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ORIGINAL PAPER

Serum lipoprotein(a) and bioprosthetic aortic valve degeneration

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Aims

Bioprosthetic aortic valve degeneration demonstrates pathological similarities to aortic stenosis. Lipoprotein(a) [Lp(a)] is a well-recognized risk factor for incident aortic stenosis and disease progression. The aim of this study is to investigate whether serum Lp(a) concentrations are associated with bioprosthetic aortic valve degeneration.

Methods and results

In a *post hoc* analysis of a prospective multimodality imaging study (NCT02304276), serum Lp(a) concentrations, echocardiography, contrast-enhanced computed tomography (CT) angiography, and 18F-sodium fluoride (18F-NaF) positron emission tomography (PET) were assessed in patients with bioprosthetic aortic valves. Patients were also followed up for 2 years with serial echocardiography. Serum Lp(a) concentrations [median 19.9 (8.4–76.4) mg/dL] were available in 97 participants (mean age 75 ± 7 years, 54% men). There were no baseline differences across the tertiles of serum Lp(a) concentrations for disease severity assessed by echocardiography [median peak aortic valve velocity: highest tertile 2.5 (2.3–2.9) m/s vs. lower tertiles 2.7 (2.4–3.0) m/s, $P = 0.204$], or valve degeneration on CT angiography (highest tertile $n = 8$ vs. lower tertiles $n = 12$, $P = 0.552$) and 18F-NaF PET (median tissue-to-background ratio: highest tertile 1.13 (1.05–1.41) vs. lower tertiles 1.17 (1.06–1.53), $P = 0.889$]. After 2 years of follow-up, there were no differences in annualized change in bioprosthetic hemodynamic progression [change in peak aortic valve velocity: highest tertile [0.0 (−0.1–0.2) m/s/year vs. lower tertiles 0.1 (0.0–0.2) m/s/year, $P = 0.528$] or the development of structural valve degeneration.

Conclusion

Serum lipoprotein(a) concentrations do not appear to be a major determinant or mediator of bioprosthetic aortic valve degeneration.

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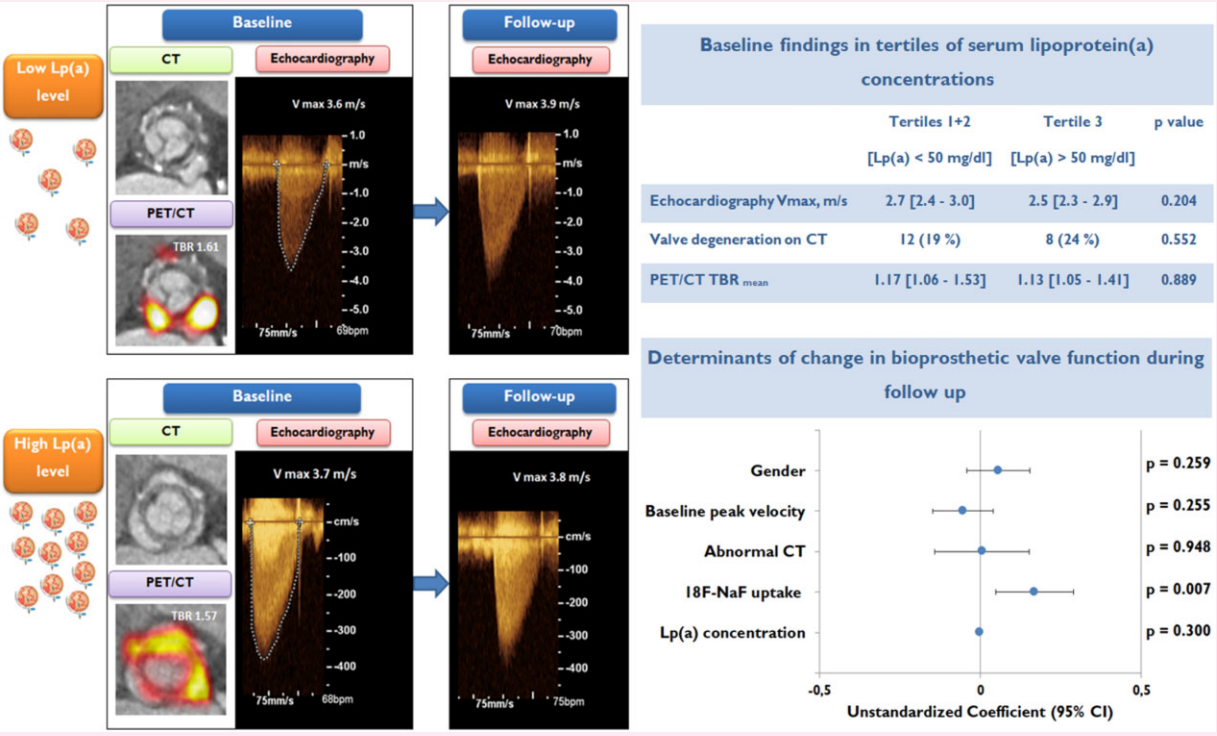
Graphical Abstract



18F-NaF, 18F-sodium fluoride; CI, confidence interval; CT, computed tomography; Lp(a), lipoprotein(a); PET, positron emission tomography; TBR, target-to-background ratio.

