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ORIGINAL PAPER

Lipoprotein(a) and long-term structural valve degeneration of aortic bioprostheses

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Aims

Structural valve degeneration (SVD) is the leading cause of late bioprosthetic valve failure. Lipoprotein(a) [Lp(a)] contributes to native aortic valve calcification, but its role in SVD is unclear. We investigated whether elevated Lp(a) is associated with SVD after bioprosthetic aortic valve replacement (AVR) and whether this differs between stenotic and regurgitant phenotypes.

Methods and results

We studied 174 bioprosthetic AVR patients with available Lp(a) levels over a median echocardiographic follow-up of 7.3 years (1372 studies). SVD was defined by VARC-3 criteria, and associations were analysed with Fine–Gray competing risk models. Lp(a) was evaluated categorically (≤ or > 125 nmol/L) and continuously using spline modelling. During follow-up, 40 patients developed SVD (22 stenotic, 9 mixed, and 9 regurgitant). The 15-year cumulative incidence was 51% with a median onset at 14.8 years. Elevated Lp(a) was associated with a higher risk of overall SVD (62% vs. 47%; SHR 2.06, 95% CI 1.09–3.91; $P = 0.026$) and specifically with stenotic/mixed phenotypes (SHR 2.57, 95% CI 1.26–5.23; $P = 0.009$). No association was observed with regurgitant phenotypes (SHR 0.85, 95% CI 0.19–3.92; $P = 0.84$). After multivariable adjustment, elevated Lp(a) remained an independent predictor of stenotic/mixed SVD (adjusted SHR 3.00, 95% CI 1.48–6.07; $P = 0.002$). Spline modelling showed a linear dose–response, with each 25 nmol/L increase in Lp(a) conferring 13% higher risk.

Conclusion

Elevated Lp(a) is independently associated with long-term risk of stenotic/mixed SVD. These findings highlight Lp(a) as a promising biomarker of prosthetic valve vulnerability and support investigation of emerging Lp(a)-lowering therapies to improve valve durability.

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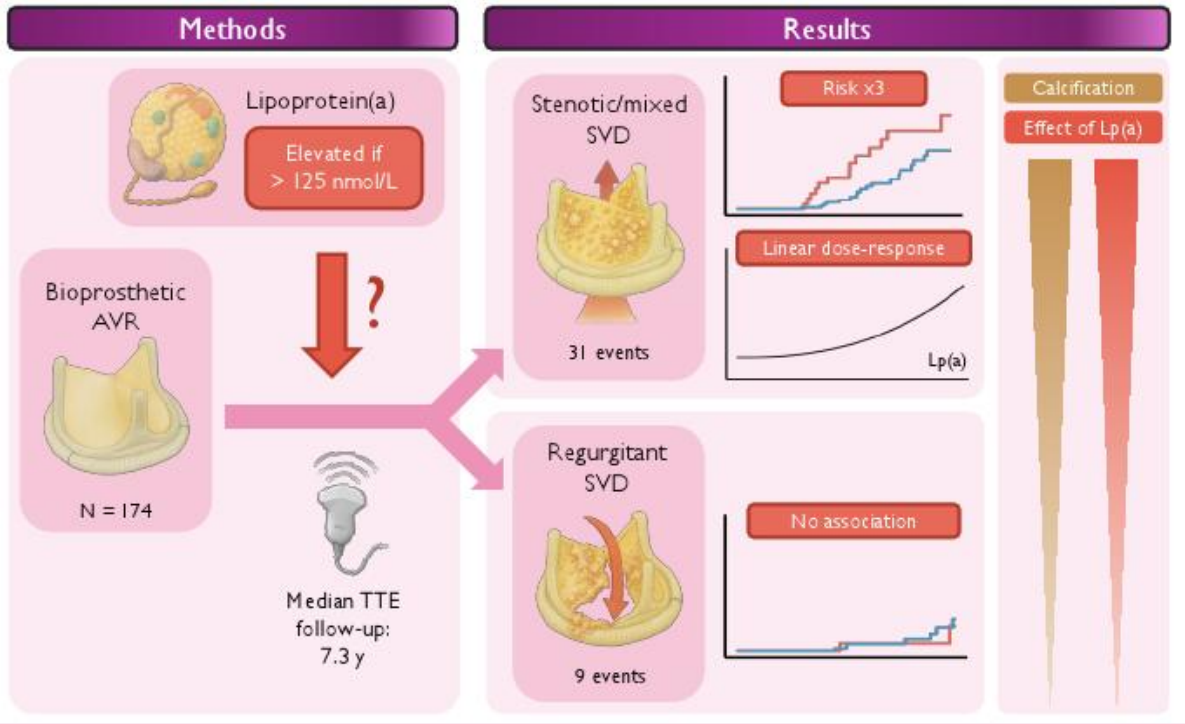
Graphical Abstract



Elevated Lp(a) and phenotype-specific risk of bioprosthetic valve degeneration. In this study of bioprosthetic aortic valve replacement recipients with long-term transthoracic echocardiographic (TTE) follow-up, elevated lipoprotein(a) [Lp(a)] was independently associated with an increased risk of stenotic/mixed structural valve degeneration (SVD), with a linear dose–response but showed no association with isolated regurgitant degeneration. These findings highlight Lp(a) as a promising biomarker of bioprosthetic valve vulnerability, particularly for calcification-driven forms of degeneration

Keywords prosthesis failure • echocardiography • biomarkers • competing risk analysis • spline modelling

