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Cohort Study

Bioprosthetic aortic valve replacement in patients aged 50 years old and younger: Structural valve deterioration at long-term follow-up. Retrospective study

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ABSTRACT

Background: Structural valve deterioration (SVD) remains the major determinant of bioprosthesis durability. The aim of this study was to investigate the SVD incidence, predictors and outcomes in patients aged 50 years and younger after bioprosthetic aortic valve replacement (bAVR).

Methods: We retrospectively analyzed 73 consecutive patients ≤50 years old who underwent bioprosthetic AVR at our center between 2005 and 2015. Median age at surgery was 44 (interquartile range [IQR]: 39–47) years. Follow-up was 93.2% complete at a median time of 7.2 (IQR: 5.5–9.5) years. Cumulative follow-up was 545.5 valve-years. Bioprosthesis SVD was determined by strict echocardiographic assessment.

Results: The overall survival-rate at 10/15 years and freedom from SVD at 10/12.5 years were 89.6 ± 5.2%/81.5 ± 9.1% and 73.5 ± 8.2%/41.9 ± 18.9%, respectively. SVD occurred at a median time of 8.2 (IQR: 6.0–9.9) years after bAVR. Age was not found as an independent predictor for SVD at the multivariable model, despite a higher rate of SVD in the age group ≤30 years. Freedom from reoperation due to SVD at 10/15 years was 71.3 ± 14.1%/13.6 ± 12.3%. Reoperation was performed at a median time of 10.0 (IQR: 8.9–11.9) years since first bAVR and was associated with a 100% 12-month survival.

Conclusions: In our study, the rate and time of SVD occurrence were comparable to those of other studies' older age groups. Strict echocardiographic monitoring of valve performance is mandatory to set the appropriate timing of eventual reoperation. This attitude can improve outcomes of bAVR in younger patients.

1. Introduction

Approximately 20% of patients undergoing aortic valve replacement (AVR) [1] are younger than 50 years old**.** We are witnessing a shift in practice towards the use of biological prosthesis for AVR (bAVR) in younger patients, related to the low thrombogenicity, avoidance of lifetime anticoagulation, the constant improvement in valve hemodynamics, the on growing field of transcatheter aortic valve replacement (TAVR) [2–4].

Theory: Time-related structural valve deterioration (SVD) is the major hurdle of bioprosthetic valves and increasing in life expectancy has raised several questions about bioprosthesis durability, with younger age being highly related to bioprosthesis SVD [5]. Moreover, patients younger than 50 years of age are represented poorly in randomized trials and registry series.

Most of the reports provided the evaluation of SVD based only on the surgical explant and thus underestimating the incidence of a clinically relevant SVD [6]. The use of a strict echocardiographic follow-up and standardized prespecified criteria to allow a timely diagnosis of SVD in larger studies could provide noteworthy imaging long-term data and

Abbreviations: **SVD**, Structural Valve Deterioration; **bAVR**, bioprosthetic Aortic Valve Replacement; **AVR**, Aortic Valve Replacement; **TAVR**, Transcatheter Aortic Valve Replacement; **TTE**, Transthoracic Echocardiography; **PPM**, Prosthesis-Patient Mismatch; **LV**, Left Ventricle; **EF**, Ejection Fraction; **PASP**, Pulmonary Artery Systolic Pressure; **NYHA**, New York Heart Association.

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thus confirming the feasibility and safety of bAVR in younger patients [6].

The main endpoints of interest of this long-term single-center retrospective study were a) to assess with clinical and echocardiographic follow-up the incidence of SVD post-bAVR in patients ≤50 years old; b) to determine the predictors of SVD c) to identify freedom from reoperation for SVD and overall survival in this population.

2. Patients and methods

From January 2005 to December 2015, 109 consecutive patients aged 50 years and younger underwent a bAVR at our center for severe symptomatic aortic valve disease. Patients with missing data, metastatic cancer and <2 years life expectancy were excluded, resulting in 93 eligible patients. From February 2018 to May 2019 patients were contacted for clinical and echocardiographic follow-up. The patients were interviewed via phone calls to collect information about clinical events, clinical status and last echocardiographic reports, when they might have failed to access our center. Out of 93 patients, 20 patients (21.5%) were lost at follow-up due to multiple reasons (study consent refusal, untraceable patients, especially foreigners). Thus, the final study population resulted in 73 patients. Study population and follow-up are graphically represented in Fig. 1. Data collection and statistical analysis adhered to current guidelines for reporting mortality and morbidity after cardiac valve interventions [7].

