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Association of Bioprosthetic Aortic Valve Leaflet Calcification on Hemodynamic and Clinical Outcomes

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ABSTRACT

BACKGROUND The prognostic value of aortic valve calcification (AVC) measured by using multidetector computed tomography imaging has been well validated in native aortic stenosis, and sex-specific thresholds have been proposed. However, few data are available regarding the impact of leaflet calcification on outcomes after biological aortic valve replacement (AVR).

OBJECTIVES The goal of this study was to analyze the association of quantitative bioprosthetic leaflet AVC with hemodynamic and clinical outcomes, as well as its possible interaction with sex.

METHODS From 2008 to 2010, a total of 204 patients were prospectively enrolled with a median of 7.0 years (interquartile range: 5.1 to 9.2 years) after biological surgical AVR. AVC measured by using the Agatston method was indexed to the cross-sectional area of aortic annulus measured by echocardiography to calculate the AVC density (AVCd). Presence of hemodynamic valve deterioration (HVD; increase in mean gradient [MG] ≥10 mm Hg and/or increase in transprosthetic regurgitation ≥1) was assessed by echocardiography in 137 patients at the 3-year follow-up. The primary clinical endpoint was mortality or aortic valve re-intervention.

RESULTS There was no significant sex-related difference in the relationship between bioprosthetic AVCd and the progression of MG. Baseline AVCd showed an independent association with HVD at 3 years. During follow-up, there were 134 (65.7%) deaths (n = 100) or valve re-interventions (n = 47). AVCd ≥58 AU/cm^2 was independently associated with an increased risk of mortality or aortic valve re-intervention (adjusted hazard ratio: 2.23; 95% confidence interval: 1.44 to 3.35; $p < 0.001$). The AVCd threshold combined with an MG progression threshold of 10 mm Hg amplified the stratification of patients at risk (log-rank, $p < 0.001$). The addition of AVCd threshold into the prediction model including traditional risk factors improved outcome prediction (net classification improvement: 0.25, $p = 0.04$; likelihood ratio test, $p < 0.001$).

CONCLUSIONS Aortic bioprosthetic leaflet calcification is strongly and independently associated with HVD and the risk of death or aortic valve re-intervention. As opposed to native aortic stenosis, there is no sex-related differences in the relationship between AVCd and hemodynamic or clinical outcomes. (J Am Coll Cardiol 2020;76:1737-48)
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ABBREVIATIONS AND ACRONYMS

AVC = aortic valve calcification

AVCd = aortic valve calcification density

AVR = aortic valve replacement

CI = confidence interval

HVD = hemodynamic valve deterioration

MDCT = multidetector computed tomography

MG = mean gradient

NRI = net classification improvement

PPM = prosthesis-patient mismatch

SVD = structural valve deterioration

Aortic valve replacement (AVR) is the only effective treatment for severe aortic stenosis. More than 200,000 surgical AVRs are performed yearly worldwide, and there has been a noticeable shift from mechanical to bioprosthetic valves over the past decades (1,2). This shift could be explained by the aging of the target population, the improvement of hemodynamic performance of aortic bioprostheses, and the emergence of transcatheter AVR (1,3). However, the ultimate aim of AVR is to provide an effective and durable treatment for aortic valve disease, and valve durability thus remains a fundamental concern in this context. Bioprosthetic valves are indeed vulnerable to structural valve degeneration (SVD), a progressive process characterized by morphological abnormalities of valve leaflets, including thickening, calcification, fibrosis, and tear, leading to valve dysfunction (3–5).

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Previous studies reported that a definition of SVD solely based on valve reoperation due to bioprosthesis failure could lead to an underestimation of the true incidence of SVD (6–8). Recent literature, therefore, proposed to define SVD on the basis of longitudinal assessment of prosthetic valve morphology and hemodynamic function by Doppler echocardiography (4). Considering that calcification of the bioprosthetic leaflets is the main culprit of SVD and that aortic valve calcification (AVC) measured by multidetector computed tomography (MDCT) imaging has been shown to be accurate and useful for the assessment of native aortic stenosis (9,10), we investigated the utility of the quantitation of AVC in patients with aortic bioprosthesis.

Very few studies have measured the extent of AVC in bioprosthetic valves or examined the association with hemodynamic and clinical outcomes following AVR. We previously reported that the presence (vs. absence) of AVC was associated with 4-fold increase in the risk of hemodynamic valve deterioration (HVD) during follow-up and with a 2-fold increased risk of death or aortic valve re-intervention (11). However, in this previous study, we did not perform a quantitative assessment of AVC score or density. Thus, we did not explore the potential sex-related differences in the relationship between AVC and outcomes, and thus in the severity cut-points to be used in women versus men. Indeed, in patients with native aortic stenosis, it has been shown that, for a given hemodynamic severity of aortic stenosis, women harbor less AVC than men, and therefore a lower severity cut-point should be used in women (1,200 AU) versus men (2,000 AU) (9,12).

The objectives of the present study were: 1) to examine the association of surgical bioprosthetic AVC score and density with HVD measured by echocardiography and risk of death or aortic valve re-intervention; and 2) to determine and validate which AVC severity cut-point predicts outcomes and whether there is any sex-related difference in these associations or AVC severity cut-point.

