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ORIGINAL INVESTIGATIONS

Hemodynamic Deterioration of Surgically Implanted Bioprosthetic Aortic Valves

Erwan Salaun, MD,[a,b] Haïfa Mahjoub, MD, PhD,[a] Abdellaziz Dahou, MD, PhD,[a] Patrick Mathieu, MD, MSc,[a] Éric Larose, MD, MSc,[a] Jean-Pierre Després, PhD,[a] Josep Rodés-Cabau, MD,[a] Benoit J. Arsenault, PhD,[a] Rishi Puri, MBBS, PhD,[c] Marie-Annick Clavel, DVM, PhD,[a] Philippe Pibarot, DVM, PhD[a]

ABSTRACT

BACKGROUND Dysmetabolic profile has been associated with native aortic valve stenosis. However, there are limited data on the effects of an atherogenic milieu and its potential implications on the structural and hemodynamic deterioration of aortic bioprosthetic valves.

OBJECTIVES This prospective longitudinal study sought to determine the predictors and impact on outcomes of hemodynamic valve deterioration (HVD) of surgically implanted aortic bioprostheses.

METHODS A total of 137 patients with an aortic bioprosthesis implanted for a median time of 6.7 (interquartile range: 5.1 to 9.1) years prospectively underwent a first (baseline) assessment with complete Doppler echocardiography, quantitation of bioprosthesis leaflet calcification by multidetector computed tomography (CT), and a fasting blood sample to assess cardiometabolic risk profile. All patients underwent a second (follow-up) Doppler echocardiography examination at 3 (interquartile range: 2.9 to 3.3) years post-baseline visit. HVD was defined by an annualized change in mean transprosthetic gradient ≥3 mm Hg/year and/or worsening or transprosthetic regurgitation by ≥1/3 class. The primary endpoint was a nonhierarchical composite of death from any cause or aortic reintervention procedure (redo surgical valve replacement or transcatheter valve-in-valve implantation) for bioprosthesis failure.

RESULTS Thirty-four patients (25.6%) had leaflet calcification on baseline CT, and 18 patients (13.1%) developed an HVD between baseline and follow-up echocardiography. Fifty-two patients (38.0%) met the primary endpoint during subsequent follow-up after the second echocardiographic examination. Leaflet calcification (hazard ratio [HR]: 2.58; 95% confidence interval [CI]: 1.35 to 4.82; $p = 0.005$) and HVD (HR: 5.12; 95% CI: 2.57 to 9.71; $p < 0.001$) were independent predictors of the primary endpoint. Leaflet calcification, insulin resistance (homeostatic model assessment index ≥2.7), lipoprotein-associated phospholipase A2 activity (Lp-PLA2 per 0.1 nmol/min/ml increase), and high level of proprotein convertase subtilisin/kexin 9 (PCSK9) (≥305 ng/ml) were associated with the development of HVD after adjusting for age, sex, and time interval since aortic valve replacement.

CONCLUSIONS HVD identified by Doppler echocardiography is independently associated with a marked increase in the risk of valve reintervention or mortality in patients with a surgical aortic bioprosthesis. A dysmetabolic profile characterized by elevated plasma Lp-PLA2, PCSK9, and homeostatic model assessment index was associated with increased risk of HVD. The presence of leaflet calcification as detected by CT was a strong predictor of HVD, providing incremental risk-predictive capacity. (J Am Coll Cardiol 2018;72:241–51) © 2018 by the American College of Cardiology Foundation.

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From the [a]Institut Universitaire de Cardiologie et de Pneumologie de Québec/Québec Heart & Lung Institute, Laval University, Quebec City, Québec, Canada; [b]Centre de Résonance Magnétique Biologique et Médicale (CRMBM), UMR 7339, Centre National de la Recherche Scientifique, Aix-Marseille Université, Marseille, France; and the [c]Cleveland Clinic Coordinating Center for Clinical Research (C5R), Cleveland, Ohio. Dr. Pibarot has received research grants from Edwards Lifesciences and Medtronic for echocardiography core lab analyses in transcatheter aortic valve replacement. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Blase Carabello, MD, served as Guest Editor for this paper.

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ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

CI = confidence interval

CT = computed tomography

HDL = high-density lipoprotein

HOMA = homeostatic model assessment

HR = hazard ratio

HVD = hemodynamic valve deterioration

LDL = low-density lipoprotein

LDLR = low-density lipoprotein receptor

Lp-PLA2 = lipoprotein-associated phospholipase A2

PCSK9 = proprotein convertase subtilisin/kexin 9

Aortic valve disease is the most frequent valvular heart disease and the most frequent cause of valve procedure in high-income countries (1). The prevalence of this disease is expected to increase dramatically in the coming decades due to the aging of the population and increase in the rates of cardiometabolic diseases such as type 2 diabetes (2). Aortic valve replacement (AVR) is indicated when aortic stenosis is severe and symptoms and/or left ventricle systolic dysfunction occur (3). The ratio of bioprostheses versus mechanical valves used for AVR has increased markedly in the past decade. This temporal change is in large part related to: 1) the low thrombogenicity of bioprostheses and the fact that they do not require lifetime anticoagulation; 2) the improvement in valve hemodynamics, particularly in the small bioprosthetic sizes; and 3) the introduction of transcatheter AVR (4,5). However, compared with mechanical prostheses, bioprostheses have a shorter durability with quasi-systematic deterioration within 20 years of implantation (5–7). Most studies have established the rate of bioprosthesis deterioration on the basis of valve reintervention due to bioprosthesis failure (8–10). However, reintervention may underestimate the rate of bioprosthesis degeneration, given that older patients with severe comorbidities may not undergo reintervention despite significant valve deterioration. Several recent studies, recommendations, and position statements propose to define bioprosthesis degeneration upon the basis of valve structural and hemodynamic deterioration assessed by Doppler echocardiography and other imaging modalities (7,11–13).

