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ORIGINAL PAPER

Calcification of surgical aortic bioprostheses and its impact on clinical outcome

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Aims Aortic valve calcification (AVC) of surgical valve bioprostheses (BPs) has been poorly explored. We aimed to evaluate *in vivo* and *ex vivo* BP AVCs and its prognosis value.

Methods and results Between 2011 and 2019, AVC was assessed using *in vivo* computed tomography (CT) in 361 patients who had undergone surgical valve replacement 6.4 ± 4.3 years earlier. *Ex vivo* CT scans were performed for 37 explanted BPs. The *in vivo* CT scans were interpretable for 342 patients (19 patients [5.2%] were excluded). These patients were 77.2 ± 9.1 years old, and 64.3% were male. Mean *in vivo* AVC was 307 ± 500 Agatston units (AU). The AVC was 562 ± 570 AU for the 183 (53.5%) patients with structural valve degeneration (SVD) and 13 ± 43 AU for those without SVD ($P < 0.0001$). *In vivo* and *ex vivo* AVCs were strongly correlated ($r = 0.88$, $P < 0.0001$). An *in vivo* AVC > 100 AU ($n = 147$, 43%) had a specificity of 96% for diagnosing Stage 2–3 SVD (area under the curve = 0.92). Patients with AVC > 100 AU had a worse outcome compared with those with AVC ≤ 100 AU ($n = 195$). In multivariable analysis, AVC was a predictor of overall mortality (hazard ratio [HR] and 95% confidence interval = 1.16 [1.04–1.29]; $P = 0.006$), cardiovascular mortality (HR = 1.22 [1.04–1.43]; $P = 0.013$), cardiovascular events (HR = 1.28 [1.16–1.41]; $P < 0.0001$), and re-intervention (HR = 1.15 [1.06–1.25]; $P <$ 0.0001). After adjustment for Stage 2–3 SVD diagnosis, AVC remained a predictor of overall mortality (HR = 1.20 [1.04–1.39]; $P = 0.015$) and cardiovascular events (HR = 1.25 [1.09–1.43]; $P = 0.001$).

Conclusion CT scan is a reliable tool to assess BP leaflet calcification. An AVC > 100 AU is tightly associated with SVD and it is a strong predictor of overall mortality and cardiovascular events.

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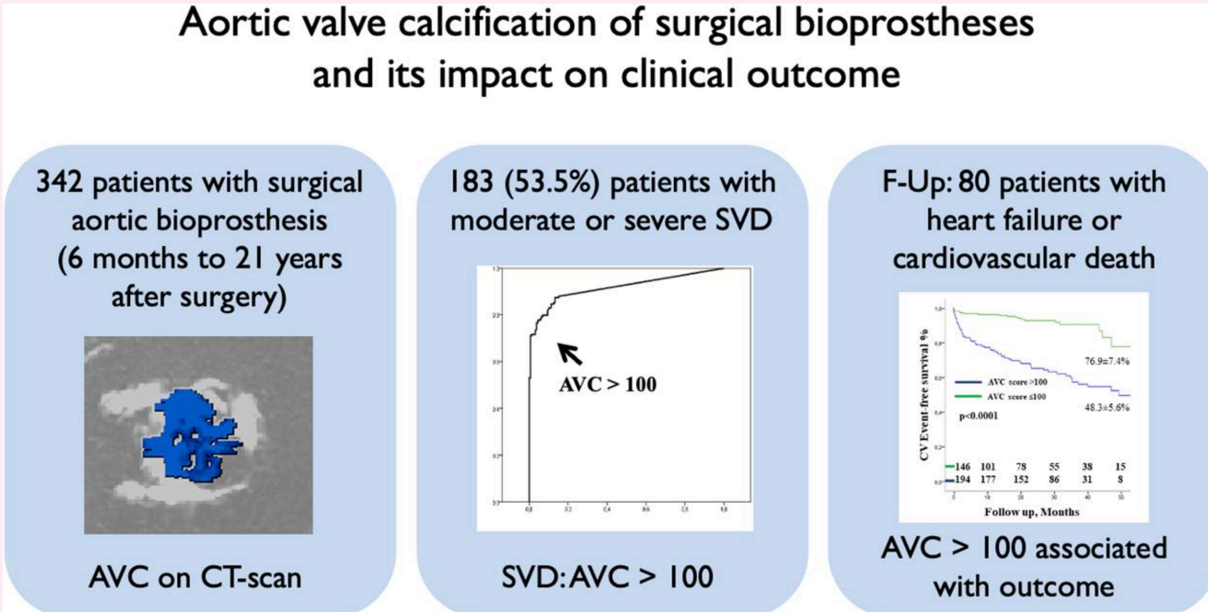
Graphical Abstract



AVC, aortic valve calcification; CT, computed tomography; SVD, structural valve deterioration; F-Up, follow-up; CV, cardiovascular.

Keywords surgical aortic valve bioprostheses • computed tomography • echocardiography • aortic valve calcification • structural valve degeneration

Introduction

Bioprostheses (BPs) are preferentially used over mechanical valves for aortic valve replacement (AVR) in patients aged >60–65 years,[1] although current guidelines also support their use in younger patients.[2,3] Structural valve deterioration (SVD) remains the Achilles' heel of BP AVR, especially in young patients. The three main underlying mechanisms of SVD may involve passive accumulation of calcium in cell remnants, an atherosclerotic-like process, or an immune-mediated process[4–6]. Although the first step of SVD is likely related to inflammation,[7] the hallmark of these pathways is progressive calcification of the leaflet tissue,[4,8] regarded as a key factor in the development of SVD. Currently, echocardiography is the first-line imaging modality to monitor BP and diagnose SVD.[9,10] However, calcifications are difficult to image and quantify by echocardiography. In contrast, computed tomography (CT) scan is a simple and easily available tool for assessing aortic valve calcification (AVC) of native valves[11,12] and BP.[13,14] Despite recent publications reporting on AVC and deterioration of BP,[14–16] limited data are available on the clinical and prognosis utility of CT scan for the assessment of BP.

Hence, we aim to evaluate the *in vivo* and *ex vivo* leaflet AVC deposit, the relation of AVC with SVD on echocardiography, and the clinical prognosis value of BP AVC.