Introduction

Bioprosthetic heart valves now represent the majority of aortic valve replacements (AVRs), with growing use in middle-aged patients expected to live for decades.[1–4] As a result, long-term structural durability has become a critical concern. Structural valve degeneration (SVD), characterized by leaflet calcification, tearing, and hemodynamic deterioration, is the leading cause of late bioprosthetic failure.[5] Established contributors include younger age, traditional cardiovascular risk factors, and prosthesis-related issues such as patient–prosthesis mismatch.[6] Recent studies have explored circulating biomarkers, particularly lipid-related ones, as tools to refine SVD risk prediction.[7]

Among these, lipoprotein(a) [Lp(a)] is a biologically plausible candidate. It plays a causal role in native aortic valve stenosis via inflammation, oxidative stress, and mineralization—processes that also contribute to SVD.[8] Yet, extrapolation is complicated by differences in timing and mechanism: SVD evolves over a shorter period and also involves bioprosthesis-specific factors such as structural fatigue and passive leaflet calcification.

Only a handful of studies have assessed the relationship between Lp(a) and SVD, with inconsistent results.[9–13] These discrepancies likely reflect the methodological challenges of studying SVD, which emerges over a decade and is sometimes pre-empted by death or non-SVD re-intervention. Addressing this question requires extended follow-up and analytical methods that account for these competing risks.

Clarifying the role of Lp(a) in SVD is increasingly relevant, as Lp(a)-lowering agents such as pelacarsen and olpasiran enter late-stage cardiovascular trials and may reach clinical practice within a few years.[14] Should a causal relationship be confirmed, Lp(a) could become a modifiable determinant of bioprosthetic valve durability.

In this study, we investigated whether elevated Lp(a) is independently associated with SVD following bioprosthetic AVR. We further hypothesized that Lp(a) might differentially influence stenotic vs. regurgitant SVD phenotypes, reflecting potentially distinct pathophysiological mechanisms.

Methods

Study design and population

This retrospective, single-centre study screened 3293 consecutive patients who underwent bioprosthetic AVR between 2001 and 2021. Of these, 174 patients had Lp(a) measured during routine follow-up and comprised the analytic cohort, after exclusion of three patients on chronic renal replacement therapy (see Supplementary data online, *Figure S1*). The primary objective was to evaluate whether elevated Lp(a) is independently associated with the risk of SVD after bioprosthetic AVR. The study was approved by the institutional review board.

Lp(a) assessment

Lp(a) was measured using an isoform-insensitive immunoturbidimetric assay [Roche Tina-quant® Lipoprotein(a) Gen.2, Roche Diagnostics,

Mannheim, Germany], which reports concentrations in molar units (nmol/L). This approach aligns with the current consensus recommending molar reporting to minimize bias from apo(a) size variation.[8] Values were obtained as part of routine clinical care, typically for cardiovascular risk assessment, at the discretion of the treating physician. Lp(a) sampling occurred a median of 1 day before surgery [interquartile range (IQR) −64 to +3632 days]. Because ∼90% of an individual's Lp(a) level is genetically determined and remains highly stable over decades, each measurement was considered representative of the patient's chronic Lp(a) exposure, independent of sampling date.[15,16] For dichotomized analyses, a cutoff of 125 nmol/L was applied, in accordance with current guidelines.[8,17]

Echocardiography and SVD definition

Transthoracic echocardiography (TTE) was performed using iE33 or EPIQ scanners (Philips Healthcare, Best, the Netherlands) by experienced operators. A post-operative TTE performed within 3 months of AVR served as the baseline reference for subsequent comparisons. Follow-up TTEs were obtained as part of routine clinical care, with frequency and timing determined by treating physicians. In total, 1372 TTEs were analysed (median 7 per patient; IQR 3–12). Measurements conformed to current guidelines and were obtained in sinus rhythm or averaged over three cardiac cycles in patients with atrial fibrillation. Parameters included mean transprosthetic gradient, effective orifice area (EOA), and Doppler velocity index (DVI); the latter two were measured when the mean gradient exceeded 20 mmHg. Prosthetic regurgitation was graded semi-quantitatively in accordance with guidelines.[18] Prosthesis–patient mismatch was defined as recommended by current consensus, using BMI-adjusted thresholds and the predicted indexed effective orifice area (EOAi) rather than measured EOAi, to minimize variability from transient haemodynamics and operator dependence.[19]

SVD was defined according to Valve Academic Research Consortium 3 (VARC-3) criteria, for events of moderate or greater severity:[5]

- Stenotic phenotype: increase in mean gradient ≥10 mmHg to a value ≥20 mmHg with ≥25% fall in EOA (≥0.3 cm^2) *or* ≥20% fall in DVI (≥0.10).
- Regurgitant phenotype: new or worsening intra-prosthetic regurgitation by ≥1 grade to at least moderate severity.
- Mixed phenotype: both criteria met.
- Overall SVD: first occurrence of stenotic and/or regurgitant phenotype.

The endpoint of the study was overall SVD. For phenotype-specific analyses, stenotic and regurgitant phenotypes were examined separately, with mixed phenotypes grouped with the stenotic category to avoid double counting of events. All cases meeting VARC-3 criteria were reviewed in consensus by two senior echocardiographers, and echocardiographic changes attributable to alternative causes (paravalvular leak, endocarditis, or leaflet thrombosis) were systematically excluded based on echocardiographic and clinical findings.

Clinical data and follow-up

Baseline clinical characteristics were recorded at the time of surgery. Follow-up information was retrieved from institutional electronic records and cross-checked with national health registries. Vital status was verified for every patient. Survivors without SVD were censored at the date of last echocardiographic contact. Death (all-cause) and redo AVR for other causes acted as competing events.