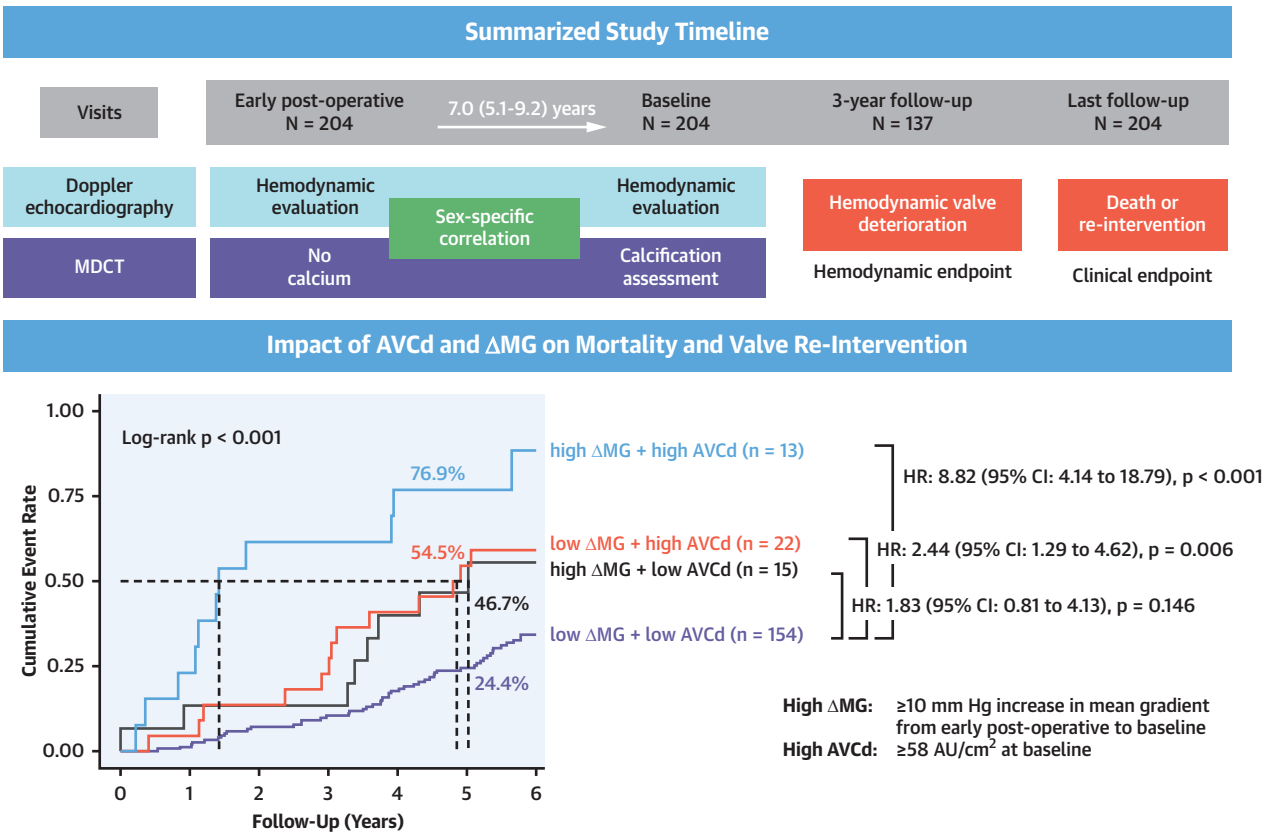
METHODS

STUDY POPULATION. From 2008 to 2010, we prospectively enrolled 204 patients who had undergone isolated surgical bioprosthetic AVR 7.0 years (interquartile range: 5.1 to 9.2 years) earlier in the Quebec Heart and Lung Institute. Early post-operative (within a median of 14 days [interquartile range: 5 to 140 days] post-AVR) Doppler echocardiographic data were retrospectively obtained. All patients underwent a baseline visit with comprehensive Doppler echocardiography and noncontrast MDCT scan. Furthermore, 137 (67% of the initial cohort) patients had a second follow-up visit with Doppler echocardiography at 3 years after the baseline visit (31 patients died or had a re-intervention before follow-up echocardiography). The remaining 36 patients refused follow-up echocardiography or had the examination exceeding the follow-up window for HVD assessment (**Central Illustration**). The sample size rationale related to the HVD is presented in the Supplemental Methods. Supplemental Table 1 compares the characteristics of the study population and those of patients without follow-up echocardiography. The study protocol has been described previously (13) and was approved by the institutional review board; signed informed consent was obtained for all patients.

CLINICAL AND OPERATIVE DATA. Comprehensive medical history, including demographic characteristics, risk factors, comorbidities, medication, and operative data, was documented. Body weight and height were measured following the standardized procedures at baseline visit. The duration of bioprosthetic valve implant was the time between AVR and baseline visit.

ECHOCARDIOGRAPHIC DATA. All echocardiograms were reviewed by the same cardiologist (H.M.). Operators were blinded to the results of clinical and MDCT data. Trans-prosthetic flow velocity was measured by using continuous wave Doppler, and the mean trans-prosthetic gradient was then calculated

CENTRAL ILLUSTRATION **Association Between Bioprosthetic Aortic Valve Calcification and the Composite of Mortality and Aortic Valve Re-Intervention**



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(Upper panel) Summarized timeline of the study. Surgery was performed at a median of 7.0 years (interquartile range: 5.1 to 9.2 years) before baseline (n = 204). Patients underwent Doppler echocardiography early after surgery and underwent both Doppler echocardiography and MDCT at baseline. Follow-up imaging (echocardiography) was performed in 137 living patients at 3 years after baseline visit. All patients completed 5-year follow-up as the end of the research protocol. Then a clinical follow-up at an interval of 3 years continued up to death or valvular re-intervention (last follow-up). The median follow-up time of subjects who are event-free was 8.8 years (95% confidence interval: 8.67 to 9.57 years), estimated by reversed Kaplan-Meier estimator. **(Lower panel)** Impact of bioprosthetic AVCd and ΔMG on mortality and valve re-intervention. Cumulative incidence curve of the composite of death and re-intervention according to mean gradient progression and AVCd progression from post-surgery to baseline. Hazard ratios (HRs) adjusted for age, sex, valve implant duration, diabetes, coronary heart disease, chronic pulmonary disease, renal insufficiency, left ventricular ejection fraction, and severe prosthesis-patient mismatch. ΔMG = change in mean gradient from early post-operative to baseline visits; AVCd = aortic valve calcification density; CI = confidence interval; MDCT = multidetector computed tomography.

by using the modified Bernoulli equation. Prosthetic regurgitation severity was assessed with a multiparametric approach recommended by the American Society of Echocardiography/European Association for Cardiovascular Imaging (14). Prosthesis-patient mismatch (PPM) was graded according to body mass index-adjusted cut-points (4).