Methods

Patients

This observational monocentric study enrolled patients who underwent a CT scan for the assessment of their surgical aortic valve BP between June 2011 and May 2019. Computed tomography was performed at any time after the BP implantation. Patients with clinical or imaging evidence of endocarditis or with confirmed leaflet thrombosis associated with haemodynamic impairment were excluded from the study. The study was accepted by the local Ethics Committee, and all patients provided an informed consent.

Clinical and biological parameters were prospectively recorded at the time of inclusion (baseline). Previous aortic valve surgery and pre- and post-operative echocardiography data were retrieved.

Echocardiography

Echocardiographic examinations were performed by experienced investigators using commercial ultrasound systems (GE Vivid E9 or E95, Waukesha, WI, USA) within 4 months of the CT scan and stored in a dedicated workstation (Image Vault and Echopac software, GE Medical Systems, Horten, Norway). Standard echocardiographic data were acquired according to the Translink protocol.[6] Regarding BP assessment, the left ventricular outflow tract diameter was cautiously measured in the parasternal long-axis view, the left ventricular outflow tract and aortic velocity time integrals were measured in the apical three- or five-chamber view with pulsed-wave and continuous wave Doppler, respectively. The BP dimensionless index and effective orifice area (EOA) were calculated. Patient prosthesis mismatch (PPM) was defined using the reference values of indexed EOA as previously published.[9] Finally, BPs were retrospectively classified in different stages of SVD.[17,18] Early morphological leaflet changes without significant haemodynamic impact defined the earliest stage (Stage 1). Stage 2 referred to morphological leaflet changes and moderate haemodynamic dysfunction (increase in mean gradient ≥ 10 mmHg from surgery to reach ≥20 mmHg and <30 mmHg, or a new or worsening ≥1 grade of an intraprosthetic regurgitation resulting in moderate regurgitation). Bioprosthetic valves with severe stenosis/regurgitation were classified as Stage 3.

In vivo and *ex vivo* CT scans of BP

A non-contrast *in vivo* CT scan was carried out for AVC evaluation using a 64-detector CT scanner (Light speed VCTR or Optima 660CT; GE Healthcare, FairField, CT, USA). The entire heart was imaged in 3 mm thick axial slices with a pitch of 0.35 and B35f core during inspiration. The recordings were made with a tube potential of 12 kV and a tube current-time product of 80 mAS. Computed tomography images were evaluated using semiautomatic software (AWR, Smartscore 4.0, GE Healthcare, Waukesha, WI, USA). The measurement of AVC was performed by two physicians (J.-M.S., G.G.) using a threshold of 130 Hounsfield units.[19] The assessment excluded the metal framework, the aortic annulus, the aortic wall immediately adjacent to the BP, and the left ventricle outflow tract. Results were expressed in Agatston units (AU).[11,14,20,21]

Explanted surgical BPs were obtained from patients undergoing redo-surgical AVR (Redo-S) and were macroscopically analysed and weighted. *Ex vivo* CT scans were performed on the same scanner. Images were analysed by two physicians (J.-M.S., G.G.), who were blinded to the echocardiography and *in vivo* CT results. Explanted BPs were also imaged using a microcomputed tomography (micro-CT) system (Skyscan 1272-Bruker, Kontich, Belgium). Three-dimensional reconstruction was performed by NRecon and CTvox softwares (Bruker, Kontich, Belgium).

Follow-up

Patient follow-up was documented from medical records, phone calls to the patients, their family, or the attending physician. All-cause mortality, cardiovascular mortality, and a composite cardiovascular event endpoint combining cardiovascular mortality and heart failure (requiring hospitalization or worsening of NYHA class) were analysed. Clinical events identified as endpoints were adjudicated on the basis of a consensus between two clinicians. The type of management, medical or invasive, i.e. Redo-S or transcatheter valve-in-valve replacement (VinV), was collected.

Statistics and data analysis

Variables were expressed as mean and standard deviation, or number and percentage as appropriate. Non-normally distributed variables were log-transformed [N-terminal pro-brain-type natriuretic peptide (NT-proBNP), AVC]. Comparisons between groups were based on Student's *t*-test, χ^2 test, or exact Fisher test, as appropriate. Interobserver and intraobserver consistency for measuring AVC was assessed by intraclass correlation (ICC) in 20 patients. The Spearman rank correlation coefficient was used to measure the strength of the association between *in vivo* and *ex vivo* AVC scoring. Thresholds of AVC score for predicting Stage 2–3 SVD were evaluated with the receiver operating characteristic (ROC) curve, and the area under the curve (AUC) was calculated. Determinants of AVC were assessed by univariable and multivariable linear regression. Overall survival, cardiovascular survival, event-free cardiovascular survival, and survival without Redo-S or VinV were assessed by the Kaplan–Meier method, and compared with a log-rank test. Univariable and stepwise forward multivariable Cox models were used to identify factors associated with the time to outcome (variable selection for $P < 0.05$). Hazard ratios (HRs) are provided with 95% confidence intervals. Hazards proportionality was graphically assessed, and all models were inspected for multicollinearity. The pre-operative variables considered as possible correlates of outcome included aortic valve disease type, BP type (porcine or not) and size, associated procedures, PPM, mean post-operative gradient, and the CT scan baseline variables were age, sex, classical cardiovascular risk factors, NYHA class 3–4, creatinine clearance, mean gradient, moderate/severe aortic regurgitation, LVEF, and AVC. A P value < 0.05 was considered statistically significant. Statistics were performed with the SPSS Version 19 (IBM Corp., Armonk, NY, USA) and R software (version 3.1.1).

Results

Baseline characteristics

An *in vivo* CT scan was performed in 361 patients who were recruited into the clinical cohort study (*Figure 1*). Among these patients, 19 (5.2%) were excluded for low quality CT scan. Finally, 342 patients (77.2 ± 9.1 years of age, 64% male) of the Translink study[6] were included after a mean post-operative period of 6.4 ± 4.3 years (range: 6 months to 21 years). Patient characteristics are detailed in *Table 1*. The patients presented a high prevalence of coronary artery disease and associated risk factors, and 101 (30%) were in NYHA class 3–4.