Transthoracic echocardiography (TTE) examinations were conducted according to the recommendations for the imaging assessment of prosthetic heart valves of the European Association of Cardiovascular Imaging [8]. Patient's own post-implant study was used as a reference for serial evaluation of valve function and morphology. Complete TTE evaluation was performed using commercially available equipment (Philips EPIQ echocardiographic system, Philips Healthcare, Andover, MA equipped with a X5-1 transducer), at baseline (prior to bAVR), pre-discharge (within 7 days after surgery) and at follow-up.

2.1. Outcome measures

An echocardiographic diagnosis of SVD was made using the predefined parameters: cusp thickness ≥3 mm, presence of calcification and abnormal cusp motion [7]. Clinically relevant SVD was defined, as valve-related dysfunction (mean aortic gradient ≥20 mmHg, effective orifice area ≤0.9–1.1 cm^2, dimensionless valve index <0.35 m/s, moderate or severe prosthetic valve regurgitation, or the need for a repeat procedure [9]. Patient Prosthesis Mismatch (PPM) was calculated using the indexed Effective Orifice Area (EOA) method, ie, the EOA of the prosthesis divided by the patient's body surface area. Severe PPM was considered when the value resulted less than 0.65 cm^2/m^2 [8].

2.2. Statistical analysis

The distribution of the continuous variables was assessed by Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± SD or median (interquartile range), according to the distribution assumed, while categorical variables were expressed as frequency (percentage). The two groups were compared using 1-way Anova test for variables presented with mean ± SD while a non-parametric test, Kruskal-Wallis, was performed for variables expressed as median (interquartile range). Categorical variables were analyzed by Chi-Square, or Fisher's exact Test if the expected cell count in contingency tables was <5. Pre-discharge and last follow-up measurements were compared by *t*-test or Wilcoxon rank-signal test. Time-to-event analyses were performed with the use of Kaplan-Meyer estimates and were compared with the use of the log-rank test. The effect of clinical and echocardiographic variables was assessed with the use of a Cox proportional hazards regression model in order to identify which of them were associated with an occurrence of SVD at long-term follow-up. All results were considered significant with P-values < 0.05. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

2.3. Ethical statement

The study was approved by the institutional ethics committee (Institutional Review Board Registration- R732/18-CCM779), registered with the unique identifying number (researchregistry7219) and reported in line with the STROCSS [10] criteria. All patients provided the written informed consent.

3. Results

3.1. Baseline clinical characteristics and follow up

Median age at surgery was 44 (IQR: 39 to 47) years (range 18–50 years) (Table 1). Baseline pre-operative echocardiographic data are presented in Table 2. The choice of bioprosthesis was made according to the patient's preference in almost all patients (85.0%). Surgical data are summarized in Table 3. The most implanted bioprosthesis type was a stented bovine pericardial Carpentier-Edwards Perimount/Magna (90.4%). Most patients were discharged with recommendation of anticoagulation/antiplatelet therapy for at least 3 months after surgery.

The median follow-up period was 7.2 (interquartile range [IQR]: 5.5 to 9.5) years, for a total of 545.5 valve-years. Echocardiographic follow-up was 93.2% (n = 68) complete.