MDCT DATA. The noncontrast CT imaging was performed with multidetector scanners. Bioprosthetic AVC was then quantified offline by using the Agatston method on the Aquarius iNtuition (TeraRecon, Inc., Foster City, California) and expressed in AUs. All AVC measurements were performed by 1 investigator (B.Z.) blinded to the clinical and echocardiographic data. Particular attention was paid to distinguish calcifications of the bioprosthesis leaflets versus high attenuation signals caused by the prosthesis stent or versus calcifications belonging to the native aortic annulus/root or left ventricular outflow tract (5). AVC load was indexed to the cross-sectional area of the aortic annulus measured by echocardiography to calculate the AVC density (AVCd) (9). Twenty patients

TABLE 1 Patient Characteristics of the Study

	Whole Cohort (N = 204)	With 3-Year Follow-Up Echocardiography (n = 137)	p Value	Women (n = 62)	Men (n =142)	p Value
Demographic characteristics and comorbidities						
Age, yrs*	67.30 ± 7.96	66.06 ± 7.86	0.156	69.40 ± 7.38	66.39 ± 8.06	0.013
Valve implant duration, yrs†	7.64 ± 3.35	7.43 ± 3.24	0.555	7.64 ± 3.25	7.65 ± 3.40	0.988
Body mass index, kg/m^2	27.08 ± 4.62	27.15 ± 4.75	0.892	27.22 ± 6.02	27.02 ± 3.87	0.78
Body surface area, m^2	1.83 ± 0.20	1.84 ± 0.20	0.53	1.66 ± 0.16	1.90 ± 0.17	<0.001
Smoking history	125 (61.3)	78 (56.9)	0.491	24 (38.7)	101 (71.1)	<0.001
Hypertension	145 (71.1)	101 (73.7)	0.681	48 (77.4)	97 (68.3)	0.249
Dyslipidemia	158 (77.5)	105 (76.6)	0.966	45 (72.6)	113 (79.6)	0.359
Diabetes mellitus	44 (21.6)	28 (20.4)	0.908	13 (21.0)	31 (21.8)	1.00
Insulin use	7 (3.4)	5 (3.6)	1.00	4 (6.5)	3 (2.1)	0.251
Coronary artery disease	98 (48.0)	62 (45.3)	0.693	21 (33.9)	77 (54.2)	0.012
Myocardial infarction	25 (12.3)	12 (8.8)	0.401	3 (4.8)	22 (15.5)	0.057
Atrial fibrillation	45 (22.1)	25 (18.2)	0.473	13 (21.0)	32 (22.5)	0.948
Chronic obstructive pulmonary disease	23 (11.3)	9 (6.6)	0.204	8 (12.9)	15 (10.6)	0.806
Renal insufficiency	15 (7.4)	6 (4.4)	0.373	4 (6.5)	11 (7.7)	0.973
Previous stroke	40 (19.6)	26 (19.0)	0.996	10 (16.1)	30 (21.1)	0.525
Previous CABG	72 (35.3)	48 (35.0)	1.00	11 (17.7)	61 (43.0)	0.001
Echocardiographic data						
LV outflow tract area, cm^2	3.50 ± 0.61	3.51 ± 0.60	0.845	3.00 ± 0.46	3.72 ± 0.54	<0.001
Peak gradient, mm Hg						
Post-surgery	22.46 ± 9.79	22.68 ± 9.73	0.853	24.66 ± 10.50	21.49 ± 9.33	0.045
Baseline	28.69 ± 13.53	28.43 ± 13.37	0.864	29.87 ± 13.03	28.17 ± 13.75	0.41
Progression	4.00 (-0.70 to 11.60)	3.30 (-0.80 to 10.00)	0.536	3.80 (-1.70 to 11.60)	4.25 (-0.23 to 11.15)	0.552
Mean gradient, mm Hg						
Post-surgery	11.82 ± 5.29	12.16 ± 5.16	0.558	13.17 ± 5.70	11.23 ± 5.01	0.015
Baseline	14.63 ± 7.48	14.51 ± 7.39	0.878	15.71 ± 7.26	14.16 ± 7.56	0.174
Progression	1.40 (-1.00 to 6.00)	1.15 (-1.52 to 4.38)	0.441	1.80 (-1.95 to 5.95)	1.40 (-1.00 to 6.00)	0.926
Aortic valve area, cm^2						
Post-surgery	1.55 ± 0.41	1.54 ± 0.41	0.728	1.29 ± 0.32	1.67 ± 0.39	<0.001
Baseline	1.30 ± 0.42	1.29 ± 0.38	0.852	1.08 ± 0.31	1.39 ± 0.43	<0.001
Progression	-0.22 (-0.50 to -0.02)	-0.23 (-0.48 to -0.00)	0.842	-0.18 (-0.32 to -0.01)	-0.26 (-0.53 to -0.03)	0.099
Indexed aortic valve area, cm^2/m^2						
Post-surgery	0.85 ± 0.22	0.84 ± 0.22	0.539	0.79 ± 0.20	0.88 ± 0.22	0.004
Baseline	0.71 ± 0.22	0.70 ± 0.20	0.682	0.66 ± 0.18	0.73 ± 0.23	0.021
Progression	-0.11 (-0.27 to -0.01)	-0.11 (-0.25 to 0.00)	0.708	-0.08 (-0.16 to 0.00)	-0.12 (-0.30 to -0.02)	0.152
LV ejection fraction, %						
Post-surgery	63.32 ± 8.52	63.58 ± 8.22	0.781	65.20 ± 8.19	62.50 ± 8.55	0.04
Baseline	63.57 ± 9.26	63.80 ± 8.91	0.816	67.65 ± 8.39	61.79 ± 9.08	<0.001
LV ejection fraction ≥50%						
Post-surgery	174 (88.3)	124 (91.2)	0.47	57 (95.0)	117 (85.4)	0.057
Baseline	174 (85.3)	119 (86.9)	0.752	58 (93.5)	116 (81.7)	0.031
Aortic regurgitation post-surgery			0.937			0.621
None	159 (79.5)	110 (80.9)		50 (82.0)	109 (78.4)	
Mild	34 (17.0)	22 (16.2)		10 (16.4)	24 (17.3)	
Moderate	7 (3.5)	4 (2.9)		1 (1.6)	6 (4.3)	
Aortic regurgitation at baseline			0.50			0.414
None	130 (65.3)	90 (67.2)		43 (70.5)	87 (63.0)	
Mild	58 (29.1)	41 (30.6)		17 (27.9)	41 (29.7)	
Moderate	10 (5.0)	3 (2.2)		1 (1.6)	9 (6.5)	
Prosthesis-patient mismatch			0.671			0.009
Nonclinically significant	108 (52.9)	67 (48.9)		27 (43.5)	81 (57.0)	
Moderate	64 (31.4)	44 (32.1)		18 (29.0)	46 (32.4)	
Severe	32 (15.7)	26 (19.0)		17 (27.4)	15 (10.6)	0.005