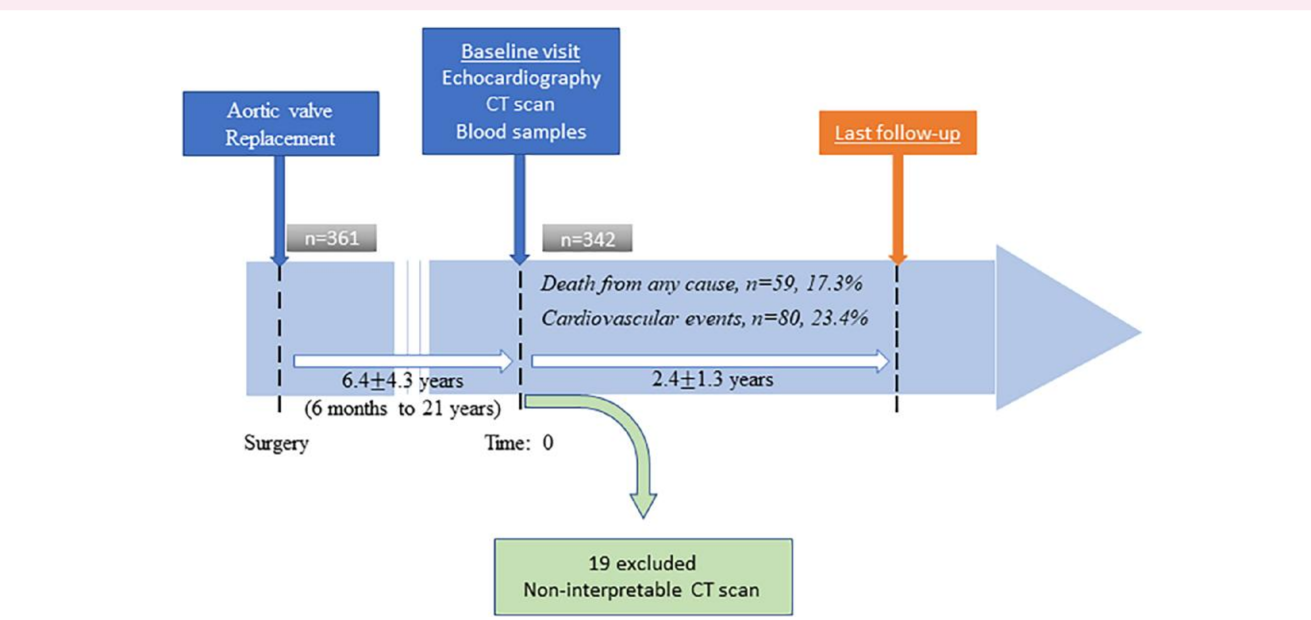


Figure 1 Study design and follow-up. CT, computed tomography.

Table 1 Baseline characteristics (at the time of CT scan) of the study population and of the subgroups CalcifBP (AVC > 100 AU) and No/LowCalcifBP (AVC ≤ 100 AU)

	All (*n* = 342)	CalcifBP (*n* = 147)	No/LowCalcifBP (*n* = 195)	*P*
Age, years	77.2 ± 9.1	77.7 ± 10.1	76.6 ± 8.3	0.26
Men, *n* (%)	220 (64.3)	75 (51.0)	145 (74.4)	<0.0001
Body surface area, m^2	1.82 ± 0.19	1.79 ± 0.21	1.84 ± 0.18	0.02
NYHA class 3–4, *n* (%)	101 (29.5)	74 (50.3)	27 (13.9)	<0.0001
Tobacco, *n* (%)	141 (41.2)	57 (38.8)	84 (43.1)	0.42
Diabetes, *n* (%)	76 (22.2)	42 (28.6)	34 (17.4)	0.014
Dyslipidaemia, *n* (%)	220 (64.3)	91 (61.9)	129 (66.2)	0.44
Hypertension, *n* (%)	254 (74.3)	113 (76.9)	141 (72.3)	0.48
CAD, *n* (%)	135 (39.5)	76 (51.7)	59 (30.3)	<0.0001
History of AF, *n* (%)	99 (28.9)	57 (38.8)	42 (21.5)	0.001
Severe kidney failure, *n* (%)	19 (5.6)	13 (8.8)	6 (3.1)	0.04
Clearance, mL/min/1.73 m^2	63.5 ± 25.2	60.6 ± 26.9	65.7 ± 23.7	0.07
Phosphate, mmol/L	1.0 ± 0.18	1.1 ± 0.2	1.0 ± 0.2	<0.0001
Calcium-phosphate product	2.4 ± 0.50	2.6 ± 0.5	2.3 ± 0.6	<0.0001
NT-proBNP, pg/mL	2183 ± 555	3358 ± 6399	1213 ± 3092	<0.0001
CRP, mg/L	6.5 ± 1.5	6.9 ± 14.9	6.2 ± 12.6	0.66

AF, atrial fibrillation; AVC, aortic valve calcium; CAD, coronary artery disease; CRP, C-reactive protein; NYHA, New York Heart Association.

Table 2 Echocardiographic characteristics of the study population and of the subgroups CalcifBP (AVC > 100 AU) and No/LowCalcifBP (AVC ≤ 100 AU)

	All (*n* = 342)	CalcifBP (*n* = 147)	No/LowCalcifBP (*n* = 195)	*P*
Initial surgery				
Mean BP gradient, mmHg	12.9 ± 5.9	14.1 ± 6.7	11.9 ± 5.1	0.0005
Initial EOA, cm^2	1.6 ± 0.3	1.4 ± 0.3	1.7 ± 0.3	<0.0001
Severe PPM, *n* (%)	24 (7.0)	19 (12.9)	5 (2.6)	<0.0001
At the time of CT scan				
LVEDD, mm	50.0 ± 9.3	52.1 ± 7.9	48.3 ± 7.8	<0.0001
LVEF, %	62.6 ± 10.2	60.1 ± 10.3	64.4 ± 9.8	0.0001
LVEF < 50%, *n* (%)	23 (6.8)	14 (9.5)	9 (4.6)	0.08
PASP, mmHg	38.2 ± 14.1	43.8 ± 14.7	33.8 ± 11.8	<0.0001
BP maximum velocity, m/s	3.2 ± 1.1	4.0 ± 0.8	2.5 ± 0.9	<0.0001
Mean BP gradient, mmHg	26.4 ± 19.1	40.5 ± 17.4	15.6 ± 12.2	<0.0001
DVI	0.39 ± 0.16	0.30 ± 0.13	0.47 ± 0.13	<0.0001
EOA, cm^2	1.4 ± 0.7	1.0 ± 0.5	1.8 ± 0.6	<0.0001
ΔEOA from surgery, cm^2	−0.12 ± 0.53	−0.42 ± 0.46	−0.10 ± 0.47	<0.0001
Stenotic SVD, *n* (%)	100 (29.2)	83 (56.5)	17 (8.7)	<0.0001
Regurgitant SVD, *n* (%)	83 (24.3)	58 (39.5)	25 (12.8)	<0.0001
Anticoagulants, *n* (%)	67 (19.6)	39 (26.4)	28 (14.4)	0.006
Statins, *n* (%)	183 (53.5)	78 (52.7)	107 (54.1)	0.79
ACEI/ARAII, *n* (%)	188 (55.0)	77 (52.0)	111 (57.2)	0.34