Keywords lipoprotein(a) • bioprosthetic valve • structural valve degeneration • aortic valve

Introduction

Bioprosthetic heart valve implantation rates are steadily increasing due to the increasing incidence of aortic stenosis, the advantages of avoiding long-term anticoagulation, and the emergence of transcatheter aortic valve implantation.[1] However, the limited durability of bioprosthetic valves due to leaflet degeneration remains a major concern, restricting their use in younger patients, and leading to repeated interventional valve procedures in later life. An improved understanding of the pathology of structural bioprosthetic valve degeneration is required so that novel therapies or valve designs can be developed to improve bioprosthetic valve longevity.

Structural bioprosthetic aortic valve degeneration shares many risk factors with aortic stenosis and demonstrates many pathological similarities including oxidized lipid deposition, foam cell formation, and inflammation.[2–4] Most notably, leaflet calcification plays a central role in both conditions, acting as a key driver of disease progression and clinical events.[5,6] Lipoprotein(a) [Lp(a)] is now well recognized as an important risk factor for incident aortic stenosis.[7] Moreover, patients with aortic stenosis and elevated serum Lp(a) concentrations demonstrate increased calcification activity within the valve, faster disease progression on echocardiography and computed tomography (CT), and more rapidly require aortic valve replacement.[8–11]

In a *post hoc* analysis of a prospective multimodality imaging study (NCT02304276), we hypothesized that serum Lp(a) concentrations would be associated with the development of bioprosthetic aortic valve degeneration.

Methods

Study design and patient population

We performed a *post hoc* analysis of data from patients enrolled in a prospective multimodality imaging study investigating bioprosthetic aortic valve degeneration: 18F-Fluoride Assessment of Aortic Bioprosthesis Durability and Outcome (18F-FAABULOUS). Although this was a multicentre observational study, only the patients enrolled in a single centre (Edinburgh) were eligible for the analysis due to the availability of serum samples for Lp(a) analysis. Patients over 40 years of age who had undergone previous surgical aortic valve replacement (SAVR), using a bioprosthetic valve made of bovine pericardial tissue or porcine valve tissue, or a transcatheter aortic valve implantation (TAVI), using a balloon-expandable or self-expanding bioprosthesis, were prospectively enrolled if they were under routine clinical follow-up and had undergone valve intervention (SAVR/TAVI) 1 month, 2, 5, or 10 years prior to study recruitment. Written informed consent was obtained from all participants. Patients unable to give informed consent, with claustrophobia, allergy to iodinated contrast, liver failure, chronic kidney disease (with estimated glomerular filtration rate <30 mL/min/1.73 m^2), Paget's disease, metastatic malignancy, or an inability to tolerate the supine position were excluded. The study (URL: http://www.clinicaltrials.gov; Unique identifier: NCT02304276) was conducted in accordance with the Declaration of Helsinki and was approved by National Health Service Scotland Research Ethics Committee (14/SS/1049), the Administration of Radioactive Substances Advisory Committee, and the institutional review board.

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Study assessments and data collection

Baseline and follow-up data have been reported previously.[5,6] Each patient underwent clinical assessment, blood sample collection, transthoracic echocardiography, contrast-enhanced ECG-gated CT angiography, and hybrid 18F-sodium fluoride (18F-NaF) positron emission tomography (PET) at baseline and was invited to return annually for the next 2 years for repeat clinical evaluation and echocardiography to assess for evidence of deterioration in the hemodynamic performance of the bioprosthetic aortic valve. Changes in the bioprosthetic valve peak velocity, mean pressure gradient, effective orifice area, and grade of aortic regurgitation were recorded.

Laboratory measurements

Baseline blood samples were collected at the time of recruitment, and plasma and serum were stored at −80° C until further use. Clinical haematology, biochemistry, and lipid panels were determined according to standardized operating procedures in a core laboratory. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula.[12] Serum Lp(a) was measured from frozen serum samples using a kringle IV type 2 independent immunoassay (Randox Laboratories).[13] We corrected LDL-C for Lp(a) by subtracting 0.15×Lp(a) mass from the LDL-C mass.[14]

Echocardiography

Two-dimensional and Doppler echocardiography was performed at baseline and annually thereafter according to American Society of Echocardiography guidelines by a single experienced echocardiographer (AW).[15] Aortic valve Doppler measurements were routinely assessed from the apex, suprasternal notch, and right sternal edge to measure the peak aortic jet velocity, the mean gradient, and the effective orifice area of the bioprosthesis. Mean values were taken from three measurements when subjects were in sinus rhythm and from five measurements if they were in atrial fibrillation. Bioprosthetic valve regurgitation was graded as mild, moderate, or severe according to guideline recommendations on the basis of visual assessment of colour Doppler images, measurement of pressure half-time, and evidence of diastolic flow reversal in the thoracic aorta.[6] Annualized change in peak aortic valve velocity, mean gradient, effective orifice area, and Doppler velocity index were calculated.