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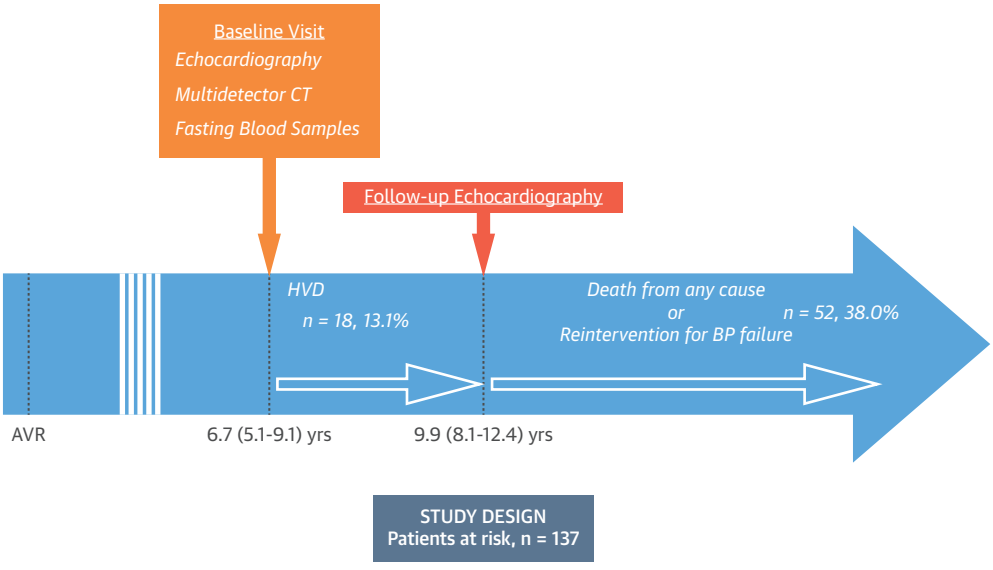
Some retrospective or cross-sectional studies reported that metabolic syndrome (14), lipid-mediated inflammation (11,15,16), and leaflet mineralization assessed by computed tomography (CT) (17,18) were associated with hemodynamic valve deterioration (HVD).

The aim of this prospective longitudinal study was to determine the predictors and impact on outcomes of bioprosthesis HVD following surgical AVR.

METHODS

STUDY POPULATION. Two hundred and three patients who underwent isolated (except coronary artery bypass grafting) bioprosthetic AVR with at least 3 years of follow-up were prospectively recruited in the study. The population characteristics and methods of this study have been previously reported (11). Briefly, Doppler echocardiography, multislice CT examination, and blood sample analyses were

FIGURE 1 Study Design and Follow-Up



AVR = aortic valve replacement; BP = bioprosthetic; CT = computed tomography; HVD = hemodynamic valve deterioration.

prospectively performed at the "baseline" visit. One hundred and thirty-seven of the 203 patients were prospectively followed and had a second ("follow-up") Doppler echocardiography examination at 3 years, and constituted the study population (Online Figure 1). Online Table 1 compares the characteristics of the study population and those of patients without follow-up. The baseline visit was performed at a median time of 6.7 (interquartile range [IQR]: 5.1 to 9.1) years post-AVR, and the follow-up visit at a median time of 3.1 (IQR: 2.9 to 3.3) years following the baseline visit (**Figure 1**). All patients gave written informed consent approved by the institutional review board of the Institut de Cardiologie et de Pneumologie de Québec (Québec, Canada).

CLINICAL AND OPERATIVE DATA. Medical history included smoking, documented diagnoses of hypertension (patients receiving antihypertensive medications or having known, but untreated, hypertension [blood pressure ≥140/90 mm Hg]), diabetes (fasting glucose ≥7 mmol/l), hypercholesterolemia (patients receiving cholesterol-lowering medication or, in the absence of such medication, having a total plasma cholesterol level >240 mg/l), coronary heart disease (history of myocardial infarction, coronary artery stenosis on coronary angiography, or previous coronary artery bypass graft), renal insufficiency (estimated glomerular filtration rate <60 ml/min/1.73 m^2), and detailed information of current medications were collected. Body weight, height, blood pressure, heart rate, and New York Heart Association functional class were assessed following standardized procedures. The clinical identification of patients with the features of the metabolic syndrome was based on the modified criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III (19). Operative data including bioprosthetic model and size were also recorded.

ECHOCARDIOGRAPHIC ASSESSMENT. All transthoracic echocardiography examinations were conducted according to the American Society of Echocardiography/European Association for Cardiovascular Imaging recommendations (20). Transprosthetic flow velocity was determined by continuous-wave Doppler, and the mean transprosthetic gradient was calculated using the modified Bernoulli formula. Prosthesis-patient mismatch was defined as not clinically significant (i.e., mild or no prosthesis-patient mismatch) if the indexed effective orifice area was >0.85 cm^2/m^2, moderate if it was >0.65 cm^2/m^2 and ≤0.85 cm^2/m^2, and severe if it was ≤0.65 cm^2/m^2 (7). Annualized change in mean gradient (mm Hg/year) was calculated by dividing the difference between the follow-up and the baseline visits by the time between the visits. Prosthetic valve regurgitation was assessed by color Doppler, and the origin of the jet was visualized in several views to differentiate para- from trans-prosthetic regurgitation. Prosthetic valve regurgitation severity was assessed with the use of a multiparametric integrative approach as recommended by the American Society of Echocardiography/European Association for Cardiovascular Imaging and classified as mild, moderate, or severe (20). The occurrence of HVD between baseline