ACEI, angiotensin converting enzyme inhibitor; ARAII, angiotensin receptor II antagonist; BP, bioprosthesis; DVI, dimensionless velocity index; EOA, effective orifice area; Δ, changes; LA, left atrium; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; PPM, patient prosthesis mismatch; SVD, structural valve degeneration.

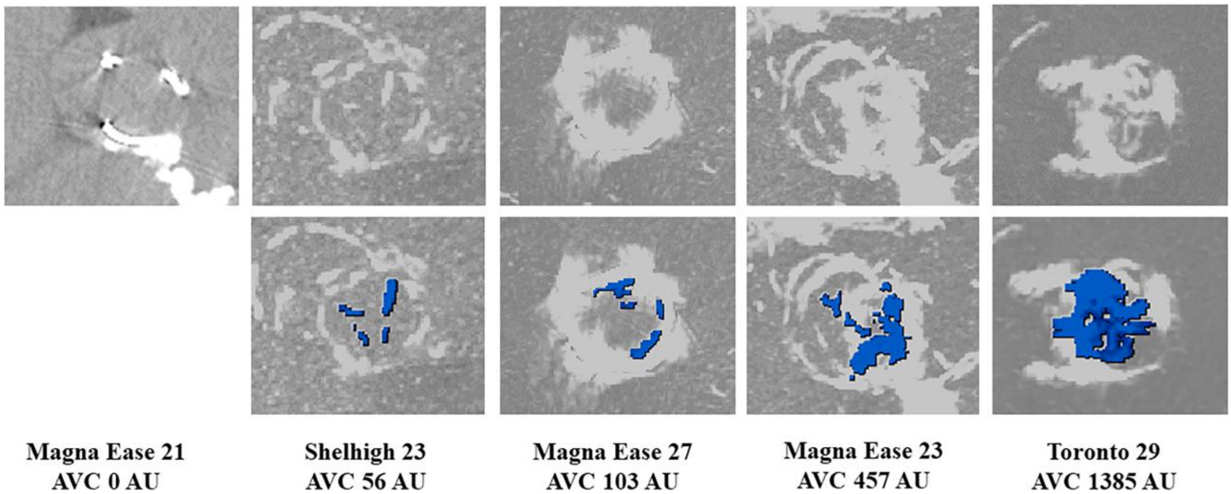


Figure 2 Measurement method of AVC with superimposition of different CT scan slices and calcifications layers from a normal to a severely calcified bioprosthesis. AVC, aortic valve calcification.