PET and CT image analysis

Abnormalities on CT angiography were evaluated using the following prespecified criteria. Pannus was defined as circumferential low-attenuation (non-calcific) material with radial thickness ≥2 mm and encroachment on the valve cusps.[16,17] Non-calcific leaflet thickening [hypoattenuated leaflet thickening (HALT)] was defined as focal areas of low-attenuation (30–200 Hounsfield Units) leaflet thickening visualized in at least 2 planes typically thickest at its base and thinning to the tips in accordance with consensus guidelines.[17,18] Leaflet calcification was defined as calcium (>500 Hounsfield Units) localized to a valve cusp in at least two planes and further classified as spotty calcification if the maximum diameter was <3 mm, or large calcification if maximum diameter was ≥3 mm.[19]

Fused 18F-NaF PET and CT angiogram images were co-registered and analysed in three planes.[20,21] PET scans were adjudicated to be abnormal if increased 18F-NaF uptake (target-to-background ratio >1.3), as a marker of calcification activity, originating from the bioprosthetic valve leaflets was observed.[5,6] 18F-NaF uptake was quantified using a circular (1-cm^2 area) region of interest (ROI) drawn around the area of maximal uptake originating in the valve cusps on the reoriented co-registered PET-CT images, employing a 'most diseased segment' (MDS) approach as described previously.[19] Where there was no visible uptake in the valve leaflets, a 1-cm^2 circular ROI was drawn in the centre of the valve.[5,22] Maximum standardized uptake values (SUV) were extracted from these ROIs and corrected for blood-pool activity measured in the right atrium (2-cm^2 ROIs, axial slices, at the level of the right coronary ostium) to calculate the target-to-background ratio (TBR). Mean SUV and TBR values were also calculated.

Definition of structural valve degeneration

The presence of structural valve degeneration and bioprosthetic valve failure was assessed at baseline and after follow-up using the definitions recommended by recent consensus papers and acknowledged by the 2021 ESC/EACTS Guidelines for the management of valvular heart disease.[23–25] Structural valve degeneration was classified as: stage 1 when morphological abnormalities (i.e. calcification, leaflet fibrosis, thickening, or new motion disorder) were present on echocardiography or CT without significant haemodynamic changes; stage 2 when moderate stenosis, moderate regurgitation or both were present; and stage 3, in the presence of severe stenosis, severe regurgitation or both. Bioprosthetic valve failure was defined as the presence of severe structural valve degeneration accompanied by clinical features of heart failure.[23,24]

Statistical analyses

Baseline characteristics are reported as mean ± SD or median [interquartile range] for continuous variables and number (percentages) for categorical variables as appropriate. Normality was assessed by inspection of histograms and the Shapiro–Wilk test. Since there are no current data to guide a threshold value for serum Lp(a) concentrations in structural valve degeneration, we therefore stratified our cohort into Lp(a) tertiles. Continuous variables were compared using the Student's *t*-test or Mann–Whitney U test whenever appropriate. Categorical data were compared using χ^2 or Fisher's exact test. Correlations were assessed with the Pearson coefficient. The effect of Lp(a) concentration on deterioration in bioprosthetic valve function was assessed in univariable and multivariable analyses. The multivariable models were constructed with the annualized change in peak bioprosthetic valve velocity (log transformed to achieve normality before inclusion in regression models) as the dependent variable and gender, baseline peak velocity, abnormal CT findings, 18F-NaF uptake, and Lp(a) concentration (as a continuous variable or as a categorical variable—the presence in the highest tertile) as independent variables. Statistical analysis was performed with SPSS version 28 (IBM SPSS Statistics for Windows, Version 28.0.1.0, IBM Corp). A two-sided *P* value <0.05 was considered statistically significant.

Results

Study population

One hundred and five patients were recruited although eight patients were unable to complete the baseline assessment. The remaining 97 patients (mean age of 75.3 ± 7.3 years, 54% males) had a high prevalence of traditional cardiovascular risk factors and coronary artery disease and a baseline prosthetic valve velocity of 2.7 [2.3–3.0] m/s (*Table 1*). Overall, 76 (78%) patients had a surgical bioprosthesis (56 bovine pericardial tissue bioprostheses, 20 porcine valve tissue bioprostheses) and 21 (22%) a transcatheter bioprosthesis. At baseline, 14 (14%) patients had echocardiographic evidence of structural valve degeneration, 20 (21%) patients had CT evidence of structural valve degeneration (calcification, HALT, or pannus), 29 (30%) showed increased 18F-NaF uptake in leaflets, and 5 (5%) patients had bioprosthetic valve failure.

The median serum Lp(a) concentration was 19.9 [8.4–76.4] mg/dL, and patients in the highest tertile had a median serum Lp(a) concentration of 91.8 [76.4–117.6] mg/dL, while patients in the middle and lower tertiles had median concentrations of 19.0 [12.8–24.5] mg/dL, and 5.7 [3.6–7.8] mg/dL, respectively, with similar baseline characteristics (*Table 1*). Comparing the upper tertile with the other 2 tertiles, both as a group and individually, there were no differences in baseline echocardiography, CT findings, or 18F-NaF PET uptake (*Table 2*; Supplementary material online, *Table S1*).