TABLE 1 Patients Demographics, Baseline Characteristics, and Medication

	All Patients (N = 137)	No HVD (n = 119)	HVD (n = 18)	p Value
Demographics and medical status at baseline visit				
Age, yrs	74 (69-79)	74 (69-79)	74 (65-79)	0.71
Male	98 (71.5)	84 (70.6)	14 (77.8)	0.52
Body surface area, m^2	1.82 ± 0.21	1.82 ± 0.21	1.81 ± 0.24	0.90
Body mass index, kg/m^2	28.0 ± 5.0	28.1 ± 5.1	27.4 ± 4.4	0.62
Systolic blood pressure, mm Hg	134 ± 17	133 ± 18	138 ± 14	0.26
Diastolic blood pressure, mm Hg	69 ± 13	69 ± 14	66 ± 12	0.29
Heart rate, beats/min	64 ± 9	64 ± 9	61 ± 7	0.18
NYHA functional class				0.75
I	71 (52.6)	63 (52.9)	9 (50.0)	
II	61 (45.2)	53 (44.5)	9 (50.0)	
III	3 (2.2)	3 (2.5)	0 (0.0)	
Hypertension	101 (73.7)	87 (73.1)	14 (77.8)	0.67
Dyslipidemia	105 (76.6)	89 (74.8)	16 (88.9)	0.19
Metabolic syndrome	68 (49.6)	59 (49.6)	9 (50.0)	0.97
Diabetes	29 (21.2)	24 (20.2)	5 (27.8)	0.46
Coronary artery disease	64 (46.7)	57 (47.9)	7 (38.9)	0.48
Previous coronary artery bypass graft	52 (38.0)	46 (38.7)	6 (33.3)	0.66
History of smoking	78 (56.9)	69 (57.9)	9 (50.0)	0.52
History of atrial fibrillation	25 (18.2)	21 (17.7)	4 (22.2)	0.64
Renal insufficiency	50 (36.8)	44 (37.3)	6 (33.3)	0.75
Medication				
Angiotensin II receptor antagonist	34 (24.8)	29 (24.4)	5 (27.8)	0.76
Angiotensin-converting enzyme	40 (29.2)	35 (29.4)	5 (27.8)	0.89
Calcium antagonist	34 (24.8)	31 (26.1)	3 (16.7)	0.39
Statin	109 (79.6)	95 (79.8)	14 (77.8)	0.84
Anticoagulant	20 (14.6)	19 (16.0)	1 (5.6)	0.24
Bisphosphonate	11 (8.0)	8 (6.7)	3 (16.8)	0.15
Calcium supplement	32 (23.4)	29 (24.4)	3 (16.8)	0.47
Vitamin D supplement	28 (20.4)	25 (21.0)	3 (16.8)	0.67
Evaluation timing				
Time interval between AVR and baseline	6.7 (5.1-9.1)	6.7 (5.0-8.8)	6.5 (5.1-12.0)	0.49
Time interval between AVR and follow-up	9.9 (8.1-12.4)	10 (8.2-12.1)	8.9 (7.6-13.7)	0.82

Values are median (interquartile range), n (%), or mean ± SD. p values refer to comparisons between HVD and No HVD groups.

AVR = aortic valve replacement; HVD = hemodynamic valve deterioration; NYHA = New-York Heart Association.

TABLE 2 Surgical Data in the Study Population

	All Patients (N = 137)	No HVD (n = 119)	HVD (n = 18)	p Value
Concomitant procedures				
Coronary artery bypass graft	52 (38.0)	46 (38.7)	6 (33.3)	0.66
Ascending aorta replacement	13 (9.5)	12 (10.1)	1 (5.6)	0.54
Bioprosthesis type				0.56
Stentless	39 (28.5)	32 (26.9)	7 (38.9)	
Stented porcine	41 (29.9)	36 (30.3)	5 (27.8)	
Stented pericardial	57 (41.6)	51 (42.9)	6 (33.3)	
Bioprosthesis size, mm				0.63
19	6 (4.4)	5 (4.2)	1 (5.6)	
21	20 (14.6)	19 (16.0)	1 (5.6)	
23	42 (30.7)	37 (31.1)	5 (27.8)	
25	42 (30.7)	36 (30.3)	6 (33.3)	
27	23 (16.8)	18 (15.1)	5 (27.8)	
29	4 (2.9)	4 (3.3)	0 (0.0)	
Size of prosthesis ≤21 mm	26 (19.0)	24 (20.2)	2 (11.1)	0.36
Moderate or severe prosthesis-patient mismatch	48 (35.0)	44 (37.0)	4 (22.2)	0.25

Values are n (%). p values refer to comparisons between HVD and No HVD groups.
HVD = hemodynamic valve deterioration.

TABLE 3 Biological Data at Baseline Visit in the Study Population

	All Patients (N = 137)	No HVD (n = 119)	HVD (n = 18)	p Value
Glycemia, mmol/l	5.4 (5.0–6.1)	5.4 (4.9–6)	5.7 (5.2–7.2)	0.23
Insulinemia, pmol/l	56.0 (40.0–100.0)	56 (38.5–92.5)	95.0 (46.8–131.8)	0.06
HOMA index	2.0 (1.3–3.5)	1.9 (1.3–3.2)	3.5 (1.4–5.0)	0.04
C-reactive protein, mg/l	1.5 (0.8–4.0)	1.5 (0.8–3.9)	1.2 (0.5–5.0)	0.49
Apo-A, g/l	1.55 (1.40–1.75)	1.56 (1.40–1.76)	1.52 (1.40–1.76)	0.42
Apo-B, g/l	0.62 (0.54–0.75)	0.64 (0.54–0.74)	0.56 (0.48–0.90)	0.62
Ratio Apo-B/Apo-A	0.39 (0.34–0.49)	0.39 (0.34–0.49)	0.40 (0.31–0.60)	0.92
Total cholesterol, mmol/l	4.06 (3.58–4.87)	4.06 (3.55–4.77)	4.37 (3.61–5.29)	0.40
LDL serum level, mmol/l	2.15 (1.73–2.58)	2.15 (1.73–2.53)	2.21 (1.44–3.39)	0.71
HDL serum level, mmol/l	1.34 (1.15–1.56)	1.37 (1.16–1.57)	1.27 (1.13–1.53)	0.60
Cholesterol/HDL ratio	3.0 (2.7–3.7)	3.0 (2.6–3.6)	3.0 (2.8–4.7)	0.31
Triglyceride serum level, mmol/l	1.39 (0.94–1.65)	1.22 (0.92–1.61)	1.38 (1.00–2.02)	0.20
Lp-PLA2 activity, nmol/min/ml	25.53 ± 5.36	24.99 ± 5.02	28.94 ± 6.29	0.003
Lp-PLA2 mass, ng/ml	104.3 (132.1–169.3)	129.6 (102.2–156.9)	161.0 (118.3–190.3)	0.02
PCSK9 (ng/ml)	305.4 (245.6–396.9)	290.9 (239.9–385.9)	364.2 (309.1–417.4)	0.06
Lipoprotein(a), mg/dl	15.29 (4.49–56.65)	14.20 (4.41–57.19)	17.52 (4.46–48.78)	0.70
Creatinine serum level, µmol/l	85.5 (77.0–100.0)	87.0 (74.8–100.3)	82.5 (78.8–89.8)	0.62
Creatinine clearance, ml/min	68.3 (48.6–84.3)	66.9 (48.4–83)	77.4 (52.8–99.7)	0.30