Continued on the next page

TABLE 1 Continued

	Whole Cohort (N = 204)	With 3-Year Follow-Up Echocardiography (n = 137)	p Value	Women (n = 62)	Men (n =142)	p Value
Multidetector computed tomography data						
Aortic valve calcification, AU	30.27 (0.00 to 105.44)	24.43 (0.00 to 86.84)	0.297	49.66 (6.41 to 149.58)	26.66 (0.00 to 91.68)	0.055
Aortic valve calcification density, AU/cm^2	8.77 (0.00 to 33.52)	7.09 (0.00 to 22.47)	0.276	12.62 (2.68 to 56.45)	7.57 (0.00 to 24.33)	0.035

Values are mean ± SD, n (%), or median (interquartile range). *The age when patients underwent aortic valve replacement. †Time interval between aortic valve replacement and baseline visit.
CABG = coronary artery bypass grafting; LV = left ventricular.

were randomly selected to perform intraobserver and interobserver (M.-A.C. vs. B.Z.) variability. For calculation of AVCd progression between early post-operative assessment and baseline visit, we assumed that AVCd was = 0 AU/cm^2 at the early post-operative time point.

ENDPOINTS. The primary hemodynamic endpoint was occurrence of HVD between baseline and follow-up echocardiography. HVD was defined as an increase in mean gradient (MG) ≥10 mm Hg with a concomitant decrease in effective orifice area and/or ≥1 grade new onset or worsening of transprosthetic aortic regurgitation with the final grade of moderate regurgitation (i.e., hemodynamic SVD in the consensus statement from the European Association of Percutaneous Cardiovascular Interventions) (11,15). This endpoint was examined in the 137 of 204 patients who had a Doppler echocardiography at the 3-year follow-up. The primary clinical endpoint was the nonhierarchical composite of all-cause mortality and aortic valve re-intervention.

Mortality and procedure information for aortic bioprosthesis failure was obtained from the Quebec Institute of Statistics. To maximize the interrogation of the central Quebec Institute of Statistics database, a list with multiple demographic characteristics (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. All patients completed a 5-year follow-up as the end of the research protocol. A clinical follow-up at a maximal interval of 3 years then continued up to death or valvular re-intervention. The median follow-up time of subjects who were event free was 8.8 years (95% confidence interval [CI]: 8.67 to 9.57 years), estimated by a reversed Kaplan-Meier estimator.

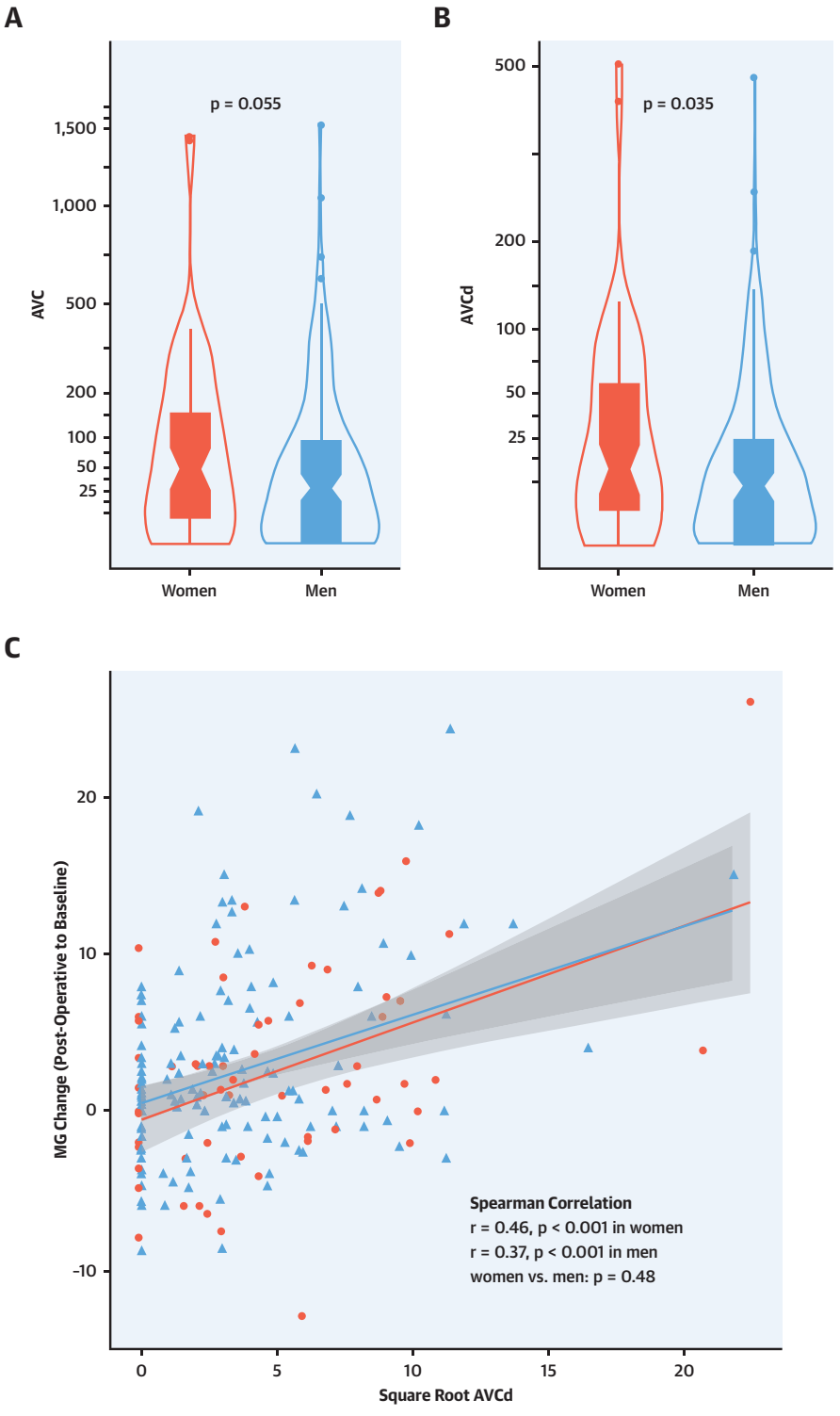
STATISTICAL ANALYSIS. Results are expressed as mean ± SD, median (interquartile range), or percentage, as appropriate. Differences in patient characteristics were compared by the analysis of variance or the Mann-Whitney *U* test for continuous variables and by the chi-square or Fisher exact test for categorical variables. AVCd was normalized by the square root transformation when analyzed as a continuous variable.