Serum Lp(a) concentrations were similar in patients with or without evidence of structural valve degeneration of any stage [15.9 (7.7–62.7)

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Table 1 Baseline characteristics of the study population

Variables	Total	Tertile 1	Tertile 2	Tertile 3
Age, years	75.3 ± 7.3	73.8 ± 7.0	74.7 ± 7.1	77.2 ± 7.8
Male, *n*	52 (54)	18 (58)	17 (52)	17 (52)
Body mass index, kg/m^2	27.0 [24.5–31.2]	27.1 [24.7–32.8]	27.7 [25.5–32.4]	26.8 [23.8–29.9]
Systolic blood pressure, mmHg	149.8 ± 21.9	148.1 ± 20.3	147.5 ± 21.4	153.5 ± 23.9
Diastolic blood pressure, mmHg	76.0 ± 11.6	78.2 ± 11.9	72.8 ± 9.6	77.2 ± 12.9
Heart rate, beats/min	71 ± 12	72 ± 13	72 ± 12	71 ± 12
Time since valve replacement				
1 month	17 (18)	7 (23)	3 (9)	7 (21)
2 years	33 (34)	13 (42)	13 (40)	7 (21)
5 years	23 (23)	7 (23)	9 (27)	7 (21)
10 years	24 (25)	4 (12)	8 (24)	12 (37)
Type of aortic valve intervention				
Surgical replacement	76 (78)	23 (74)	25 (76)	28 (84)
Transcatheter implantation	21 (22)	8 (26)	8 (24)	5 (16)
Comorbidities				
Hypertension	72 (74)	21 (70)	25 (76)	26 (79)
Hypercholesterolaemia	76 (78)	22 (73)	28 (85)	26 (79)
Diabetes	12 (12)	6 (20)	1 (3)	5 (15)
Obesity	27 (28)	8 (26)	11 (33)	8 (25)
Coronary artery disease	42 (43)	10 (33)	16 (49)	16 (49)
Coronary bypass surgery	33 (34)	7 (23)	13 (39)	13 (39)
Medication				
Aspirin	63 (65)	17 (55)	23 (70)	23 (70)
Clopidogrel	13 (13)	3 (10)	4 (12)	6 (18)
ACEi/ARB	54 (56)	13 (42)	19 (58)	22 (67)
Beta-blocker	47 (48)	16 (52)	18 (55)	13 (39)
Statin	70 (72)	16 (52)	28 (85)	26 (79)
Lipid profile				
Total cholesterol, mmol/L	4.5 ± 1.1	4.8 ± 1.0	4.4 ± 1.1	4.3 ± 1.0
HDL-cholesterol, mmol/L	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.4
LDL-cholesterol, mmol/L	2.5 ± 0.9	2.7 ± 0.9	2.4 ± 0.9	2.3 ± 0.9
Corrected LDL-cholesterol, mmol/L	2.3 ± 0.9	2.7 ± 0.9	2.3 ± 0.9	1.9 ± 0.8
Triglycerides, mmol/L	1.4 [1.1–1.9]	1.5 [1.1–1.8]	1.5 [1.1–2.0]	1.2 [1.0-1.9]
Electrocardiogram				
Sinus rhythm	81 (84)	24 (77)	24 (73)	33 (100)
Atrial fibrillation	9 (9)	5 (16)	4 (12)	0 (0)
Left ventricular hypertrophy	29 (30)	8 (26)	12 (36)	9 (27)
Strain pattern	16 (16)	5 (16)	7 (21)	4 (12)

Values are displayed as *n* (%), mean ± SD, median [interquartile range].
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol.

mg/dL vs. 31.8 (13.2–87.7) mg/dL], but also in patients with or without bioprosthetic valve failure [18.6 (7.9–77.2) mg/dL vs. 24.8 (22.9–38.8) mg/dL] ($P > 0.05$ for all; *Figure 1*). There were also no differences in serum Lp(a) concentrations between patients with normal or increased leaflet 18F-NaF uptake on PET [18.6 (7.9–76.5) mg/dL vs. 21.0 (10.3–74.0) mg/dL; $P = 0.725$].

Follow-up

No differences were found between tertiles regarding hemodynamic progression of bioprosthetic function expressed as annualized change in peak bioprosthetic valve velocity, mean pressure gradient, effective orifice area, and Doppler velocity index ($P > 0.05$ for all; *Table 3* and *Figure 2*). No correlation was observed between serum Lp(a)

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Table 2 Baseline echocardiography, computed tomography, and 18F-sodium fluoride positron emission tomography imaging findings in tertiles of serum lipoprotein(a) concentrations

Variables	Tertiles 1 + 2 ($n = 64$)	Tertile 3 ($n = 33$)	*P* value
Echocardiography			
Evidence of valve failure	4 (6)	1 (3)	0.659
Reduced LVEF	11 (17)	9 (27)	0.212
Vmax, m/s	2.7 [2.4–3.0]	2.5 [2.3–2.9]	0.204
Mean valve gradient, mmHg	15.4 [12.0–19.3]	13.0 [10.8–17.9]	0.150
Effective orifice area, cm^2	1.20 [0.99–1.46]	1.20 [0.94–1.52]	0.985
Dimensionless velocity index	0.38 [0.33–0.43]	0.42 [0.36–0.56]	0.118
Acceleration time, ms	80.2 [75.8–87.0]	82.0 [74.7–88.0]	0.876
Acceleration time/LVET	0.26 [0.24–0.27]	0.25 [0.23–0.29]	0.910
Computed tomography			
Abnormal CT findings	12 (19)	8 (24)	0.552
Spotty calcification	8 (13)	3 (9)	0.737
Hypoattenuated leaflet thickening	5 (8)	2 (6)	1.0
Pannus	3 (5)	4 (12)	0.412
18F-sodium fluoride PET			
Increased leaflet 18F-sodium fluoride	20 (31)	9 (27)	0.615
TBR_{mean}	1.17 [1.06–1.53]	1.13 [1.05–1.41]	0.889
TBR_{max}	1.32 [1.21–1.60]	1.32 [1.20–1.51]	0.758

Values are displayed as *n* (%), median [interquartile range].
CT, computed tomography; LVEF, left ventricular ejection fraction; LVET, left ventricular ejection time; PET, positron emission tomography; TBR, target-to-background ratio.