Values are median (interquartile range) or mean ± SD. p values refer to comparisons between HVD and No HVD groups.
Apo-A = apolipoprotein A; Apo-B = apolipoprotein B; HDL = high-density lipoprotein; HOMA = homeostatic model assessment; HVD = hemodynamic valve deterioration; LDL = low-density lipoprotein; Lp-PLA2 = lipoprotein-associated phospholipase A2; PCSK9 = proprotein convertase subtilisin/kexin 9.

and follow-up echocardiography was defined as an annualized increase in mean gradient ≥3 mm Hg/year associated with a decrease in effective orifice area and/or ≥1/3 degree worsening of transprosthetic regurgitation.

LABORATORY DATA. Fasting blood samples were collected at baseline visit to obtain plasma levels of glucose, insulin, creatinine, and complete lipid profile, which included total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and apolipoprotein A and B using automated techniques standardized with the Canadian reference laboratory. After centrifugation, plasma samples were stored at −80°C until measurement of other biological parameters. Lipoprotein(a) was measured with chemiluminescent immunoassays (21–23). Blood plasma lipoprotein-associated phospholipase A2 (Lp-PLA2) activity was determined by a colorimetric activity method (Cayman). The level of Lp-PLA2 activity in nmol/min/ml was calculated from the absorption curve (410 nm). The assay was carried out in duplicate. Plasma Lp-PLA2 mass was determined by an enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, Minneapolis) (16). The level of proprotein convertase subtilisin/kexin 9 (PCSK9) was measured by enzyme-linked immunosorbent assay (Cell Biolab, San Diego, California) (15). To assess insulin resistance, we calculated the homeostatic model assessment (HOMA) index using the formula: insulin (µU/ml) × (glucose [mmol/l]/22.5).

MULTIDETECTOR CT DATA. Bioprosthesis leaflet calcification was quantified by multidetector CT with the use of the volumetric method that identifies calcium within the bioprosthesis leaflets as areas of at least 1 contiguous pixel with a density ≥130 HU (24). The volume of calcified tissue expressed in cubic millimeters was individually calculated by summing the lesion volumes for all sections containing calcium. Particular attention was paid to distinguishing calcifications located in the region of the bioprosthesis leaflet from those located in the region of the prosthesis sewing ring and aortic annulus. The complete method was previously described (6). Operators were blinded to the results of the echocardiograms.

PRIMARY ENDPOINT. The primary clinical endpoint was a nonhierarchical composite of death from any cause or reintervention procedure for bioprosthesis failure. Late mortality data were obtained from Quebec Institute of Statistics. To maximize the interrogation of the central Quebec Institute of Statistics database, a list with multiple demographics (including first and last names, dates of birth, and social security numbers) and a delay of 1 year

between interrogation and closing follow-up dates were used. There was no loss to follow-up for the clinical endpoint.

STATISTICAL ANALYSIS. Continuous data were expressed as mean ± SD or median (interquartile range), according to variable distribution (tested with the Shapiro-Wilk test), and compared using unpaired Student's *t*-test or a Wilcoxon rank sum test. Categorical data were expressed as number (percentage) and compared by use of the chi-square or Fisher exact tests, as appropriate. Variables that were not normally distributed (PCSK9 levels) were expressed as median and interquartile ranges. We used a cutoff of HOMA index >2.7, which represents the upper tertile of the study population as well as the previously reported threshold to detect insulin-resistance (25). For lipoprotein(a), we used the cutoff values (>30 and >50 mg/dl) that have been proposed to define elevated lipoprotein(a) in the clinical setting. Blood biomarkers such as HOMA index and PCSK9, which were not normally distributed, were expressed as continuous variables after logarithmic transformation.

Univariable logistic regression analysis was used to identify the factors independently associated with HVD, and each factor was adjusted for age at baseline visit, sex, and time interval from AVR to baseline. We built a series of nested bivariable models, and Bonferroni correction was used to correct for multiple testing. A p value <0.05 after Bonferroni correction was considered statistically significant.

Time-to-event analyses were performed with the use of Kaplan-Meier estimates and were compared with the use of the log-rank test. The effect of baseline variables and HVD occurrence were assessed with the use of a Cox proportional hazards regression model with a starting time at the follow-up echocardiogram. Multivariable Cox regressions were adjusted for age, sex, and time interval since AVR. The incremental predictive value of bioprosthesis calcification was assessed by calculating the net reclassification index at 2 years, using the category-free NRI and IDI program codes (for Stata software, StataCorp, College Station, Texas) downloaded online. Cox proportional hazards regression curves were used to display the adjusted cumulative hazard of the primary endpoint according to the presence of HVD, isolated leaflet calcification, or the absence of both leaflet calcification and HVD. The sample size rationale related to the echocardiographic (HVD) and clinical endpoints is presented in the Online Appendix.

A p value <0.05 was considered statistically significant. The p values were from 2-sided test. Statistical analysis was performed with JMP V.13 (SAS, Cary, North Carolina) and Stata 14 software.