Statistical analysis

Continuous variables were summarized as mean ± SD or median [IQR] and categorical variables as counts and percentages. Between-group comparisons used Welch's *t*-test, Wilcoxon rank sum test, Pearson's chi-squared test, or Fisher's exact test as appropriate. Given the competing risk of death or redo AVR for non-SVD causes, cumulative incidence of SVD was assessed with Fine–Gray subdistribution hazard models (*cmprsk* package v2.2), truncated at 15 years when <10% of patients remained at risk. Candidate predictors of valve failure were selected based on prior literature: age, sex, body surface area, hypertension, smoking, diabetes, LDL cholesterol, chronic kidney disease, and prosthesis–patient mismatch.[6] All were included in a full multivariable model, with a parsimonious model derived by backward selection using the Akaike Information Criterion. To assess model stability, we performed bootstrap internal validation ($B = 2000$) of the full multivariable Fine–Gray model, applying the optimism-corrected calibration slope as a global shrinkage factor. We also explored penalized Fine–Gray regression (LASSO; *fastcmprsk* package v1.24.10) including the same covariates. To examine continuous associations, Lp(a) was modelled using a natural spline within a Fine–Gray competing risk model, with bootstrapped 95% confidence intervals. A Cox proportional hazards model using a restricted cubic spline (*rms* package v8.0) was also fitted for comparison. Finally, we performed a time-matched nested case–control analysis. Each SVD case was matched to up to two controls with similar follow-up duration (±6 months) using nearest-neighbour matching based on Mahalanobis distance (*MatchIt* package v4.7.2). Analyses were also stratified by sex to explore potential effect modification. All analyses were conducted using R version 4.5.0. Statistical significance was set at a two-sided $P < 0.05$.

Results

Baseline characteristics and follow-up

We included 174 patients (mean age 72.6 ± 7.9 years; 36% female), of whom 133 (76%) had Lp(a) ≤ 125 nmol/L and 41 (24%) had Lp(a) > 125 nmol/L (*Figure 1A*). Baseline characteristics (*Table 1*) were well balanced between groups, except for a higher prevalence of coronary artery disease in the high Lp(a) group (51.2% vs. 33.1%; $P = 0.036$). Median echocardiographic follow-up was 7.3 years (IQR 4.5–10.9), with comparable durations in the low- and high-Lp(a) groups (7.3 vs. 7.2 years; $P = 0.840$). During follow-up, 40 patients developed SVD: 22 with a stenotic phenotype, 9 with a mixed (stenotic + regurgitant) phenotype, and 9 with an isolated regurgitant phenotype. The 15-year cumulative incidence of overall SVD was 51.0% (95% CI 38.1–62.5), with a median time to onset of 14.8 years (*Figure 1B*). Competing events (28 deaths and 3 redo AVRs for endocarditis) occurred in 31 patients, corresponding to a 15-year cumulative incidence of 22.7%, with no significant difference between Lp(a) groups ($P = 0.806$).

Association of lp(a) by SVD phenotype

By 15 years, elevated Lp(a) was associated with a higher cumulative incidence of overall SVD [62% vs. 47% for lower Lp(a); Gray's test $P = 0.030$], with divergence between groups apparent by 10 years (37% vs. 18%; *Figure 2A*). Corresponding 10- and 15-year cumulative incidences for stenotic/mixed and regurgitant SVD phenotypes are shown in *Figure 2B* and *C*. In univariable Fine–Gray competing risk analysis, elevated Lp(a) (>125 nmol/L) was associated with a twofold higher risk of overall SVD [subdistribution hazard ratio (SHR) 2.06, 95% CI 1.09–3.91; $P = 0.026$]. When phenotypes were analysed separately, this association was evident for stenotic/mixed SVD (SHR 2.57, 95% CI 1.26–5.23; $P = 0.009$) but no association was observed for regurgitant SVD (SHR 0.85, 95% CI 0.19–3.92; $P = 0.84$). Cumulative incidence curves were concordant, with clear separation between Lp(a) groups for stenotic/mixed SVD but not for regurgitant cases. In multivariable Fine–Gray models restricted to the stenotic/mixed SVD endpoint (*Table 2*), elevated Lp(a) remained an independent predictor (adjusted SHR 3.05, 95% CI 1.41–6.61; $P = 0.005$) in the full model including all predefined covariates. In the parsimonious model, only elevated Lp(a) (adjusted SHR 3.00, 95% CI 1.48–6.07; $P = 0.002$) and diabetes (adjusted SHR 2.68, 95% CI 1.30–5.55; $P = 0.008$) were retained as