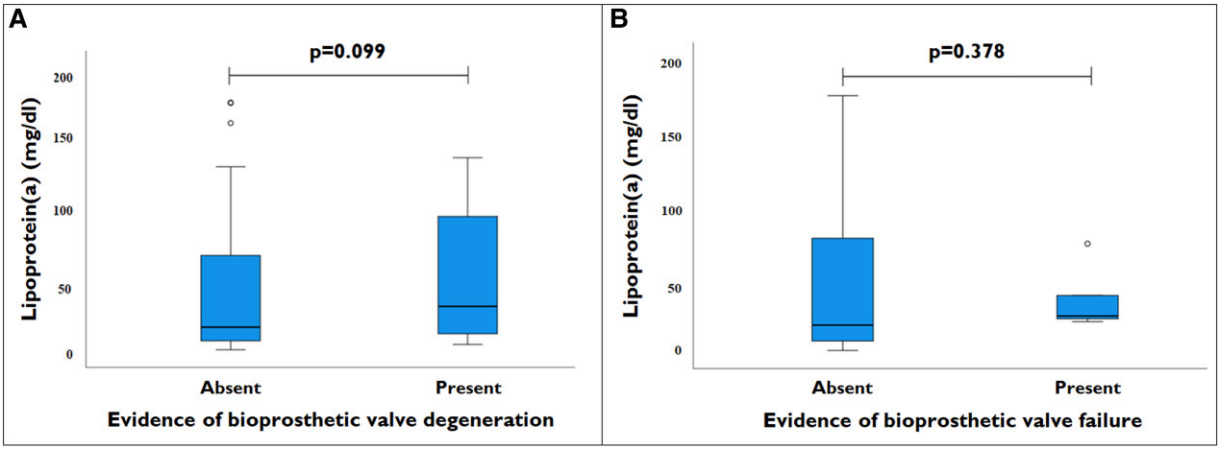

Figure 1 Serum lipoprotein(a) [Lp(a)] concentrations and bioprosthetic aortic valve degeneration or failure at baseline. Serum Lp(a) concentrations are similar in patients with and without both structural valve degeneration and bioprosthetic valve failure at baseline. There were similar serum Lp(a) concentrations in (*A*) patients with or without evidence of structural valve degeneration of any stage [15.9 (7.7–62.7) mg/dL vs. 31.8 (13.2–87.7) mg/dL] (*A*), but also in (*B*) patients with or without defined bioprosthetic valve failure at baseline [18.6 (7.9–77.2) mg/dL vs. 24.8 (22.9–38.8) mg/dL] (*B*) ($P > 0.05$ for all).

concentrations considered as a continuous variable and the subsequent annualized change in bioprosthetic valve peak velocity ($r = -0.032$, $P = 0.768$), mean pressure gradient ($r = -0.024$, $P = 0.823$), effective orifice area ($r = 0.108$, $P = 0.349$) or Doppler velocity index ($r = 0.056$, $P = 0.643$) on echocardiography.

On univariable analysis, only 18F-NaF uptake was associated with deterioration in bioprosthetic valve function (expressed by an annualized change in bioprosthetic valve peak velocity; Supplementary material online, *Table S2*). On multivariable linear regression analysis, 18F-NaF uptake remained the only predictor of deterioration in

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Table 3 Annualized change in bioprosthetic aortic valve function by tertiles of serum lipoprotein(a) concentrations

Variables	Tertiles 1 + 2 ($n = 60$)	Tertile 3 ($n = 31$)	*P* value
Annual change in peak velocity, m/s/year	0.1 [0.0 ; 0.2]	0.0 [−0.1 ; 0.2]	0.528
Annual change in mean gradient, mmHg/year	0.3 [−0.8 ; 2]	0.3 [−1.0 ; 1.8]	0.902
Annual change in EOA, cm^2/year	−0.02 [−0.10 ; 0.02]	−0.06 [−0.08 ; 0.01]	0.687
Annual change in DVI	−0.01 [−0.03 ; 0.01]	−0.02 [−0.03 ; 0.00]	0.691

EOA, effective orifice area; DVI, dimensionless velocity index.