TABLE 4 Echocardiographic and Multidetector CT Data in the Study Population

	All Patients (N = 137)	No HVD (n = 119)	HVD (n = 18)	p Value
Echocardiography				
Baseline visit echocardiography				
Mean gradient, mm Hg	13 (9–18)	13 (9–17)	17 (10–26)	0.09
Aortic valve area, cm^2	1.2 (1.0–1.6)	1.2 (1.0–1.6)	1.1 (0.9–1.6)	0.35
Indexed aortic valve area, cm^2/m^2	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.6 (0.5–0.9)	0.27
Aortic regurgitation				
None/trace	131 (95.6)	115 (96.6)	16 (88.9)	0.13
Mild	6 (4.4)	4 (3.4)	2 (11.1)	
Left ventricular ejection fraction, %	65 (60–70)	65 (60–70)	65 (54–70)	0.74
Follow-up echocardiography				
Mean gradient, mm Hg	14 (9–19)	13 (9–18)	27 (18–42)	<0.001
Annualized change in gradient from baseline to follow-up, mm Hg/yr	1.2 ± 5.9	0.0 ± 1.2	9.5 ± 13.5	<0.001
Aortic valve area, cm^2	1.2 (1.0–1.4)	1.2 (1.0–1.5)	0.9 (0.7–1.3)	0.005
Indexed aortic valve area, cm^2/m^2	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.5 (0.4–0.7)	0.003
Aortic regurgitation				<0.001
None/trace	116 (84.7)	109 (91.6)	7 (38.9)	
Mild	11 (8.0)	10 (8.4)	1 (5.6)	
Moderate	6 (4.4)	0 (0.0)	6 (33.3)	
Severe	4 (2.9)	0 (0.0)	4 (22.2)	
Left ventricular ejection fraction, %	60 (59–65)	60 (58–65)	60 (58–70)	0.47
Multidetector CT				
Presence of leaflet calcification	34 (25.6)	25 (21.6)	9 (52.9)	0.006
Leaflet calcification, mm^3	75 ± 21	60 ± 19	174 ± 31	0.003

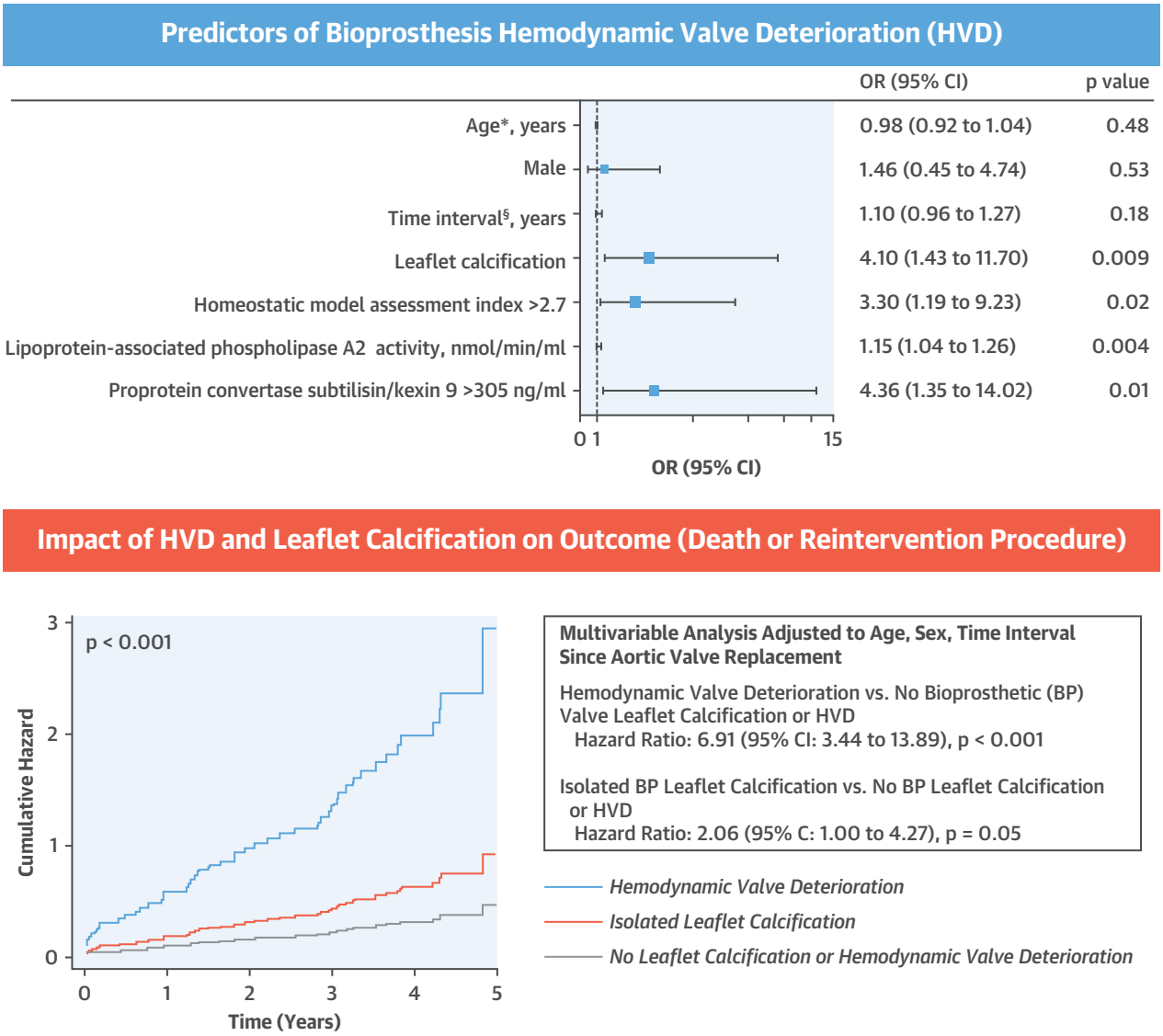
Values are median (interquartile range), n (%), or mean ± SD. p values refer to comparisons between HVD and No HVD groups.
CT = computed tomography; HVD = hemodynamic valve deterioration.

RESULTS

PATIENT CHARACTERISTICS. Baseline characteristics and medications are presented in Table 1. Median age at baseline visit was 74 (69 to 79) years; 71.5% were men; and median time interval since surgery was 6.7 (5.1 to 9.1) years (Figure 1). Surgical data and biological variables are summarized in Tables 2 and 3. Among these patients, 34 (25.6%) had bioprosthesis leaflet calcification detectable at CT. Echocardiographic and CT data are presented in Table 4. Follow-up echocardiography was performed at a median time of 9.9 (IQR: 8.1 to 12.4) years post-AVR.