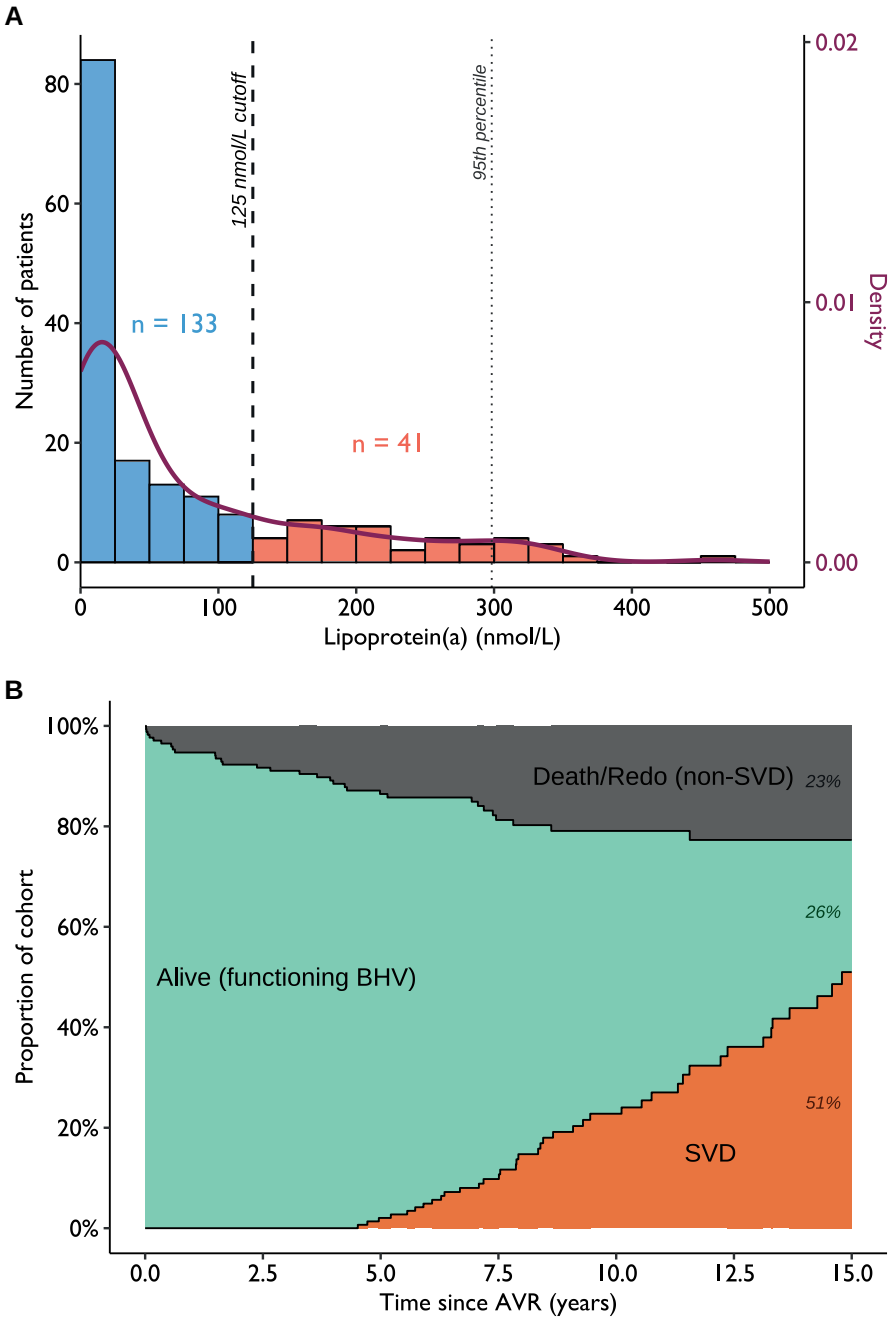


Figure 1 Baseline distribution of Lp(a) and competing event dynamics. (*A*) Histogram of lipoprotein(a) [Lp(a)] values in the cohort ($n = 174$) with overlaid kernel density curve. Patients are stratified by Lp(a) ≤ 125 nmol/L and >125 nmol/L (23% of the cohort). (*B*) Event distribution and competing risks over time. Stacked areas depict the cumulative incidence of structural valve degeneration (SVD) and competing events (death or redo for endocarditis), while the remaining area represents patients with functioning bioprostheses still at risk.

significant covariates. Bootstrap calibration confirmed that the association between elevated Lp(a) and stenotic/mixed SVD was robust, suggesting it was not driven by statistical overfitting (see Supplementary data online, *Table S2*). Penalized Fine–Gray regression likewise supported this finding, retaining Lp(a) and diabetes as predictors. The association between Lp(a) and stenotic/mixed SVD remained consistent when restricted to samples obtained before or within 12 months after AVR (SHR 2.77, 95% CI 1.10–6.96; $P = 0.030$).

Lp(a) as a continuous predictor

When modelled as a continuous variable, each 25 nmol/L increment in Lp(a) conferred a 13% increase in the risk of stenotic/mixed SVD (SHR 1.13 per 25 nmol/L; 95% CI 1.05–1.22; $P = 0.002$). Results were consistent when Lp(a) was analysed on a log-transformed scale (SHR 1.39 per log-unit; $P = 0.024$). Spline analysis in the Fine–Gray model revealed an approximately linear dose–response, with no significant