Sex-specific correlation between MG and AVCd progressions from post-surgery to baseline was assessed by using Spearman correlation analysis and robust linear regression. Logistic regression analysis was performed to test the association between baseline AVCd and HVD. We built a series of nested bivariate logistic models, and multiple testing was adjusted by Bonferroni correction (11).

In survival analyses, the pattern of the association between AVCd and the clinical endpoint was initially examined with AVCd modeled as a penalized spline (16). We then modeled AVCd as both a continuous and a categorical variable according to the optimal threshold determined by maximally selected rank statistics (17) as well as quartile of the AVCd distribution. Survival curves were built by using the Kaplan-Meier estimator and compared by using the log-rank test. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% CIs for the association between AVCd and clinical outcomes. The proportional hazards assumption was examined by inspection of Schoenfeld residuals. Clinically relevant variables and variables with a p value ≤ 0.1 on individual analysis were considered in a background multivariate model, including age, sex, valve implant duration, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, renal insufficiency, baseline MG, left ventricular ejection fraction, and severe PPM.

To validate the clinical value of the defined AVCd threshold, cumulative incidence of the clinical endpoint was computed by using the Kaplan-Meier estimator according to the AVCd threshold and the established MG progression threshold (with a cut-off of 10 mm Hg based on the American and European position statements) simultaneously. The incremental value of AVCd (as a binary variable) over the background model was evaluated by C-index, the category-less net classification improvement (NRI)

FIGURE 1 **Bioprosthetic AVCd Burden and its Correlation With Hemodynamic Progression by Sex**



(A) Bioprosthetic aortic valve calcification (AVC) burden according to sex. The notch in boxplot displays a confidence interval around the median. The violin plot shows the kernel probability density of aortic valve calcification. **(B)** Bioprosthetic aortic valve calcification density (AVCd) burden according to sex. **(C)** Correlation between AVCd progression and mean gradient (MG) progression from post-surgery to baseline. Regression lines were plotted by using robust linear regression. The **red line** represents women and the **blue line** represents men, with 95% confidence intervals (**gray area**).

index, and the integrated discrimination improvement index using R package survC1 (18) and survIDINRI (19). The likelihood ratio test and Bayesian information criteria were used to assess calibration properties. Moreover, we introduced decision curve analysis (20,21) to corroborate the superiority of including the AVCd threshold to the background model. All analyses were performed by using R version 3.5.2 software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

BIOPROSTHETIC AVCd IN WOMEN AND MEN. Patient characteristics (Table 1) were as expected and representative of patients who undergo AVR in our institution (22). The cohort consisted of 142 (70%) men and 62 (30%) women. Women were older (69.4 ± 7.4 vs. 66.4 ± 8.1 years; p = 0.013), with higher early postoperative MG (13.2 ± 5.7 vs. 11.2 ± 5.0 mm Hg; p = 0.015) and more frequent severe PPM (27.4% vs. 10.6%; p = 0.005). At the baseline visit, AVCd was significantly higher in women (12.6 AU/cm^2 [interquartile range: 2.7 to 56.5 AU/cm^2] vs. 7.6 AU/cm^2 [interquartile range: 0 to 24.3 AU/cm^2]; p = 0.035) (Figure 1). There was no significant correlation between AVCd and MG at baseline or in the whole cohort (r = 0.03; p = 0.65), nor in the male (r = 0.07; p = 0.41) or female (r = −0.09; p = 0.48) subcohort. No significant difference in AVCd was found between women and men after adjustment for postoperative MG and severe PPM (p = 0.138).

From early post-surgery to the baseline visit, AVCd progression showed significant correlations with MG progression in both men (r = 0.37; p < 0.001) and women (r = 0.46; p < 0.001), and the 2 correlation coefficients were not statistically different (p = 0.48) (Figure 1). Moreover, linear regression revealed that AVCd progression was the strongest factor associated with hemodynamic progression without significant interaction with sex (p = 0.91).

BIOPROSTHETIC AVCd AND HVD. Eighteen (13.1%) patients developed HVD between baseline and follow-up echocardiograms over a median period of 3.1 years (2.9 to 3.3 years). Type of HVD comprised isolated stenosis (n = 6), isolated transvalvular regurgitation (n = 7), and mixed dysfunction (n = 5). Baseline AVCd (odds ratio: 1.12; 95% CI: 1.01 to 1.25; p = 0.033) and valve implant duration (odds ratio: 1.16; 95% CI: 1.01 to 1.34; p = 0.037) were associated with HVD in univariate analysis, and patient age presented a marginally significant association (odds ratio: 0.95; 95% CI: 0.90 to 1.01; p = 0.097). In the nested bivariate models, AVCd remained associated with HVD after successive adjustments for age, sex, and valve implant duration (Table 2).