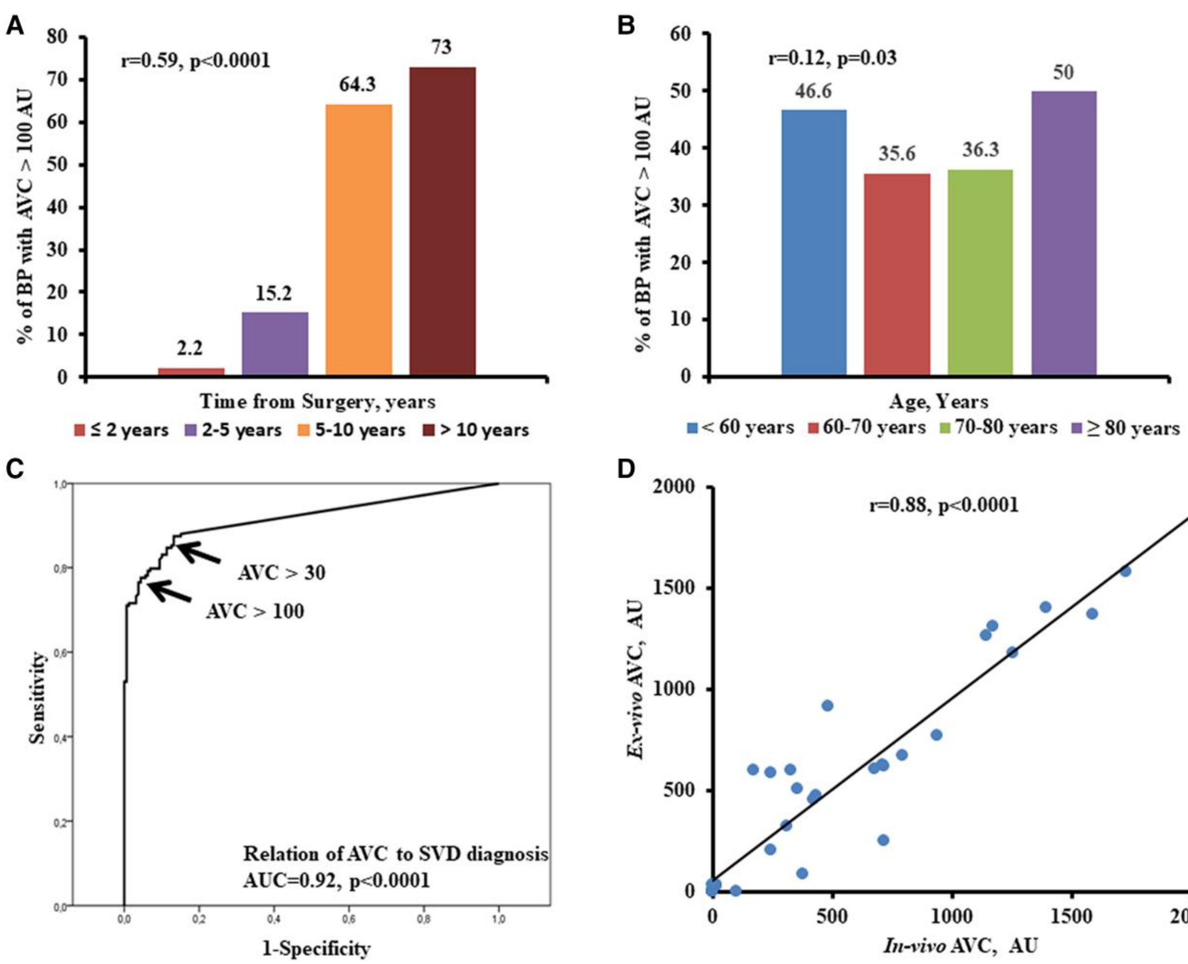


Figure 3 *A*) Distribution of BP with AVC > 100 AU according to time since surgery, *B*) distribution of BP with AVC > 100 AU according to patient's age, *C*) ROC analysis for diagnosing Stage 2–3 SVD using AVC (arrows indicating 30 AU and 100 AU thresholds) on CT scan. *D*) Correlation between *in vivo* and *ex vivo* AVCs in the 37 explanted BPs. AVC, aortic valve calcification; BP, bioprosthesis; ROC, receiver operating characteristic; SVD, structural valve deterioration.

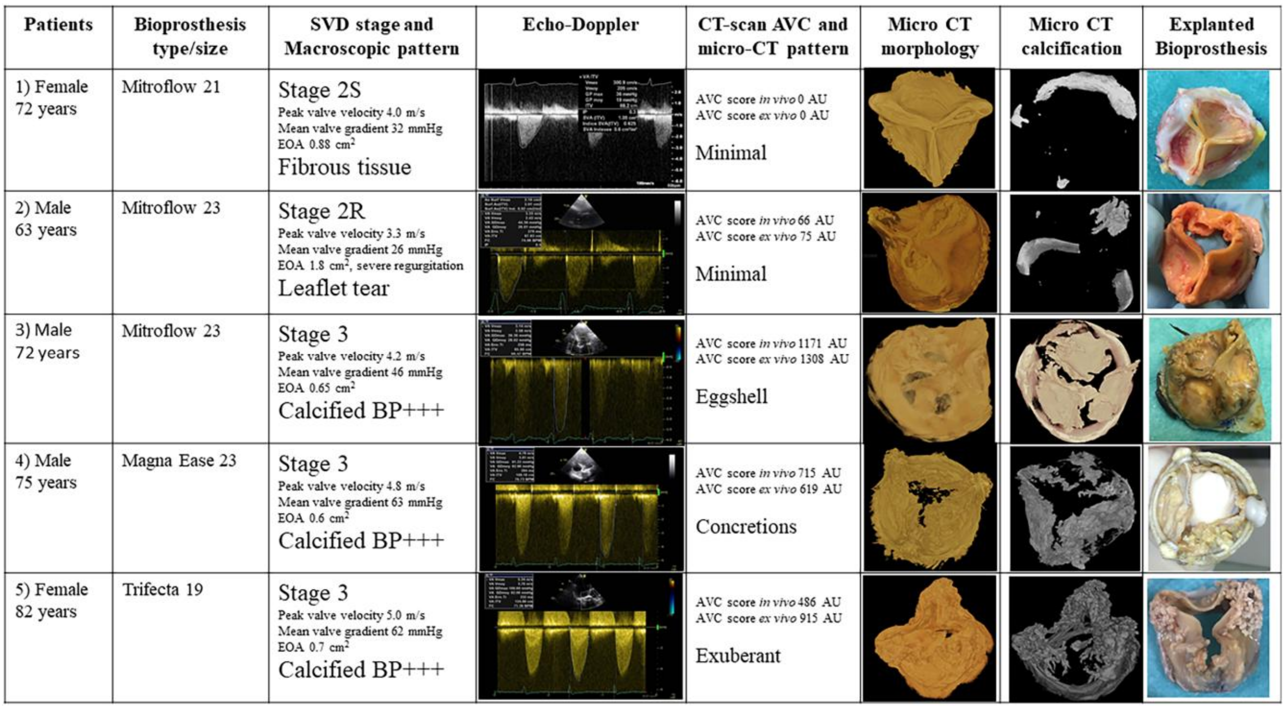


Figure 4 Characteristics of five aortic BPs explanted: Of the 37 explanted BPs, the calcification pattern was classified as punctiform (minimal) in 12 (32%) patients (AVC: 176 ± 301 AU), important with a regular soft surface (eggshell) in 15 (41%) patients (645 ± 506 AU), important with an irregular surface (concretions) in 7 (19%) patients (629 ± 308 AU), and frankly exuberant (coraliform) in 3 (8%) BPs (930 ± 583 AU); commissural calcifications were observed in 32 (86%) patients; in two patients, BP calcifications were minimal, the BP dysfunction being manly due to a proliferation of fibrous tissue limiting leaflet motility (photo of Patient 1), or to a leaflet tear (photo of Patient 2). AVC, aortic valve calcification; BP, bioprosthesis; EOA, effective orifice area; SVD, structural valve deterioration.

The implanted BPs were stented bovine pericardial BP ($n = 316$, 92.3%), stented porcine BP ($n = 17$, 4.9%), and stentless porcine BP ($n = 9$, 2.6%). They included pericardial Magna-Ease ($n = 108$, 31.6%, Edwards Lifesciences, Irvine, CA, USA), Mitroflow ($n = 101$, 29.5%, Sorin Biomedica Cardio, Saluggia, Vercelli, Italy), Perimount ($n = 79$, 23.1%, Edwards Lifesciences, Irvine, CA, USA), Trifecta ($n = 26$, 7.6%, St Jude Medical Inc., St. Paul, MN, USA), Perceval ($n = 2$, 0.6%, Sorin Biomedica Cardio, Saluggia, Vercelli, Italy), stented porcine Mosaic ($n = 16$, 4.7%, Medtronic Inc., Minneapolis, MN, USA), and Labcor ($n = 1$, 0.3%, Labcor, Belo Horizonte, Brazil), and stentless porcine ($n = 9$, 2.6%).