Table 1 Baseline characteristics by Lp(a) group

Characteristic	*n*	Overall *n* = 174	Low Lp(a) *n* = 133	High Lp(a) *n* = 41	*P*-value
Lp(a) concentration (nmol/L)	174	32.9 (10.0—117.4)	15.4 (8.4—47.8)	223.8 (175.0—291.0)	**<0.001**
Baseline characteristics					
Age (years)	174	72.6 ± 7.9	72.6 ± 8.0	72.8 ± 7.5	0.880
Male	174	112 (64.4%)	90 (67.7%)	22 (53.7%)	0.101
Body surface area (m^2)	174	1.88 ± 0.19	1.89 ± 0.18	1.86 ± 0.19	0.369
Body mass index (kg/m^2)	174	27.3 ± 4.6	27.3 ± 4.7	27.3 ± 4.4	0.993
Medical history					
Hypertension	174	125 (71.8%)	92 (69.2%)	33 (80.5%)	0.159
Smoking	174	78 (44.8%)	59 (44.4%)	19 (46.3%)	0.824
Diabetes	174	39 (22.4%)	31 (23.3%)	8 (19.5%)	0.610
Coronary artery disease	174	65 (37.4%)	44 (33.1%)	21 (51.2%)	**0.036**
Extracardiac arteriopathy	174	30 (17.2%)	21 (15.8%)	9 (22.0%)	0.361
Chronic kidney disease	174	48 (27.6%)	35 (26.3%)	13 (31.7%)	0.499
GFR ($mL/min/1.73m^2$)	174	70.0 ± 17.7	70.0 ± 17.8	69.9 ± 17.5	0.966
LDL cholesterol (mg/dL)	174	87.8 ± 33.8	86.7 ± 34.6	91.2 ± 31.2	0.440
Postoperative haemodynamics					
True internal diameter	174	22.5 ± 2.3	22.7 ± 2.3	21.6 ± 2.2	**0.004**
Projected EOAi (cm^2/m^2)	174	1.02 ± 0.17	1.03 ± 0.17	0.98 ± 0.16	0.060
Projected patient-prosthesis mismatch	174				>0.999
None		154 (88.5%)	118 (88.7%)	36 (87.8%)	
Moderate		20 (11.5%)	15 (11.3%)	5 (12.2%)	
Severe		0 (0.0%)	0 (0.0%)	0 (0.0%)	
Type of valve	174				0.074
Bovine stented		108 (62.1%)	76 (57.1%)	32 (78.0%)	
Porcine stented		17 (9.8%)	16 (12.0%)	1 (2.4%)	
TAVR		19 (10.9%)	17 (12.8%)	2 (4.9%)	
Sutureless or stentless		30 (17.2%)	24 (18.0%)	6 (14.6%)	
Postoperative mean gradient (mmHg)	174	9.6 ± 4.5	9.3 ± 4.7	10.4 ± 4.0	0.147
Postoperative LVEF (%)	174	64.6 ± 12.7	64.2 ± 12.8	65.9 ± 12.2	0.456
Timing and follow-up					
Year of intervention	174	2015 (2013—2017)	2015 (2013—2016)	2016 (2013—2017)	0.623
Length of echocardiographic follow-up (years)	174	7.3 (4.5—10.9)	7.3 (4.5—10.9)	7.2 (5.0—10.6)	0.807

Values are mean ± SD or median (IQR) for continuous variables and *n* (%) for categorical variables; high vs. low Lp(a) levels were defined using a threshold of >125 vs. ≤125 nmol/L; GFR was estimated using the CKD-EPI equation; EOAi and TID were derived from manufacturer-labelled orifice areas and dimensions. Nominal valve sizes are presented in Supplementary data online, *Table S1* for reference but are not directly comparable across manufacturers.
EOAi, indexed effective orifice area; GFR, glomerular filtration rate; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LVEF, left ventricular ejection fraction; TAVR, transcatheter aortic valve replacement; TID, true internal diameter.

evidence of non-linearity ($P = 0.76$; *Figure 3*). A Cox model using a restricted cubic spline produced a similar shape (see Supplementary data online, *Figure S2*), supporting the consistency of the association across modelling frameworks.

Sensitivity analysis

In the nested case–control study (31 cases, 62 matched controls), cases and controls were matched on follow-up time (maximum 6-month difference), resulting in comparable echocardiographic follow-up (mean 8.6 ± 2.7 years in both groups; $P = 0.912$). Patients with stenotic/mixed SVD had higher Lp(a) levels than controls (median 93.3 vs. 23.6 nmol/L, $P = 0.012$) and more often exceeded the 125 nmol/L threshold (41.9% vs. 19.4%, $P = 0.021$; Supplementary data online, *Table S3*). Other baseline characteristics were similar between groups. Elevated Lp(a) (>125 nmol/L) conferred threefold higher odds of SVD (OR 3.04, 95% CI 1.12–8.28; $P = 0.029$), and each 25 nmol/L increment was associated with a 16% higher odds (OR 1.16, 95% CI 1.03–1.29; $P = 0.013$).

Exploratory sex-stratified analyses

In analyses stratified by sex, elevated Lp(a) was associated with a higher risk of stenotic/mixed SVD in men (SHR 4.22, 95% CI 1.66–10.8; $P = 0.003$; *Figure 4A*), whereas the association was weaker among women and not statistically significant (SHR 1.48, 95% CI 0.49–4.47; $P = 0.50$;