TABLE 2 Association Between AVCd and Hemodynamic Valve Deterioration

	OR (95% CI)	p Value	p Value*
Univariate			
Age†	0.95 (0.90–1.01)	0.097	–
Male	1.04 (0.36–3.44)	0.945	–
Valve implant duration‡	1.16 (1.01–1.34)	0.037	–
AVCd§	1.12 (1.01–1.25)	0.033	–
Bivariate model #1			
AVCd§	1.13 (1.01–1.27)	0.025	0.072
Age†	0.94 (0.88–1.01)	0.079	–
Bivariate model #2			
AVCd§	1.13 (1.01–1.26)	0.031	0.075
Male	1.22 (0.41–4.32)	0.734	–
Bivariate model #3			
AVCd§	1.14 (1.02–1.30)	0.019	0.057
Valve implant duration‡	1.17 (1.02–1.36)	0.024	–

*p value after Bonferroni correction. †Age when receiving aortic valve replacement. ‡Time interval between aortic valve replacement and baseline visit. §Aortic valve calcification density (AVCd) was normalized by square root transformation.

CI = confidence interval; OR = odds ratio.

BIOPROSTHETIC AVCd AND CLINICAL OUTCOMES. One hundred thirty-four (65.7%) patients met the primary clinical endpoint with 100 deaths and 47 aortic valve re-interventions (13 patients had re-intervention prior to death). The univariate analysis revealed a strong association between continuous AVCd and the composite endpoint (HR: 1.19; 95% CI: 1.12 to 1.27 per 30 U increase in AVCd; p < 0.001). On multivariate analysis, continuous as well as quartiles of AVCd remained statistically significant after adjustment for traditional risk factors (adjusted HR: 1.18; 95% CI: 1.09 to 1.26 per 30 units increase in AVCd, p < 0.001) (Table 3, Supplemental Figure 1). In penalized spline analyses, relative hazard approximatively showed an exponential increase in mortality or re-intervention with increasing AVCd before and after comprehensive adjustment for traditional risk factors (Figure 2). Notably, no interaction with sex was observed in this association (Supplemental Figure 2).

Penalized spline and maximal standardized log-rank statistics suggested an optimal threshold (58 AU/cm^2) in the whole cohort (Supplemental Figure 3). No significant differences were noted regarding demographic characteristics and comorbidities between 2 groups dichotomized by the threshold. Patients with AVCd ≥58 AU/cm^2 had higher MG and smaller aortic valve area at baseline (Supplemental Table 2). The Kaplan-Meier survival curve according to this threshold revealed that

TABLE 3 Univariate and Multivariate Analyses of Risk Factors for Mortality or Re-Intervention

	Univariate		Multivariate	
	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Age, 5-yr increase	1.13 (1.00–1.28)	0.043	1.16 (1.01–1.33)	0.040
Sex	0.99 (0.68–1.43)	0.949	1.28 (0.84–1.95)	0.258
Valve implant duration, 2-yr increase	1.10 (0.99–1.21)	0.064	1.19 (1.07–1.33)	0.001
Body mass index, kg/m^2	1.00 (0.97–1.03)	0.870	-	-
Hypertension	0.87 (0.60–1.27)	0.481	-	-
Dyslipidemia	0.98 (0.66–1.47)	0.939	-	-
Diabetes mellitus	1.29 (0.87–1.91)	0.204	1.54 (0.65–1.02)	0.041
Coronary artery disease	1.55 (1.10–2.18)	0.012	1.43 (0.99–2.07)	0.056
Atrial fibrillation	1.02 (0.68–1.52)	0.939	-	-
COPD	1.95 (1.22–3.11)	0.005	1.93 (1.18–3.16)	0.009
Renal insufficiency	1.80 (1.01–3.20)	0.047	1.40 (0.73–2.68)	0.316
Stroke	0.89 (0.58–1.37)	0.605	-	-
Mean gradient, 5 mm Hg increase	1.26 (1.12–1.42)	<0.001	1.23 (1.07–1.33)	0.003
Indexed aortic valve area, cm^2/m^2	0.72 (0.29–1.82)	0.488	-	-
LV ejection fraction, 5% increase	0.95 (0.87–1.04)	0.257	0.97 (0.89–1.07)	0.579
Severe PPM	1.40 (0.91–2.15)	0.126	0.96 (0.58–1.59)	0.860
AVCd, 30 AU/cm^2 increase	1.19 (1.12–1.27)	<0.001	1.18 (1.09–1.26)	<0.001

COPD = chronic obstructive pulmonary disease; HR = hazard ratio; PPM = prosthesis-patient mismatch; other abbreviations as in Tables 1 and 2.

patients with higher AVCd had significantly increased risk of mortality or re-intervention (Figure 3). With adjustment for age, sex, valve implant duration, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, renal insufficiency, MG, left ventricular ejection fraction, and severe PPM, AVCd ≥58 AU/cm^2 was strongly and independently associated with excess risk of mortality or re-intervention (adjusted HR: 2.23; 95% CI: 1.44 to 3.45; $p < 0.001$). After further adjustment for the interaction between sex and severe PPM, AVCd was still independently associated with clinical outcomes (adjusted HR: 2.18; 95% CI: 1.41 to 3.38; $p < 0.001$).

Moreover, we performed analysis accounting for the combined effect of MG progression and AVCd. Association with outcome was stronger in individuals with evidence of both MG increase (absolute increase ≥10 mm Hg from early post-surgery to baseline) and AVCd (≥58 AU/cm^2) compared with individuals with either MG increase or high AVCd alone. Patients with elevations of both MG and AVCd had the highest risk (76.9% cumulative event rate at 5 years), whereas those with only 1 of these 2 risk factors were at intermediate risk without statistical difference (no MG increase + high AVCd vs. MG increase + low AVCd: 54.5% vs. 46.7% at 5 years) (Central Illustration).

The addition of AVCd as a dichotomic variable (< vs. ≥58 AU/cm^2) to the background model containing traditional clinical and echocardiographic risk factors improved both the discrimination (integrated discrimination improvement index = 0.052, $p = 0.027$; NRI = 0.25, $p = 0.040$ for 5-year outcomes) and calibration (likelihood ratio test $p < 0.001$) for prediction of clinical outcomes (Table 4). Decision curve analysis further corroborated the superiority of the prediction model including AVCd. The decision-making strategy based on this prediction algorithm achieved higher net benefit across a wide scale of threshold probability for 5-year outcomes (Supplemental Figure 4).