After the initial surgery, a severe PPM was found in 24 (7%) patients. Baseline echocardiographic characteristics are presented in *Table 2*. Out of the 342 patients, 19 (5.6%) had Stage 1 SVD and 183 (53.5%) had Stage 2–3 SVD (100 [29.2%] with stenotic SVD, and 83 [24.3%] with regurgitant SVD). Regurgitant SVD was more frequent in porcine compared with pericardial BP (71% vs. 42%, $P = 0.011$). The delay from surgery to Stage 2–3 SVD was 9.0 ± 3.3 years. On echocardiography, we observed leaflet thickening and/or limitation of motion in 201 (58.8%) patients, leaflet tearing/prolapse in 81 (24%), perforation was suspected/diagnosed in 2 (0.6%), partial delamination in 3 (0.9%), and pure fibrotic SVD in 2 (0.6%) patients.

In vivo and *ex vivo* calcifications

The mean *in vivo* AVC at inclusion was 307 ± 500 AU. The ICC was 0.97 (95% CI [0.93–0.99]) for interobserver and 0.98 (95% CI [0.94–0.99]) for intraobserver AVC measurements. The interobserver difference was 8.18 ± 4.63%, while the intraobserver difference was 8.06 ± 5.47%. The mean *in vivo* AVC was 9 ± 37 AU for normal BP, it was 51 ± 66 AU in Stage 1 SVD, 544 ± 551 AU in Stage 2 SVD, and 573 ± 577 AU in Stage 3 SVD (*Figure 2*). The mean AVC was higher for stenotic than for regurgitant Stage 2–3 SVD (688 ± 624 vs. 428 ± 469 AU, $P = 0.018$).

Early calcifications were observed in 10% (12/124) of the patients who had a CT < 3 years after the initial surgery, but an increase in mean gradient > 10 mmHg was found in only 1 of these 12 patients. Patient's age was weakly associated with AVC ($r = 0.12$, $P = 0.03$), but AVC increased strongly ($r = 0.59$, $P < 0.0001$) with time since surgery (*Figure 3*). The type of BP was not a predictor of AVC, but compared with pericardial BP, AVC tended to be lower in porcine BP (419 ± 550 vs. 585 ± 573 AU, $P = 0.074$). Predictors of *in vivo* AVC in multivariable analysis were post-operative LVEF ($\beta = -0.28$, $P < 0.0001$), mean gradient ($\beta = 0.23$, $P < 0.0001$), EOA ($\beta = -0.44$, $P < 0.0001$), and severe PPM ($\beta = 0.21$, $P < 0.0001$).

From the ROC curve analysis (AUC = 0.92), an AVC > 100 AU had a sensitivity of 77% and a specificity of 96% for diagnosing SVD Stage 2–3 (*Figure 3*).

Ex vivo AVC was assessed for 37 BP explanted 8.1 ± 2.4 years after the initial surgery. *In vivo* AVC was measured 49 ± 28 days (range: 6–115 days) before explantation. The explanted BP comprised 36 stented pericardial devices (including 9 Perimount or Magna-Ease [24.3%], 26 Mitroflow [70.2%], 1 Trifecta [2.7%] BP), and 1 (2.7%) porcine stented BP (Mosaic). The BP size was 21.8 ± 2.3, and the weight at explantation