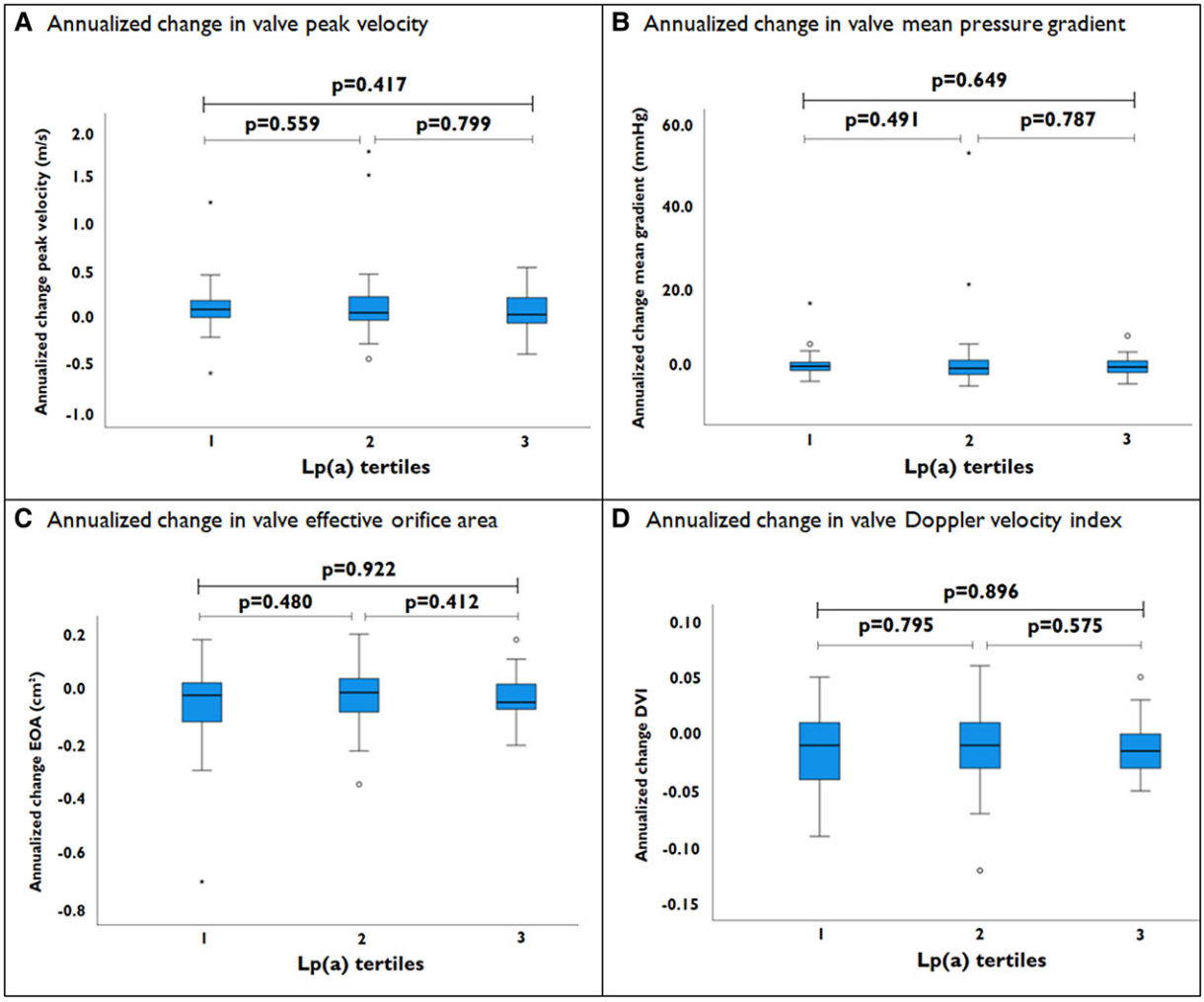

Figure 2 Tertiles of serum lipoprotein(a) [Lp(a)] concentrations and change in bioprosthetic aortic valve function assessed by echocardiography. Serum Lp(a) concentration tertiles and annualized change in (*A*) prosthetic valve peak velocity [0.1 (0.0–0.2) m/s/year vs. 0.1 (0.0–0.2) m/s/year vs. 0.0 (−0.1–0.2) m/s/year], (*B*) mean pressure gradient [0.5 (−0.5–1.5) mmHg/year vs. 0.0 (−1.5–2.0) mmHg/year vs. 0.3 (−1.0–1.8) mmHg/year], (*C*) effective orifice area [EOA; −0.03 (−0.12–0.01) cm^2/year vs. −0.02 (−0.09–0.03) cm^2/year vs. −0.06 (−0.08–0.01) cm^2/year] and (*D*) Doppler velocity index [DVI; −0.01 (−0.04–0.01)/year vs. −0.01 (−0.03–0.01)/year vs. −0.02 (−0.03–0.00)/year] ($P > 0.05$ for all).

bioprosthetic valve function. Serum Lp(a) concentration was not associated with deterioration in prosthetic valve function when it was considered either as a continuous variable [unstandardized coefficient −0.001 (95% confidence interval: −0.002 to 0.000); $P = 0.300$], or as a categorical variable [unstandardized coefficient −0.067 (95% confidence interval: −0.166 to 0.031); $P = 0.177$], nor were sex, baseline peak velocity or abnormalities on CT (*Figure 3*; Supplementary material online, *Tables S3 and S4*).