PREDICTORS OF HVD. Eighteen (13.1%) patients developed HVD between baseline and follow-up visits, that is, over a period of 3 years (Table 4). Patterns of HVD were isolated stenosis, isolated regurgitation, and mixed dysfunction in 8, 5, and 5 patients, respectively. The surgical data, clinical data, and medications were similar in patients with and

CENTRAL ILLUSTRATION **Predictors and Impact on Outcomes of Valve Hemodynamic Deterioration and Leaflet Calcification in Patients With an Aortic Bioprosthesis**



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(Top) Forest plot of the predictors of valve hemodynamic deterioration in univariable analysis. **(Bottom)** Cox proportional cumulative hazard of the composite of death or aortic valve reintervention according to the presence of bioprosthetic valve leaflet calcification measured by computed tomography and hemodynamic valve deterioration measured by Doppler-echocardiography.*Age at baseline visit. §Time interval since aortic valve replacement to baseline visit. BP = bioprosthetic; CI = confidence interval; HVD = hemodynamic valve deterioration; OR = odds ratio.

without HVD (Tables 1 and 2). Patients with HVD had a higher HOMA index (3.5 [1.4 to 5.0] vs. 1.9 [1.3 to 3.2]; p = 0.04), Lp-PLA2 activity (28.94 ± 6.29 nmol/min/ml vs. 24.99 ± 5.02 nmol/min/ml; p = 0.003), and Lp-PLA2 mass (161 ng/ml [118.3 to 190.3 ng/ml] vs. 129.6 ng/ml [102.2 to 156.9 ng/ml]; p = 0.02) and a trend toward higher level of PCSK9 (364.2 ng/ml [309.1 to 417.4 ng/ml] vs. 290.9 ng/ml [239.9 to 385.9 ng/ml]; p = 0.06) compared with those without HVD (Table 3). Presence of leaflet calcification at baseline CT, HOMA index >2.7, Lp-PLA2 activity (per 0.1 nmol/min/ml increase), and PCK9 ≥305 ng/ml were associated with HVD in univariable analysis (Central Illustration). These factors remained

TABLE 5 Risk Factors Associated With Hemodynamic Valve Deterioration Adjusted for Age, Sex, and Time Interval Since Surgery

	Adjusted for Age*			Adjusted for Sex			Adjusted for Time Interval†		
	OR (95% CI)	p Value	p Value‡	OR (95% CI)	p Value	p Value‡	OR (95% CI)	p Value	p Value‡
Age, yrs*	–	–	–	0.98 (0.92–1.04)	0.55	0.99	0.96 (0.91–1.03)	0.27	0.85
Male	1.37 (0.41–4.53)	0.61	0.99	–	–	–	1.48 (0.45–4.85)	0.51	0.98
Time interval†	1.13 (0.97–1.31)	0.27	0.85	1.10 (0.96–1.27)	0.17	0.67	–	–	–
Leaflet calcification	4.03 (1.41–11.56)	0.01	0.05	4.28 (1.48–12.38)	0.007	0.04	3.53 (1.16–10.75)	0.03	0.14
HOMA index >2.7	3.28 (1.17–9.15)	0.02	0.11	3.31 (1.19–9.23)	0.02	0.11	3.37 (1.20–9.47)	0.02	0.11
Lp-PLA2 activity, nmol/min/ml	1.15 (1.04–1.27)	0.005	0.03	1.15 (1.04–1.27)	0.005	0.03	1.15 (1.04–1.26)	0.006	0.04
PCSK9 ≥305 ng/ml	4.26 (1.31–13.83)	0.02	0.12	4.33 (1.34–13.94)	0.01	0.06	4.09 (1.26–13.27)	0.02	0.11

*Age at baseline visit. †Time interval between aortic valve replacement and baseline visit. ‡p value after Bonferroni correction.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 3.

significantly associated with HVD after successive adjustments for age, sex, and time interval since surgery (Table 5).

Comprehensive multivariate logistic regression analysis was limited in the number of risk factors that could be included (a total of 2) in a single model because of sample size and number of cases with HVD. We thus built 6 different bivariable models of interest in Online Table 2. These limited bivariable analyses revealed that all previously described parameters remained associated with HVD. However, following Bonferroni correction, only leaflet calcification and Lp-PLA2 remained independently associated with HVD (all $p \geq 0.05$). Additional models including blood biomarkers such as HOMA index and PCSK9 entered as continuous variables after logarithmic transformation as well as lipoprotein(a) dichotomized according to the clinical thresholds (>30 and >50 mg/dl) are presented in Online Tables 3 and 4. Online Figure 2 presents the risk of HVD according to severity of valve leaflet calcification (large vs. mild, defined as a volume of leaflet calcification > vs. < median value in the subset of patients with detectable calcification). Large calcification, but not mild calcification, was associated with increased risk of HVD.

DEATH AND REINTERVENTION FOR BIOPROSTHESIS FAILURE. The median time of clinical follow-up after the follow-up visit was 3.8 (2.9 to 4.4) years. During this period, 52 (38.0%) patients met the primary clinical composite endpoint with 30 reintervention procedures for bioprosthesis failure and 22 deaths. The reintervention procedure was a redo surgical AVR in 20 patients and a transcatheter valve-in-valve procedure in 10 patients.