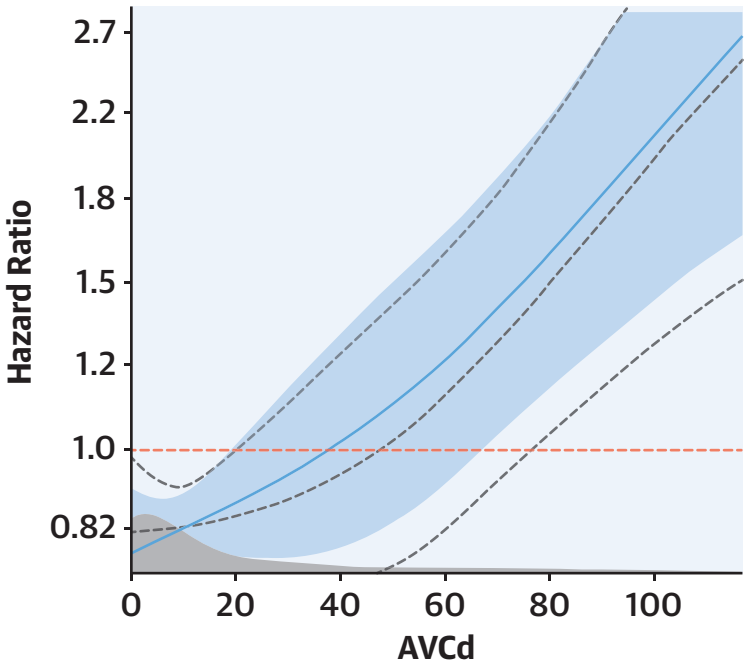
AVCd calculated with the use of the effective prosthesis area from manufacturer's data demonstrated similar results (Supplemental Figure 5).

DISCUSSION

The main findings of the study are that: 1) bioprosthetic AVCd is associated with subsequent HVD; and 2) bioprosthetic AVCd is strongly and independently associated with increased risk of mortality or re-intervention with incremental risk-predictive capacity over traditional predictors (Central Illustration). In addition, the association of bioprosthetic AVCd with hemodynamic and clinical outcomes did not differ in women versus men.

In aortic bioprostheses, levels of calcification load were substantially lower compared with native aortic valves when reaching the comparable severity of hemodynamic dysfunction. More importantly, no difference in calcification burden between men and women was observed in bioprostheses in the present study. This observation corresponds to previous research in explanted aortic bioprostheses, which

FIGURE 2 **Impact of Bioprosthetic AVCd on Clinical Outcome**



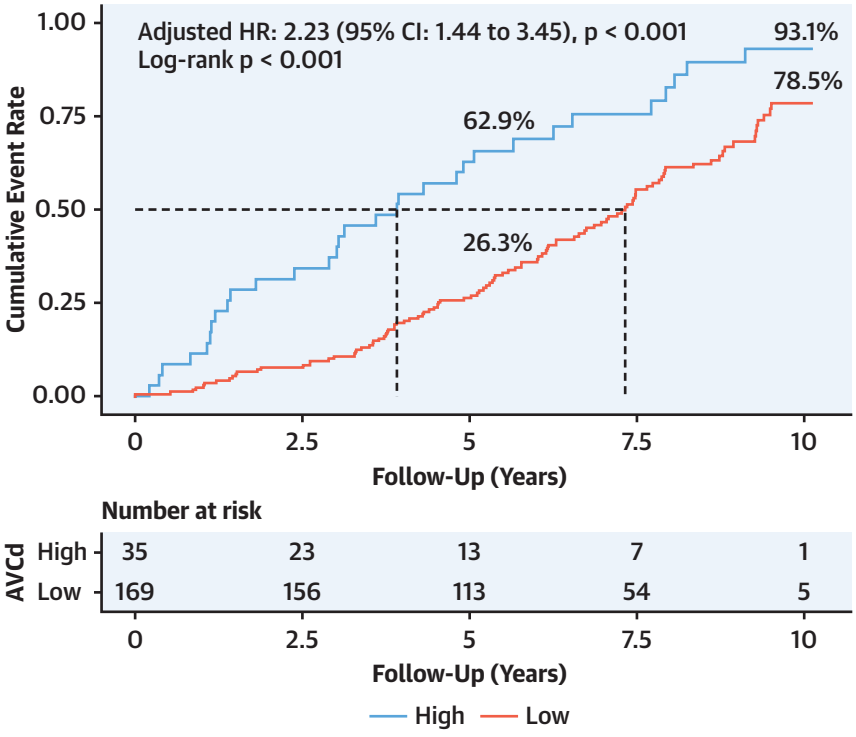
Unadjusted (**blue line** with 95% confidence interval **shaded in light blue**) and adjusted (**gray dotted line** with 95% confidence interval) penalized splines of aortic valve calcification density (AVCd) in relation to relative hazard ratio for the composite of death or re-intervention.

found that leaflet calcium levels, quantified by atomic adsorption spectrometry, did not differ between explants of male and female patients (23). Considering the radical change of the cellular basis of aortic valves post-AVR, it may conceivably be hypothesized that the sex disparity on calcification load is more derived from the "soil" (the cellular composition of the valve) rather than the "seeds" (internal milieu). Moreover, because the women with bioprostheses are largely post-menopausal, the deficiency of estrogen might also have a role, weakening the protective effect against ectopic calcification and osteoporosis.

AVCd AND HEMODYNAMIC OUTCOMES. The diagnostic and prognostic value of AVCd has been well validated in native aortic stenosis (9,10) and is now included in the European guidelines to confirm disease severity in patients with discordant gradient at echocardiography. In particular, it has been shown that AVCd is a powerful predictor of aortic stenosis hemodynamic severity, progression, and outcomes (9,10,24-27) and that different severity cut-points should be used in women (>300 AU/cm^2) versus men (>500 AU/cm^2). In the present study of patients with aortic bioprosthetic valves, we observed a modest correlation between progression of AVCd and progression of MG during the same period (from early post-operative to baseline visit), with no sex-related difference in the strength or slope of this relationship. Furthermore, an independent association between baseline AVCd and HVD over the subsequent 3-year period was observed. This later finding further expands our previous observation that presence of any detectable leaflet calcification at MDCT imaging is associated with higher risk of HVD during subsequent follow-up (11). AVCd quantitated by noncontrast MDCT imaging, as a flow-independent marker, seems to be an early and sensitive marker of the SVD process and a strong predictor of HVD of aortic bioprostheses.