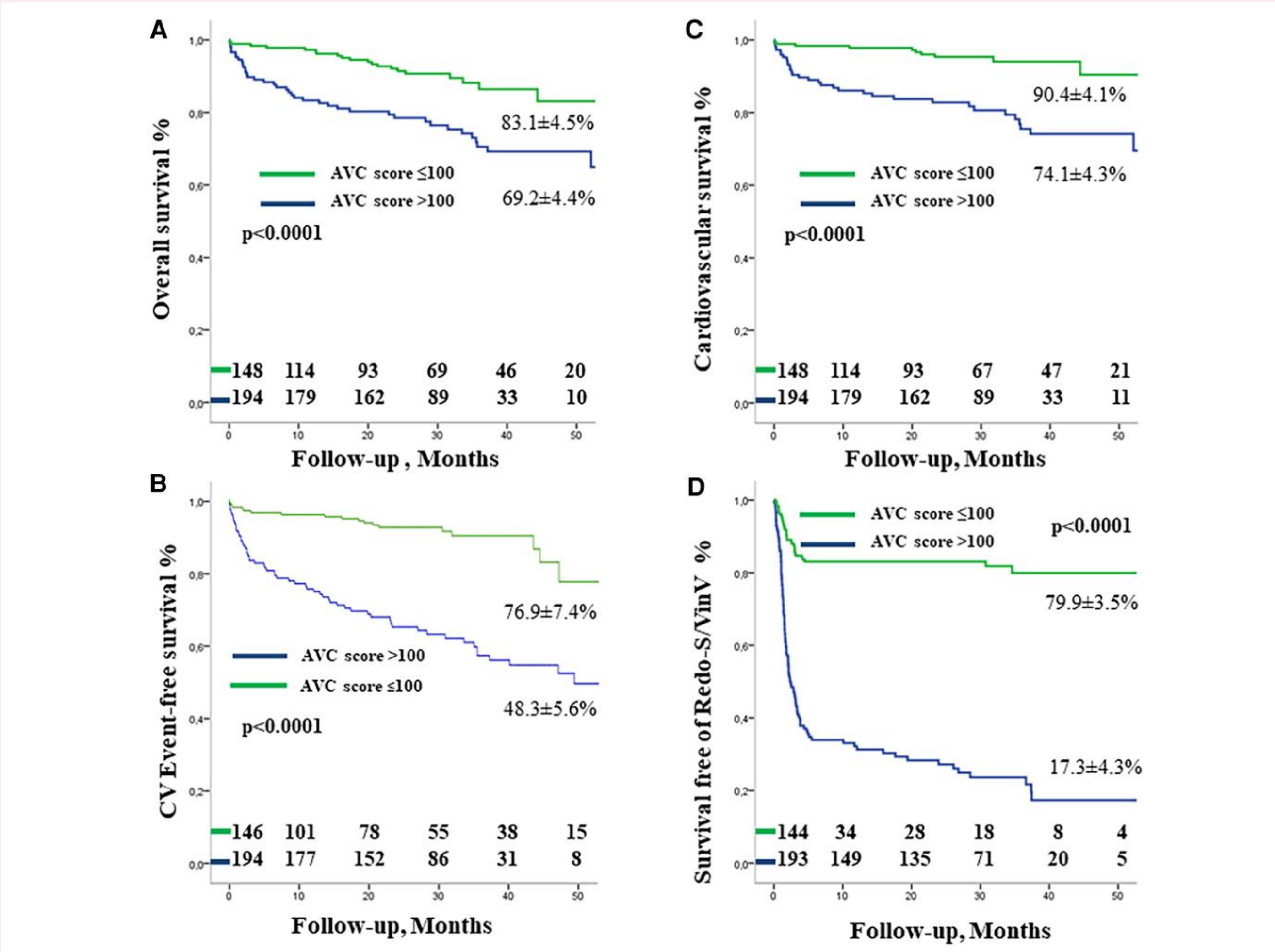


Figure 5 Association between AVC score (> or ≤100 AU) and *A*) overall survival; *B*) cardiovascular event-free survival; *C*) cardiovascular survival; and *D*) survival without Redo-S/VinV, for up to 50 months. BP, bioprosthesis; AVC, aortic valve calcification; Redo-S, redo-surgery; VinV, transcatheter valve-in-valve replacement.

was 2.84 ± 1.07 g. For the 37 explanted BPs, the *in vivo* AVC was 472 ± 498 AU and the *ex vivo* AVC was 499 ± 493 AU ($r = 0.88$, 95% CI [0.77–0.94]; $P < 0.0001$) (*Figure 3D*). Calcification pattern was assessed in the 37 BPs on micro-CT (*Figure 4*). Interestingly, 8/12 explanted BPs with minimal calcifications on micro-CT were considered as not calcified with standard CT.

Patients were classified according to AVC > 100 AU (CalcifBP, $n = 147$, 43%) or AVC ≤100 AU (No/LowCalcifBP, $n = 195$, 57%) (*Tables 1* and *2*). *In vivo* AVC was 703 ± 555 AU and 9 ± 22 AU in the CalcifBP and in the No/LowCalcifBP groups, respectively. In the CalcifBP group, the proportion of men was lower (51% vs. 74%; $P < 0.0001$), diabetes mellitus was more frequent (28.6% vs. 17.4%; $P = 0.014$), and patients were more symptomatic (NYHA class 3–4: 50.3% vs. 13.9%; $P < 0.0001$). Serum phosphate level, calcium-phosphate product, and NT-proBNP level were higher in the CalcifBP group ($P < 0.0001$).

Follow-up and prognosis

Patients were followed-up for 29.1 ± 15.6 months; no patient was lost to follow-up. Among the patients with SVD ($n = 183$), 44 (24%) received only medical treatment, 64 (35%) underwent Redo-S, and 75 (41%) had VinV. Indications and timing for Redo-S or VinV were discussed by the Heart Valve Team on the basis of conventional clinical and echocardiographic parameters, in symptomatic patients with Stage 3 SVD with a life expectancy of more than 1 year. At the time of CT scan, AVC did not differ between the 3 groups, but initial BP size was greater ($P = 0.004$) and regurgitant SVD was more frequent ($P = 0.013$) in patients referred to VinV, compared with the other two groups. The mean time from CT scan to Redo-S or VinV was 4.4 ± 8.1 (range 0–43) months. Management was significantly more invasive in the regurgitant than in the stenotic SVD group (83.3% vs. 69.7%; $P = 0.037$).

Fifty-nine (17.3%) patients died during follow-up including 42 cardiovascular deaths. Cardiovascular events occurred in 80 (23.4%) patients, including heart failure in 55 (16.1%) patients. Compared with the No/LowCalcifBP group (*Figure 5*), the CalcifBP group had a decrease in overall survival (69.2 ± 4.4 vs. 83.1 ± 4.5%, $P < 0.0001$), in cardiovascular survival (74.1 ± 4.3 vs. 90.4 ± 4.1%, $P < 0.0001$), and in cardiovascular event-free survival (48.3 ± 5.6 vs. 76.9 ± 7.4%, $P < 0.0001$) at 50 months. Finally, survival without invasive management was strongly decreased in the CalcifBP group (17.3 ± 4.3 vs. 79.9 ± 3.5%; $P < 0.0001$).

In multivariable analysis (*Table 3*), AVC was a predictor of overall mortality (HR = 1.16 [1.04–1.29]; $P = 0.006$), cardiovascular mortality (HR = 1.22 [1.04–1.43]; $P = 0.013$), cardiovascular events (HR = 1.28

Table 3 Predictive factors of outcome in multivariable Cox model analyses

	HR	95% CI	*P*
Overall mortality			
Age at CT scan	1.07	[1.02–1.12]	0.003
Obesity (BMI ≥ 30)	2.57	[1.52–4.33]	<0.0001
NYHA 3–4	2.01	[1.13–3.55]	0.017
AVC[a]	1.16	[1.04–1.29]	0.006
Cardiovascular mortality			
NYHA 3–4	2.99	[1.47–6.01]	0.002
BP diameter	0.78	[0.66–0.92]	0.004
AVC[a]	1.22	[1.04–1.43]	0.013
Cardiovascular events			
Age at CT scan	1.04	[1.01–1.08]	0.01
BP diameter	0.87	[0.77–0.98]	0.019
AVC[a]	1.28	[1.16–1.41]	<0.0001
Redo-S/VinV			
Age at CT scan	0.97	[0.95–0.98]	0.001
NYHA 3–4	2.04	[1.38–302]	<0.0001
Moderate–severe AoReg	3.91	[2.72–5.63]	<0.0001
LVEF	0.97	[0.95–0.98]	<0.0001
BP mean gradient	1.03	[1.02–1.04]	<0.0001
AVC[a]	1.15	[1.06–1.25]	<0.0001

AoReg, Aortic regurgitation; AVC, aortic valve calcification; BP, bioprosthesis; Cardiovascular events, cardiovascular mortality or heart failure; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; Redo-S, redo-surgery; VinV, transcatheter valve-in-valve replacement.
[a]AVC was log-transformed.