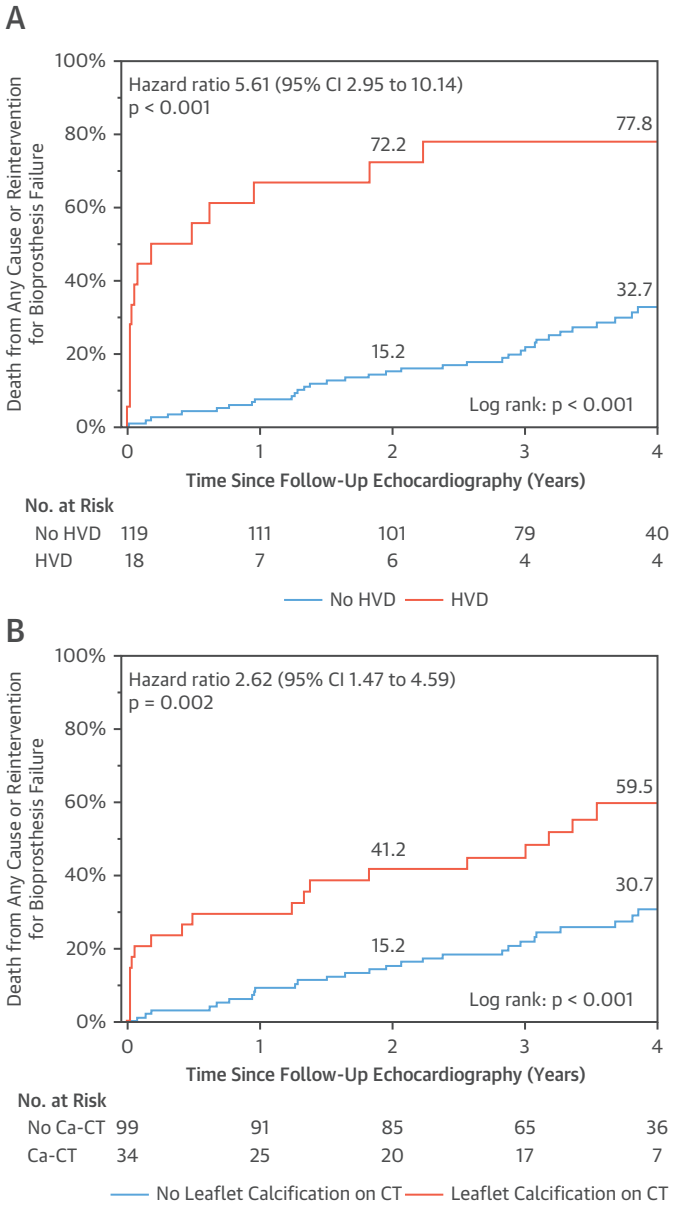
The primary clinical endpoint occurred more frequently in patients with HVD between baseline and follow-up visits compared with those without HVD (hazard ratio [HR]: 5.61; 95% confidence interval [CI]: 2.95 to 10.14; $p < 0.001$) (Figure 2). Patients with leaflet calcification at baseline visit had significantly more events (HR: 2.62; 95% CI: 1.47 to 4.59; $p = 0.02$) than patients without leaflet calcification (Figure 2). Both large and mild leaflet calcifications were associated with increased risk of events (Online Figure 2, Online Appendix). However, the association with events was stronger with large calcifications than with mild. In a multivariable Cox analysis adjusted for age, sex, and time interval since AVR, HVD (HR: 5.12; 95% CI: 2.57 to 9.71; $p < 0.001$) and leaflet calcification (HR: 2.58; 95% CI: 1.35 to 4.82; $p = 0.005$) remained independently associated with occurrence of reintervention or death (Figure 3). In comparison with patients without HVD or leaflet calcification, patients with HVD (HR: 6.91; 95% CI: 3.44 to 13.89; $p < 0.001$) or patients with isolated leaflet calcification (HR: 2.06 [95% CI: 1.00 to 4.27]; $p = 0.05$) demonstrated a higher occurrence of the primary clinical endpoint after adjustment with age, sex, and time interval since surgery (Central Illustration). Moreover, the addition of leaflet calcification into the model provided incremental prognostic value with a net reclassification index of 0.58 ($p = 0.006$).

DISCUSSION

The main findings of this study are: 1) dyslipidemic/dysmetabolic profile characterized by elevated plasma Lp-PLA2, PCSK9, and HOMA index are associated with increased risk of HVD at mid-term follow-up in patients with aortic bioprostheses; 2) HVD is strongly associated with adverse outcomes; and 3) the presence of leaflet calcification on CT is strongly associated with HVD and subsequent adverse clinical outcomes, independently of HVD.

PREDICTORS OF HVD. Until recently, bioprosthesis deterioration was described as a purely passive degenerative process (26). However, association of

FIGURE 2 Time to Event for the Primary Composite Clinical Endpoint



(A) Clinical endpoint (valve reintervention for bioprosthesis failure or death) according to presence or absence of HVD. **(B)** Clinical endpoint according to presence or absence of leaflet calcification on CT. Ca = calcification; CI = confidence interval; other abbreviations as in Figure 1.

traditional atherosclerotic risk factors such as dyslipidemia, metabolic syndrome, or diabetes with HVD and valve reintervention following AVR supports the implications of atherosclerotic-like processes in the structural deterioration of bioprosthetic valves (8,14,27,28). Beyond these traditional risk factors, other emerging risk factors including: HOMA index, PCSK9, and Lp-PLA2 were associated with HVD.

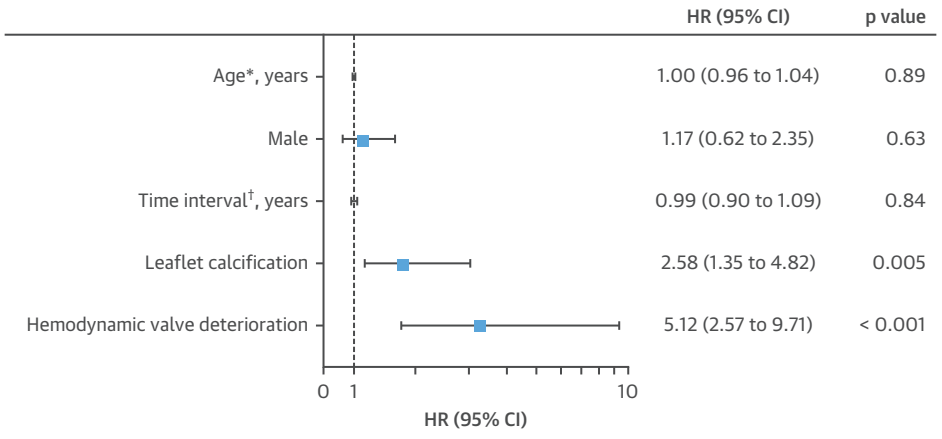
HOMA index is a marker of insulin resistance and was previously associated with faster hemodynamic progression in patients with native aortic stenosis (29). This highlights the importance to identify viscerally obese patients and to assess the degree of insulin resistance in patients with aortic bioprosthesis. Patients with a high HOMA index could thus benefit from aggressive lifestyle changes (29).

PCSK9 is a protein primarily secreted from liver cells and causes down-regulation of the LDL receptor (LDLR) by binding to the LDLR, and subsequently, leading to lysosomal destruction of LDLR, which results in high LDL cholesterol levels in the blood (30). PCSK9 is also positively associated with body mass index, waist circumference, and insulin resistance (31), and has a crucial role in lipid metabolism (32). There is growing evidence that PCSK9 plays a key role at both the systemic and tissue levels in promoting atherosclerosis (33). In a prior cross-sectional study, the combination of an oxidized LDL plasma level ≥25.4 U/l and a PCSK9 level >298 ng/ml was associated with bioprosthesis dysfunction (15). Future studies are necessary to assess the efficacy of PCSK9 inhibitors to reduce the risk of bioprosthesis structural and hemodynamic deterioration following AVR.