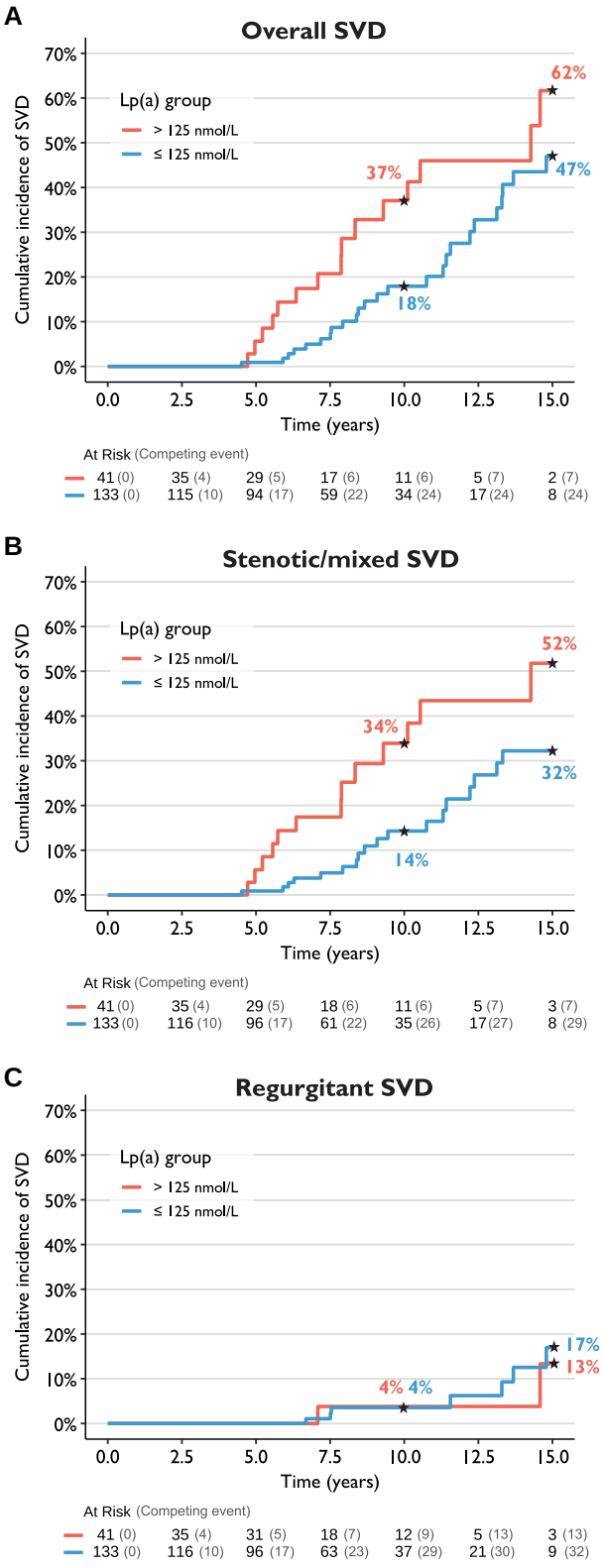


Figure 2 Cumulative incidence of SVD by phenotype and Lp(a) group. Fine–Gray competing risk curves stratified by lipoprotein(a) [Lp(a)] group (≤125 nmol/L vs. >125 nmol/L) for (*A*) overall, (*B*) stenotic/mixed, and (*C*) regurgitant structural valve degeneration (SVD). Numbers at risk and competing events are displayed beneath each panel. Ten- and 15-year cumulative incidences are annotated on the curves. Gray's test *P*-values are indicated within each panel.

Table 2 Predictors of stenotic/mixed SVD after bioprosthetic AVR

		Univariate estimates			Full multivariable model (AIC = 267.5)			Parsimonious multivariable model (AIC = 259)		
Characteristic	***n***	**SHR**	**95% CI**	***P*-value**	**aSHR**	**95% CI**	***P*-value**	**aSHR**	**95% CI**	***P*-value**
Lp(a) group	174									
≤ 125 nmol/L		—	—		—	—		—	—	
> 125 nmol/L		2.57	1.26, 5.23	**0.009**	3.05	1.41, 6.61	**0.005**	3.00	1.48, 6.07	**0.002**
Age (per 10 years)	174	0.75	0.51, 1.11	0.15	0.79	0.47, 1.31	0.4			
Male	174	0.71	0.36, 1.41	0.33	0.72	0.27, 1.94	0.5			
Body surface area (per 0.1 m^2)	174	0.98	0.84, 1.14	0.79	0.97	0.76, 1.24	0.8			
Hypertension	174	1.99	0.85, 4.70	0.11	1.90	0.71, 5.09	0.2			
Smoking	174	0.89	0.44, 1.80	0.75	0.74	0.33, 1.63	0.5			
Diabetes	174	2.23	1.08, 4.62	**0.030**	2.39	1.12, 5.11	**0.024**	2.68	1.30, 5.55	**0.008**
Chronic kidney disease	174	0.75	0.33, 1.73	0.50	0.76	0.32, 1.81	0.5			
LDL cholesterol (per 10 mg/dL)	174	0.91	0.79, 1.03	0.14	0.96	0.83, 1.12	0.6			
Patient-prosthesis mismatch	174	0.44	0.11, 1.76	0.24	0.54	0.13, 2.14	0.4			

Risk estimates are from Fine–Gray competing-risk models accounting for death and valve reintervention. The 'full model' included all prespecified covariates; the 'parsimonious model' was selected via stepwise regression, minimizing the Akaike Information Criterion (AIC). Bold values indicate $P < 0.05$.
aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; SHR, subdistribution hazard ratio; other abbreviations as in *Table 1*.

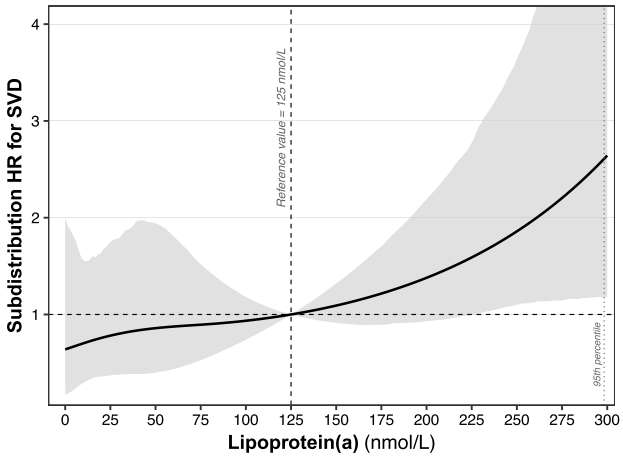


Figure 3 Continuous association between Lp(a) concentration and risk of stenotic/mixed SVD (Fine–Gray model). A natural spline (3 degrees of freedom) was fitted in a Fine–Gray competing risk model. The curve depicts the estimated subdistribution hazard ratio (SHR) for stenotic/mixed structural valve degeneration (SVD) across the observed range of lipoprotein(a) [Lp(a)], relative to the reference value of 125 nmol/L (vertical dashed line). Shaded bands represent bootstrapped 95% confidence intervals ($B = 2000$). The relationship was approximately linear, with no significant evidence of non-linearity ($P = 0.761$).