AVCd AND CLINICAL OUTCOMES. As illustrated by the results of the present study, AVCd precedes (in time) and predicts the occurrence of HVD. In turn, HVD is associated with an increased risk of adverse clinical outcomes. We previously reported an independent association between HVD and increased mortality (11,28). Accordingly, in the present study, AVCd was found to be strongly and independently associated with mortality and re-intervention. In a recent study, "microscopic" calcification assessed by ^{18}F-fluoride positron emission tomography-CT imaging was the only independent factor associated with

FIGURE 3 Impact of Bioprosthetic AVCd on Clinical Outcome According to Optimal Threshold



Cumulative incidence curve for clinical outcome by threshold. Adjusted for age, sex, valve implant duration, diabetes, coronary heart disease, chronic obstructive pulmonary disease, renal insufficiency, baseline mean gradient, baseline left ventricular ejection fraction, and severe prosthesis-patient mismatch. AVCd = aortic valve calcification density; CI = confidence interval; HR = hazard ratio.

future bioprosthetic dysfunction (defined as severe hemodynamic valve dysfunction combined with patient symptoms, the need for redo valve intervention, or valve-related death) (29). The present study shows that "macroscopic" AVCd quantitated by using MDCT imaging provides important incremental prognostic information beyond traditional risk factors. Furthermore, we establish the threshold of AVCd (≥58 AU/cm²) that provides the best predictive value for clinical outcomes. As opposed to native aortic stenosis (9,25), we found no sex-related difference in the AVCd severity cut-points, and thus for patients with aortic bioprostheses, the same threshold can be used in men and women. The severity cut-point of AVCd for bioprosthetic valves (58 AU/cm²) seems much lower than that for native aortic stenosis (300 AU/cm² for women and 500 AU/cm² for men) (9). However, in the context of bioprosthetic valves, a small amount of macroscopic calcification is likely a marker of already advanced SVD and accelerated progression in the future.

Of clinical importance, the combination of MG progression and AVCd thresholds identified a group of patients with a strikingly high risk of adverse clinical outcomes, which suggests that the 2 parameters are complementary rather than redundant in assessing prognosis. Meanwhile, patients with

TABLE 4 Incremental Value of AVCd for Prediction of Mortality or Re-Intervention

	5-Year Clinical Outcomes	
	Background Model*	Background Model + AVCd Threshold
Discrimination		
C-statistic†	0.66	0.69
IDI (95% CI)†	0.052 (0.006–0.105), p = 0.027	
Category-less NRI (95% CI)†	0.250 (0.015–0.397), p = 0.040	
Calibration		
LR test, p value	p < 0.001	
BIC	1,249	1,239

*Background model included age, sex, valve implant duration, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, renal insufficiency, mean gradient, LV ejection fraction, and severe prosthesis-patient mismatch. †Indicators were calculated based on the cumulative incidences of clinical outcomes at 5 years, using proportional hazards models as working models (R package survC1 and survIDINRI).

BIC = Bayesian information criteria; IDI = integrated discrimination improvement; LR = likelihood ratio; NRI = net reclassification improvement; other abbreviations as in Tables 1 and 2.

elevated MG or AVCd alone incurred a similar intermediate risk, which implies that AVCd could serve as a valuable addition to identify patients at risk despite negative findings by echocardiography due to the complicated hemodynamic conditions. Moreover, AVCd dichotomized by our threshold was incremental to traditional predictors and thus could be a promising candidate in the future derivation of prediction models.

STUDY LIMITATIONS. The present study is an ambispective cohort involving multimodality imaging in patients with implanted bioprostheses. First, early post-surgery data were collected retrospectively. Second, although follow-up for clinical outcomes had been completed in all patients, the follow-up echocardiography data were obtained in 137 (67%) patients, owing to the high short-term mortality/reoperation in this target population. Analysis confined to this subset of patients could introduce bias and thus should be regarded as exploratory. Due to the limited sample size in this subset, we could not comprehensively adjust for all potential covariables. However, we performed successive adjustment for verification, and these analyses may lend credence to the findings. In addition, the baseline characteristics in the study were measured at a mid-term after AVR, and the findings can therefore not be directly extrapolated to early SVD post-AVR. Lastly, our study only included surgical bioprostheses, and thus the results cannot be transposed to transcatheter bioprostheses.

CLINICAL IMPLICATION. Our findings have several implications for clinical practice. First, bioprosthetic leaflet calcification assessed by MDCT imaging, which generally precedes HVD, provides an early and objective marker for both hemodynamic deterioration and ensuing adverse clinical outcomes. Second, given the complementary nature of MG and AVCd in stratifying patients at risk, multimodality imaging including echocardiography and MDCT imaging could improve detection, quantitation, and monitoring of structural and hemodynamic valve deterioration after AVR and therefore optimize the management of patients with failing aortic bioprosthetic valves.

CONCLUSIONS

Bioprosthetic AVCd is strongly and independently associated with HVD and the risk of death or valve re-intervention. A cut-point of AVCd ≥58 AU/cm^2 provides the best performance for prediction of clinical outcomes. As opposed to native aortic stenosis, there are no sex-related differences in the relationship between AVCd and hemodynamic or clinical outcomes. Combination of bioprosthetic AVCd and MG progression improves risk stratification and could assist patient management after AVR. The quantitation of bioprosthetic leaflet calcification by noncontrast MDCT imaging should be incorporated into the clinical assessment and follow-up of patients with aortic bioprostheses.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Bioprosthetic AVC as assessed by multidetector cardiac computerized tomography is associated with valve malfunction and adverse clinical outcomes.

TRANSLATIONAL OUTLOOK:

Further studies are needed to identify combinations of AVC and hemodynamic measurements that have greatest utility to guide patient management after aortic valve replacement.

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KEY WORDS aortic leaflet calcification, aortic valve replacement, hemodynamic valve deterioration, outcome, surgical bioprosthesis

APPENDIX For supplemental figures and tables, please see the online version of this paper.