Lp-PLA2 is encoded by the *PLA2G7* gene and is an enzyme using oxidized LDL as a substrate, producing free fatty acids and lysophosphatidylcholine, which harbors proinflammatory activity. We previously reported that Lp-PLA2 was highly expressed in stenotic native aortic valves (16,34), and that plasma Lp-PLA2 activity was associated with faster progression rate of native aortic stenosis (35). Lp-PLA2 was the cardiometabolic factor demonstrating the strongest association with bioprosthesis HVD in the present study. Lp-PLA2 may thus represent a novel potential biomarker and/or therapeutic target in the context of native and bioprosthetic valves; although inhibitors of Lp-PLA2 failed to retard coronary atheroma progressions or reduce cardiovascular events in the context of established coronary artery disease (36,37).

IMPACT OF HVD ON OUTCOMES. Recent publications recommend the assessment of bioprosthesis durability to not solely rely on valve reintervention for bioprosthesis failure, but to also incorporate valve morphological/hemodynamic deterioration as documented by echocardiography or multimodality imaging (7,12,13,18). Several parameters and criteria have been proposed to define bioprosthesis HVD

FIGURE 3 Multivariable Cox Analysis of the Factors Associated With the Primary Clinical Endpoint



*Age at follow-up echocardiography (HR is per 1-year increase). †Time interval since surgery to follow-up echocardiography (HR per 1-year increase). HR = hazard ratio; other abbreviations as in Figures 1 and 2.

following AVR (7,12,15,38-40). In the present study assessing HVD over a 3-year period, we elected to use the annualized rate of change in mean gradient >3 mm Hg to define HVD, as previously proposed (14). Prior studies have reported that severe HVD (i.e., progression of mean gradient ≥30 mm Hg or transprosthetic regurgitation >2/4 [12]; mean gradient >40 mm Hg and/or severe aortic regurgitation [18]) was associated with an increased risk of valve reintervention (AVR or valve-in-valve) or death (12,18). In the present study, with less stringent criteria for hemodynamic severity to define HVD, we found that HVD was a powerful, independent predictor of the composite of death or reintervention for bioprosthesis failure. This provides further support toward a definition of bioprosthesis valve deterioration that includes HVD as measured by echocardiography. A definition solely based on valve reintervention would grossly underestimate the incidence of structural/functional valve deterioration.

IMPACT OF LEAFLET CALCIFICATION ASSESSED ON MULTIDETECTOR CT. Leaflet calcification is found in the vast majority of bioprostheses explanted for valve failure (18). Bioprosthesis leaflet calcification generally precedes occurrence of HVD, thus providing an early marker of structural valve deterioration. Transthoracic echocardiography has limited sensitivity to detect minor degrees of bioprosthesis leaflet calcification. In the present study, we used multidetector CT scan (without contrast) to detect and quantitate bioprosthesis leaflet calcification, and the presence of any detectable calcification at baseline was a strong predictor of HVD during the subsequent 3 years. Furthermore, leaflet calcification assessed by CT provided incremental value beyond HVD to predict the risk of death or valve reintervention. Hence assessing leaflet calcification by CT and HVD by Doppler echocardiography in the surveillance of patients with an aortic bioprosthesis may help to better identify those who are at risk of bioprosthesis failure and associated cardiac events.

STUDY LIMITATIONS. This study included a subset of 137 patients who had an implanted bioprosthesis for at least 3 years and who participated in both the baseline and follow-up prospective visits. Of the initial cohort of patients (N = 203) who underwent the baseline visit, 66 (32.5%) could not come back for their follow-up visit and were thus excluded from the present study. This study design is subject to survivorship bias. However, the baseline characteristics including the incidence of bioprosthetic leaflet calcification were similar between included versus excluded subsets (Online Table 1, Online Appendix). In this study, the baseline factors were measured at mid-term follow-up, and further studies are needed to confirm that their associations with outcomes reported in this study also hold if these factors are measured early after AVR. The results of this study can therefore not be directly transposed to the context of early structural/functional valve deterioration post-AVR. A cutoff of

decrease in valve effective orifice area was not included in the definition of HVD. However, given that left ventricular ejection fraction and stroke volume index were stable during the 3-year follow-up, the change in gradient is thus a reliable marker of HVD. This study only included surgical bioprostheses and the results can thus not be extended to transcatheter bioprostheses.

CONCLUSIONS

In this prospective longitudinal study of patients with an aortic bioprosthesis and being in the mid-term post-operative phase, the presence of HVD as detected by echocardiography was independently associated with a major increase in the risk of aortic valve reintervention or death during follow-up. A dysmetabolic profile characterized by elevated plasma Lp-PLA2, PCSK9, and HOMA index was associated with increased risk of HVD. Presence of leaflet calcification as detected by CT was a strong predictor of HVD, providing added value to HVD for predicting aortic valve reintervention and death.

ADDRESS FOR CORRESPONDENCE: Dr. Philippe Pibarot, Laval University, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Sainte-Foy #A2075, Québec, G1V-4G5 Québec, Canada. E-mail: Philippe.Pibarot@med.ulaval.ca. Twitter: @universitelaval, @PPibarot.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Hemodynamic deterioration of bioprosthetic aortic valves is often echocardiographically evident approximately 7 years post-operatively and is a strong predictor of adverse clinical outcomes.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Leaflet calcification identified by multidetector computed tomography is an early and sensitive marker of structural deterioration of bioprosthetic heart valves with prognostic implications additive to the hemodynamic assessment by Doppler echocardiography.

TRANSLATIONAL OUTLOOK: Future studies should investigate whether insulin resistance and increased levels of Lp-PLA2 or PCSK9 are causally related to the hemodynamic deterioration of bioprosthetic aortic valves and whether modification of these factors can improve the durability of these prostheses.

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KEY WORDS bioprosthesis, calcification, computed tomography, dysmetabolic, structural valve degeneration

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.