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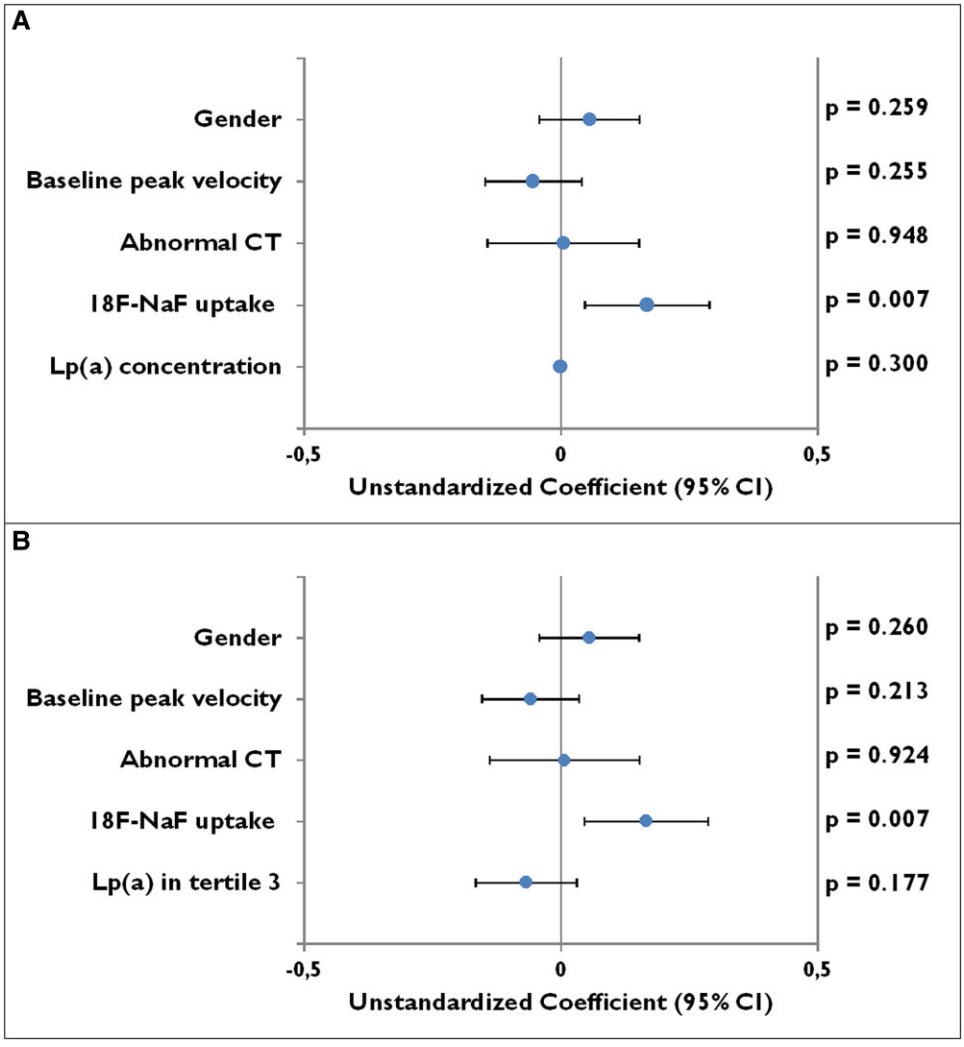

Figure 3 Determinants of change in bioprosthetic valve function. Forest plots of unstandardized coefficients (95% confidence intervals) from a multivariable linear regression analysis predicting change in bioprosthetic valve function (annualized change in peak velocity) during follow-up. When examining all relevant baseline characteristics, 18F-sodium fluoride uptake was the only independent predictor of hemodynamic deterioration in valve function when serum Lp(a) concentration was used both as (*A*) a continuous variable and (*B*) as a dichotomous variable (either in the highest tertile or not). 18F-NaF, 18F-sodium fluoride; CI, confidence interval; CT, computed tomography; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

During follow-up, 11 patients had progression of, or developed new, bioprosthetic valve dysfunction of which two with valve regurgitation, seven with valve stenosis, and two with mixed dysfunction. Serum Lp(a) concentrations were similar in these patients compared with the remaining population [24.9 (0.3–92.0) mg/dL vs. 15.9 (7.7–72.4) mg/dL, $P = 0.503$]. We found no differences between tertiles for patients who did or did not have evidence of structural valve degeneration during the follow-up period (see Supplementary material online, *Tables S5* and *S6*). Two patients developed bioprosthetic valve failure during a 2-year follow-up, both had serum Lp(a) concentrations within the second tertile [median serum Lp(a) concentration of 19.0 (12.8–24.5) mg/dL].

Sensitivity analyses

Studies in coronary artery disease have examined serum Lp(a) concentration thresholds of >50 and >70 mg/dL as being associated with increased cardiovascular risk.[7,26,27] The lower limit for serum Lp(a) concentration in tertile 3 was 50 mg/dL. Further analysis based on a serum Lp(a) concentration threshold of >70 mg/dL demonstrated results consistent with the tertile analysis (see Supplementary material online, *Tables S7–S9*).

When the same analyses were restricted to the SAVR cohort (76 patients), we observed similar results with no clear association between Lp(a) levels and imaging markers of bioprosthetic valve degeneration (see Supplementary material online, *Tables S10* and *S11*).

Discussion

We demonstrate that serum Lp(a) concentrations are not associated with an incident or progressive structural bioprosthetic aortic valve degeneration. This lack of association was consistent across echocardiography, CT, and PET imaging which provided a comprehensive assessment of valve function in nearly 100 participants (*Graphical Abstract*).

