multivariable analysis but with estimates (mean difference in GFR for 10 mg/dL increase in Lp(a) among hypertensive patients of − 0.49 mL/min and mean difference in EF for 10 mg/dL increase in Lp(a) among normotensive patients − 0.16%) that are very far from being clinically significant. Taken into account with previously cited findings our results are not conclusive but should be used to design specific study in the future.

The third main result of our study was the absence of an association between Lp(a) and CV events and mortality during the subsequent 10 years of follow-up. Although a substantial body of genetic and epidemiological evidence supports Lp(a) as a causal risk factor for CV disease [45, 46], several large primary-prevention studies have failed to demonstrate consistent associations with incident CV events or mortality. A meta-analysis of 67 prospective cohorts (181,700 subjects) found elevated Lp(a) to be significantly associated with coronary heart disease, but not with stroke or all-cause mortality (relative risk 1.12; 95% CI 0.94–1.33; p=0.20) [47]. In the Brisighella Heart Study (1,215 subjects, aged 40–69), Lp(a) only emerged as a mortality predictor in specific subgroups (e.g., high-risk individuals or younger women), but not in the whole population (both in primary and secondary prevention settings) [48]. Also in secondary-prevention cohorts some studies have reported null or weak associations between Lp(a) and subsequent outcomes. In a pooled analysis of three statin-era trials in patients with established coronary disease (PEACE, CARE, PROVE IT–TIMI 22; 8,900 total patients), baseline Lp(a) was not independently associated with CV death or non-fatal myocardial infarction [49]. Similarly, in a large post–acute coronary syndrome biomarker study (dal-OUTCOMES; 4,800 patients), Lp(a) concentrations did not predict major CV events over a median 31 months [50]. In the LURIC cohort and across 27 validation cohorts from the GENIUS-CHD consortium (116,000 patients with coronary disease), neither circulating Lp(a) nor LPA risk variants were associated with CV or all-cause mortality over long-term follow-up (~10 years) [51]. Consistent null findings have also been reported for mortality after acute coronary syndrome in contemporary practice [52].

Taken together our findings suggest that in a relatively young and healthy population, Lp(a) may not exert measurable effects on early markers of CV damage. Alternatively, the effects of Lp(a) might be more evident in higher-risk groups or operate through pathways not captured by subclinical HMOD evaluation. In fact, it could be possible that our population is too healthy for identifying a significant association. The same also applies to CV events and mortality, in fact, only 5% of our population had a combined outcome (CV events or death) within 10 years of follow-up. So, a larger population or a longer follow-up could result in

the evidence of significant association between Lp(a) and CV outcomes.

Another point of our study that could influence our negative results deserved to be mentioned, i.e. the possible effects that CV drugs could have on both HMOD evaluation and CV events. In fact, both anti-hypertensive therapies and lipid lowering therapies could reduce CV events and the presence of HMOD.

Antihypertensive treatment effectively reduces vascular and cardiac remodeling [53, 54]. Similarly, lipid-lowering therapies, especially statins, have consistently been shown to slow the progression of IMT and arterial stiffness [55, 56]. In our cohort, antihypertensive medications were taken by more than one third of participants, with 23.2% on ACE inhibitors and 18.9% on ARBs, while nearly 10% were on statin therapy. These therapies likely damped early markers of HMOD, thereby weakening any detectable relationship between Lp(a) and subclinical damage or clinical events. Hence, our null findings may not reflect the absence of a true Lp(a) effect, but rather the pharmacological suppression of early vascular and cardiac remodeling in a treated, low-risk sample. Our study has some elements of strength: firstly, HMOD has been measured by state-of-the-art techniques and at various organ levels, a peculiar feature which is not shared by the investigations published so far that thereby fail to provide in the same population systematic information on different organs. Furthermore, we adopt an isoform-insensitive method to ensure analytical comparability across individuals regardless of isoform size. In fact, accurate quantification of Lp(a) is complicated by the marked heterogeneity in apolipoprotein(a) isoform size, which arises from genetic variation in the number of Kringle IV type 2 (KIV-2) repeats. This variability affects immunoassays that are isoform-sensitive, leading to underestimation of Lp(a) concentrations in individuals with large isoforms. To overcome this limitation, standardized and isoform-insensitive assays—such as those traceable to WHO/IFCC reference material SRM 2B—are recommended for both clinical use and research [57]. Some studies evaluating Lp(a) could be flawed by this methodological issue.

However, our paper has also several limitations that need to be acknowledged. Firstly, the HMOD evaluation were done only at baseline precluding causal inference or longitudinal assessment of organ damage progression. Secondly, despite the high total number of subjects in the whole population some subgroup presents such a low number of subjects (i.e. LVH): this sample size can limit our power to detect important associations or findings. Furthermore, IMT measurements were performed manually, lacking the precision of automated echo-tracking systems [35]. However, our measurement approach aligns with methodologies used in most of the previous studies on this topic. Moreover, in the multifactorial context linking Lp(a) with numerous HMOD and subsequent CV events and mortality, is indeed difficult to assess all parameters that can influence the relationship and some of them have not been evaluated. Finally, although the availability of Lp(a) doesn't follow any specific rule, there were some significant differences between patients with available Lp(a) and patients without it. As already described in the methods section, they had lower PWV but with higher IMT values and prevalence of carotid plaque. This could have affected the HMOD analysis, and the results of the whole population could be different. However, no differences were seen regarding follow-up CV events and mortality between the two groups (composite outcome 12.4% in patients with available Lp(a) and 11.2% in patients without, p=0.928).

So, we can conclude that in our primary prevention population, high Lp(a) is a frequent risk factor (26.5% of the subjects) but is not a strong determinant of early structural or functional changes in the vasculature, myocardium or kidney nor with all-cause mortality or future CV events.

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Data availability Data will be available after a reasonable request to the corresponding author.

Declarations

Conflict of interest None.

Ethical approval The study protocol complies with the Helsinki Declaration and was approved by the San Gerardo Hospital Ethics Committee and all participants provided informed written consent.

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