Figure 4B). The interaction term did not reach statistical significance (interaction SHR 2.96, 95% CI 0.68–12.9; $P = 0.20$).

Discussion

In this retrospective cohort study with a median echocardiographic follow-up exceeding 7 years, elevated Lp(a) concentrations were independently associated with an approximately three-fold higher risk of stenotic and mixed SVD phenotypes. No association was observed with isolated regurgitant degeneration, although precision was limited by only nine events. Dose–response analyses supported a largely monotonic relationship between Lp(a) levels and SVD risk. Findings were consistent in a time-matched nested case–control analysis, underscoring the robustness of the association. This work represents the longest longitudinal analysis of Lp(a) and aortic bioprosthetic SVD,

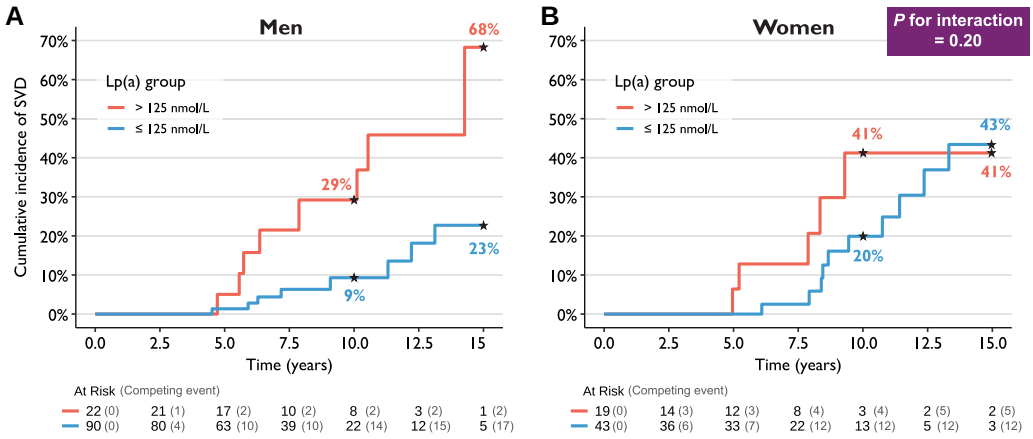


Figure 4 Cumulative incidence of stenotic/mixed SVD by sex and Lp(a) group. Fine–Gray competing risk curves stratified by lipoprotein(a) [Lp(a)] group (≤125 nmol/L vs. >125 nmol/L) in (*A*) men and (*B*) women for stenotic/mixed structural valve degeneration (SVD). Numbers at risk and competing events are displayed beneath each panel. Ten- and 15-year cumulative incidences are annotated on the curves. *P* for interaction = 0.20.

and the first to distinguish between stenotic, regurgitant, and mixed phenotypes. Among previously identified risk factors for SVD, diabetes also emerged in our cohort as an independent predictor of stenotic/mixed degeneration. This finding is consistent with prior studies reporting that diabetes accelerates bioprosthetic valve failure.[9,20] Hyperglycaemia and the associated dysmetabolic environment may promote leaflet calcification through endothelial dysfunction, oxidative stress, lipid retention, glycation, and inflammatory pathways.[21]

Prior investigations into Lp(a) and bioprosthetic degeneration have yielded heterogeneous findings, broadly falling into three categories: two prospective cohorts reported neutral associations, two retrospective series observed higher SVD risk with elevated Lp(a), and one study identified a genetic signal related to apo(a) isoform size (see Supplementary data online, *Tables S4* and *S5*).[9–13] Because SVD often emerges only after 10–15 years and encompasses heterogeneous phenotypes, variation in follow-up duration and endpoint definitions across studies likely contributed to the divergent findings.[6] In addition, studies of aortic SVD are inherently prone to index-event (collider) bias, since inclusion occurs only after AVR, an event itself strongly influenced by Lp(a).[22] Such bias tends to attenuate or even mask true associations and is especially pronounced in cohorts enrolling patients several years after AVR (see Supplementary data online, *Figure S3*). Retrospective designs, while still vulnerable to residual confounding, start follow-up at the time of AVR and provide the extended observation window required to meaningfully assess long-term SVD. Because such timelines are rarely feasible in prospective cohorts, retrospective analyses represent a valuable and complementary approach for studying SVD.

The observed pattern with stenotic and mixed SVD fits a biologically coherent framework. In native calcific aortic valve disease, Lp(a) carries oxidized phospholipids and activates pro-inflammatory and osteogenic signalling, thereby promoting fibro-calcific remodelling.[8] Such pathways align with stenotic and mixed phenotypes, which typically display progressive leaflet thickening and restriction, whereas isolated regurgitant degeneration more often reflects non-calcific structural fatigue (leaflet tears or perforations) with abrupt presentation.[6,18] Extrapolation from native valves must, however, be tempered by the distinct biology of bioprosthetic tissue: xenografts lack viable interstitial cells (key mediators of inflammatory and osteogenic responses), are exposed to residual immune-mediated injury, and can undergo passive calcification of glutaraldehyde-treated leaflets.[23] In addition, SVD typically develops within 10–15 years of implantation, a far shorter timeline than the decades-long exposure implicated in native valve disease.[6] Taken together, these considerations suggest that while Lp(a) may contribute to calcific forms of SVD, it likely acts as one element within a multifactorial pathological cascade.