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We conclude that serum Lp(a) concentrations do not appear to be a major determinant or mediator of bioprosthetic aortic valve degeneration.

Given the increasing use of bioprosthetic valves, there is an important need to understand the processes driving structural bioprosthetic valve degeneration to develop methods to inhibit or slow valve degeneration. Lp(a) has recently been shown to be an important factor in both driving the incidence and progression of aortic stenosis. Considering the molecular similarities between the pathological processes driving aortic stenosis and bioprosthetic heart valve degeneration, it has been suggested that lipid fractions might also drive the latter.[28] However, despite the apparent pathological similarities between aortic stenosis and structural bioprosthetic valve degeneration, our data imply that Lp(a) does not appear to be a major factor in the pathogenesis of bioprosthetic valve degeneration.

An important strength of our study is the comprehensive multimodality imaging strategy that we have employed. Indeed, we investigated structural bioprosthetic valve degeneration using three different and complementary imaging methods to identify any potential imaging evidence of structural bioprosthetic valve degeneration that may be associated with serum Lp(a) concentrations. Echocardiography provides the reference standard for imaging patients with bioprosthetic heart valves by assessing hemodynamic changes and gross leaflet abnormalities. In our study, Lp(a) was not associated with any of the baseline echocardiographic assessments of valve function or change in these measures during the 2 years of follow-up. Contrast-enhanced CT angiography provides different but complementary information on structural bioprosthetic valve degeneration focusing on the presence of anatomical valve changes including pannus, leaflet calcification, and thrombus.[16,29] Again, no differences in bioprosthetic CT abnormalities were observed across the tertiles of serum Lp(a) concentrations. Finally, we investigated calcification activity in the bioprosthetic valve leaflets using 18F-NaF PET.[30] We have recently demonstrated that 18F-NaF PET provides more sensitive detection of structural valve degeneration than echocardiography and CT as well as a more powerful prediction of subsequent deterioration in bioprosthetic valve function.[5,6] However, once again we found no association between serum Lp(a) concentrations and 18F-NaF PET uptake in the valves. The lack of association between Lp(a) and these imaging assessments of structural valve degeneration remained true whether we considered Lp(a) across tertiles, as a continuous variable or using thresholds of either 50 or 70 mg/dL. It was also consistent with our clinical outcome data, where we failed to demonstrate an association between serum Lp(a) concentration and the development of clinically defined structural valve degeneration or bioprosthetic valve failure. In totality, our clinical and multimodality imaging data suggest that Lp(a) is not an important mediator in the development of structural bioprosthetic valve degeneration.

In 'native' aortic valves, Lp(a) has been widely accepted as a causal factor in mediating aortic valve stenosis, attested by both mendelian randomization as well as epidemiological studies.[7,31,32] Previous studies have also suggested Lp(a) concentrations are associated with faster disease progression on echocardiography and CT[9,11] and increased calcification activity assessed by 18F-NaF PET,[9,10] although one recent study found no association between Lp(a) and 18F-NaF uptake.[14] In totality, our study here indicates important differences between the pathophysiology of aortic stenosis and bioprosthetic valve degeneration.

Further research is now required to improve our understanding of the pathophysiology of bioprosthetic valve degeneration so that treatments prolonging valve durability can be developed. Other lipid-mediated inflammatory pathways beyond Lp(a) may contribute, with several studies indicating cholesterol fractions, the ratio between apolipoprotein B and apolipoprotein A-I (ApoB/ApoA-I), the ratio between oxidized low-density lipoprotein and high-density lipoprotein (OxLDL/HDL) as well as proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations may serve as predictors of bioprosthetic degeneration.[33,34] Other factors may include dysregulation of calcium-phosphate metabolism and increased valvular mechanical stress,[35] as well as, pathways involving immune rejection. The latter is supported by the increase in circulating antibodies against galactose-α1,3-galactose (αGal) and *N*-glycolylneuraminic acid (Neu5Gc) observed after valve implantation and their link with the calcification process.[36–38] Leaflet thrombosis, which can be subclinical, is another potential trigger for inflammation, calcification, and subsequent valve degeneration.[5] Such thrombosis can be detected via hypoattenuated leaflet thickening on CT and with even greater sensitivity using 18F-GP1 PET-CT. Both imaging techniques hold promise in improving our understanding of the role of leaflet thrombosis in prosthetic valve degeneration.[39,40]

Study limitations

Whilst our study is extensively phenotyped, the sample size is relatively modest, conferring the risk of a type II error. Furthermore, our study is a single-centre study comprising largely Caucasian, elderly participants. In particular, the number of patients with a TAVI valve is too small for individual subgroup analysis. Our findings should therefore be confirmed in larger and more diverse patient populations, given the emergence of new drugs targeting Lp(a) concentrations and their potential benefit in various pathologies. Studies with longer follow-up would also be welcome, some later follow-up visits in this study were not possible because of restrictions due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

In conclusion, we have demonstrated that serum Lp(a) concentrations were not associated with imaging or clinical markers of bioprosthetic aortic valve degeneration at baseline or over 24 months of follow-up. Alternative mechanisms involved in the pathogenesis of structural bioprosthetic valve degeneration need to be investigated in order to improve our understanding of this disease and to accelerate the development of novel treatments to prevent or inhibit its progression.

Supplementary material

Supplementary materials are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

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

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