[1.16–1.41]; $P < 0.0001$), and Redo-S/VinV (HR = 1.15 [1.06–1.25]; $P < 0.0001$).

When a diagnosis of Stage 2–3 SVD was forced into the model, AVC remained a predictor of overall mortality (HR = 1.20 [1.04–1.39]; $P = 0.015$) and cardiovascular events (HR = 1.25 [1.09–1.43]; $P = 0.001$).

Discussion

In this large series of patients with surgical aortic BP assessed by *in vivo* CT scan, AVC was accurately measurable in 95% of patients, and correlated tightly with *ex vivo* AVC. Some degree of calcification was already detected in 10% of patients within 3 post-operative years, despite the absence of clear BP alteration on echocardiography. An AVC value > 100 AU was associated with SVD, and was a predictor of overall mortality, cardiovascular mortality, cardiovascular events, and survival with invasive management. In addition, AVC remained a predictor of outcome after adjustment for Stage 2–3 SVD diagnosis. Thus, AVC on CT scan provides additional prognosis information that is not available with echocardiography.

BP leaflet calcification

The calcification process is regarded as a common pathophysiological event in the development of SVD.[5,9] Leaflet tissue mineralization leads to cusp stiffening and progressive stenosis, and/or regurgitation caused by calcification-associated cusp tearing. The early calcification process, as identified by ^{18}F-sodium fluoride uptake in positron emission tomography, has been associated with the development of SVD,[13] but such an assessment is more complex to implement in clinical practice. In contrast, recent publications have associated any level of CT scan leaflet calcification with a higher risk of haemodynamic alteration during follow-up.[14,15]

Calcium scoring of BP may be challenging in some patients owing to artefacts related to patient movement or breathing, to the BP frame, or to aortic wall calcifications. However, we were able to measure calcium content in 95% of patients thus demonstrating the feasibility of this measurement in clinical practice. In addition, *in vivo* and *ex vivo* AVCs carried out on the same CT scanner have confirmed the validity of the measurement. Hence, *in vivo* AVC, a flow-independent marker, appears to be a reliable tool to detect and evaluate the early signs of the calcification process, which can be used as an early and relatively sensitive marker of the SVD process.[14] *In vivo* assessment of AVC should therefore be proposed as a part of routine BP follow-up to identify those at risk of early SVD. Notably, it might be used to evaluate new BP designs or brands and to assess leaflet tissue susceptibility to calcification in humans.

Post-operative factors associated with BP calcification

Classical haemodynamic parameters, recorded after initial surgery, related to small size BP such as mean gradient, EOA, and PPM, were found to be predictors of higher AVC during follow-up, in agreement with previous studies.[15,22,23] A small aortic orifice is thought to enhance mechanical stress on the surface of BP leaflets by increasing both pressure load and shear stress,[22] which could accelerate the calcification process and thus SVD. This awareness has encouraged the efforts of the manufacturers to optimize BP haemodynamics,[22,23] as well as the efforts of the surgeons to prevent mismatch by selecting the largest possible BP size.

Association between BP leaflet calcification and clinical outcome

It is noteworthy that AVC measurement on CT scan strongly predicts overall mortality, cardiovascular mortality, cardiovascular events, and the need for invasive treatment. In the multivariable model, AVC systematically emerged as a predictor of clinical outcome suggesting that it provides additional prognosis information beyond haemodynamic characteristics, in agreement with native aortic valve disease.[12] It is conceivable that despite a similar mean gradient and EOA, both dependent on stroke volume, greater AVC is a more reliable marker of BP degeneration and ventricular afterload than haemodynamic parameters. Furthermore, in native aortic valve disease, calcification has been shown to be a non-linear process that increases exponentially and accelerates disease progression.[12] Of note, disease acceleration has also been demonstrated in some BP.[10] Beyond the BP itself, the process of leaflet calcification might also be a more general marker of risk in these patients[24–28]. Indeed, native aortic valve sclerosis[24,25] and native AVC on CT scan[11,12] have been associated with impaired patient prognosis.

Limitations

In this observational study, we face potential data collection biases inherent to this type of study. Although CT scan was performed in a large range of BP types, haemodynamics, and time since surgery, it was not systematically implemented in all patients presenting with a BP during the study period. Owing to long time gaps between initial implantation and last follow-up, many BP included in this study are old generation prostheses, and we cannot extrapolate with certainty our results to all types of BP. The type of BP was neither a predictor of AVC magnitude nor of outcome. Hence, our results suggest a prognosis value for AVC that is independent of the type of BP. However, the results cannot be extended to transcatheter BP. We have identified two different AVC thresholds for predicting the diagnosis of SVD, namely 30 and 100. Although the 100 threshold is more specific for diagnosing Stage 2–3 SVD, the 30 threshold is important to consider in the assessment of BP as a marker of a degenerative process to organize close monitoring. It is possible that the threshold associated with SVD differs slightly depending on the stenotic or regurgitant nature of the SVD, or on the tissue nature of BP. Further studies involving larger group of patients with periodic and long-term AVC measurements will be needed to confirm and extend our results. Microcalcifications, explored with ^{18}F-sodium fluoride uptake in positron emission tomography, is useful for assessing the early stages of SVD, but is not currently suitable to clinical practice.[7,13,29] The interplay between BP AVC and coronary artery calcification, or mitral annulus calcification, should be assessed in future studies. The limited number of explanted BP, in relation with the development of VinV procedures, did not allow definite conclusions regarding BP-, tissue-, or patient-related patterns on micro-CT. However, the current development of VinV procedures will preclude in the future the enrolment of a large number of explanted surgical BP.

Conclusion

Computed tomography scan is a reliable and useful tool to assess the *in vivo* calcification of surgical aortic BP in most patients. As such, it could be used for monitoring early leaflet tissue alteration before haemodynamic modifications are identified, and to confirm calcified SVD, with a low threshold as compared with native aortic valve stenosis. Leaflet AVC is strongly associated with overall mortality, cardiovascular mortality, and cardiovascular events. The assessment of AVC using CT scan should therefore be part of the clinical toolbox in the follow-up of patients with an implanted surgical BP. Finally, the detection of early leaflet calcification with CT scan could be used to monitor new types of BP, or as an opportunity for personalized management in some patients with modifiable risk factors.

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Data availability

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

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