Finally, sex-related differences may further influence the impact of Lp(a) on calcific degeneration. In native aortic stenosis, men tend to accumulate greater valve calcium burden, whereas women often reach comparable hemodynamic severity with less calcium and a relatively larger fibrotic component.[24] In that context, a pro-calcific Lp(a) effect would be expected to weigh more heavily in men. Our sex-stratified analyses were directionally consistent with this hypothesis, but small numbers preclude firm conclusions and render the findings exploratory. Clarifying these mechanistic aspects, including potential sex-specific modulation, will require dedicated studies of bioprosthetic valve pathology and molecular remodelling.

Clinical implications

Lp(a) emerges as a promising biomarker for predicting SVD. Its practical advantages—including broad assay availability, long-term biological stability, and minimal sensitivity to fasting or systemic inflammation—make it especially well-suited for clinical use.[25] Elevated Lp(a) is relatively frequent in patients with aortic stenosis, with contemporary studies reporting a prevalence of around one in four.[26] This underscores the existence of a sizable subgroup readily identifiable by a single assay. If validated in larger, prospective cohorts, Lp(a) measurement could complement established predictors to guide prosthesis selection, particularly in younger patients in whom durability is a critical concern. It could also help calibrate follow-up intensity, for instance, by shortening echocardiographic surveillance intervals when Lp(a) is elevated. Looking ahead, several Lp(a)-lowering therapies, including pelacarsen and olpasiran, have shown substantial, sustained reductions in circulating Lp(a) and are now in phase III trials.[27,28] Although these are currently focused on atherosclerotic outcomes (Lp(a)HORIZON, OCEAN[a]), our findings support investigating whether such therapies could improve long-term valve durability in dedicated studies.[14] Ultimately, any clinical role for Lp(a)-lowering therapies will need to be considered within the multifactorial pathogenesis of SVD.

Study limitations

This study has several limitations. First, its retrospective, single-centre design may limit generalizability. However, prospective trials designed to capture long-term SVD outcomes face major logistical constraints due to the extended follow-up required. Second, Lp(a) testing was not performed systematically but at the discretion of treating physicians, raising the possibility of selection bias. Compared with the overall AVR population, the included patients were somewhat younger, with fewer comorbidities and more frequent implantation in later eras (see Supplementary data online, *Table S6*). While these limits representativeness, it is unlikely to explain the observed association between Lp(a) and SVD. Third, Lp(a) measurements were obtained at variable time points, but this is unlikely to have affected the results because Lp(a) concentrations are strongly genetically determined and highly stable over time. Notably, the association with stenotic/mixed SVD persisted when restricted to measurements obtained before or within 12 months after AVR, supporting the robustness of our conclusions. Finally, the analysis of isolated regurgitant SVD was limited by the small number of events, and sex-specific results remain underpowered given the smaller female subgroup. Both findings should therefore be considered exploratory. These limitations highlight the need for external validation in larger, multi-centre studies.

Conclusion

Elevated Lp(a) levels were independently associated with a higher long-term risk of stenotic and mixed SVD after bioprosthetic AVR, whereas no association was observed with isolated regurgitant degeneration. This phenotype-specific pattern suggests that Lp(a) may contribute predominantly to calcification-driven prosthetic valve failure. If confirmed in larger, multi-centre cohorts, a single Lp(a) measurement could refine SVD risk stratification and help tailor follow-up strategies. As the use of bioprosthetic valves continues to rise, dedicated studies represent a key next step to establish whether emerging Lp(a)-lowering therapies can translate into improved valve durability.

Supplementary data

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

Author contributions

Marin Boute (Conceptualization [supporting]; Data curation [lead]; Formal analysis [lead]; Investigation [equal]; Methodology [equal]; Software [lead]; Visualization [lead]; Writing—original draft [lead]; Writing—review and editing [supporting]), Paul Salembier (Data curation [supporting]; Methodology [supporting]; Software [supporting]; Writing—review and editing [supporting]), Anne-Catherine Pouleur (Conceptualization [supporting]; Investigation [supporting]; Methodology [supporting]; Resources [equal]; Supervision [supporting]; Writing—review and editing [supporting]), Agnès Pasquet (Investigation [supporting]; Methodology [supporting]; Supervision [supporting]; Writing—review and editing [supporting]), Bernhard L Gerber (Investigation [supporting]; Methodology [supporting]; Resources [supporting]; Writing—review and editing [supporting]), David De Azevedo (Formal analysis [supporting]; Methodology [supporting]; Software [supporting]; Validation [supporting]; Writing—review and editing [supporting]), Damien Gruson (Data curation [supporting]; Resources [supporting]; Writing—review and editing [supporting]), Laurent de Kerchove (Data curation [supporting]; Resources [supporting]; Writing—review and editing [supporting]), Joelle Kefer (Data curation [supporting]; Resources [supporting]; Writing—review and editing [supporting]), Christophe Beauloye (Investigation [supporting]; Methodology [supporting]; Writing—review and editing [supporting]), Sandrine Horman (Conceptualization [supporting]; Investigation [supporting]; Methodology [supporting]; Writing—review and editing [supporting]), Frédéric Maes (Data curation [supporting]; Resources [supporting]; Writing—review and editing [supporting]), Sophie Pierard (Data curation [supporting]; Investigation [supporting]; Methodology [supporting]; Resources [supporting]; Writing—review and editing [supporting]), and David Vancraeynest (Conceptualization [lead]; Funding acquisition [supporting]; Investigation [supporting]; Methodology [supporting]; Project administration [supporting]; Supervision [equal]; Validation [supporting]; Writing—original draft [supporting]; Writing—review and editing [lead])

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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