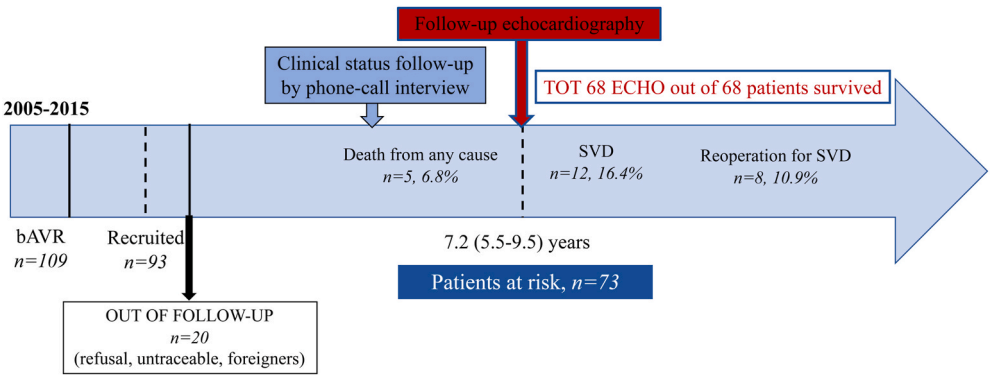

Fig. 1. Study design and follow-up.
bAVR = bioprosthetic aortic valve replacement; FU = follow-up; SVD = structural valve deterioration.

Table 1
Baseline clinical characteristics.

Variables	All patients (n = 73)	No SVD (n = 61)	SVD (n = 12)	p Value
Age (years)	44(39–47)	44(40–48)	36(26–44)	
Female	16(21.9)	12(19.7)	4(33.3)	0.44
BSA (m^2)	1.86 ± 0.2	1.86 ± 0.2	1.86 ± 0.2	0.95
BMI (kg/m^2)	24.7 ± 3.9	24.6 ± 4	25.1 ± 3.8	0.71
NYHA functional class				
I-II	62(84.9)	52(85.2)	10(83.3)	1.00
III-IV	11(15.1)	9(14.8)	2(16.7)	
Hypertension	22(30.1)	22(36.1)	0	0.014
Diabetes mellitus	1(1.4)	1(1.6)	0	1.00
Coronary artery disease	1(1.4)	1(1.6)	0	1.00
Previous myocardial infarction	1(1.4)	1(1.6)	0	1.00
Previous CABG	1(1.4)	1(1.6)	0	1.00
Smoking	18(24.7)	15(24.6)	3(25)	1.00
Peripheral vascular disease	2(2.7)	2(3.3)	0	1.00
Atrial fibrillation	2(2.7)	2(3.3)	0	1.00
Previous stroke/TIA	1(1.4)	1(1.6)	0	1.00
Serum Creatinine (mg/dL)	0.89 ± 0.3	0.91 ± 0.3	0.81 ± 0.3	0.27

Values are n (%), median (IQR), or mean ± SD.
BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass graft; IQR = interquartile range; NYHA= New York Heart Association; SVD = structural valve deterioration; TIA = transient ischemic attack.

Table 2
Baseline echocardiographic characteristics.

Variables	All patients (n = 73)	No SVD (n = 61)	SVD (n = 12)	p Value
LVEDVi (mL/m^2)	83 (59–111)	83.5 (59–112)	81 (60–102.5)	0.78
LVESVi (mL/m^2)	30.5(23–49)	31(22–49)	28.5 (25.5–51.5)	0.68
LVEF (%)	60(54.5–65)	61 (55.5–65.5)	57 (52.5–60.5)	0.10
LA area (cm^2)	23 (19–26)	22 (19–26)	23 (16.5–30.5)	0.83
IVS (mm)	11.5 (10–13)	12 (10–13)	10 (8–12)	0.08
AVA index (cm^2/m^2)	0.52 (0.46–0.63)	0.52 (0.46–0.63)	0.53 (0.36–0.62)	0.64
Mean aortic pressure gradient (mmHg)	41(19–55)	42(19–56)	37 (20.5–47.5)	0.63
Peak velocity (m/sec)	3.6(2.2–4.6)	3.45 (2.2–4.7)	3.6(2.1–4.4)	0.68
Aortic valve lesion				
Bicuspid	42(57.5)	34(55.7)	8(66.7)	0.54
Rheumatic	4(5.5)	3(6.6)	1(8.3)	0.52
Stenosis	17(23.3)	16(26.2)	1(8.3)	0.18
Regurgitation ≥2+	39(53.4)	33(54.1)	6(50)	0.79
Mixed lesion	17(23.3)	12(19.7)	5(41.7)	0.09
Tricuspid regurgitation ≥2+	0	0	0	
PASP (mmHg)	31 (25–37)	31 (25–37)	29 (25–39.5)	0.90

Values are n (%), median (interquartile range).
AVA = aortic valve area; IVS = interventricular septum; LA = left atrial; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; PASP = pulmonary artery systolic pressure; SVD = structural valve deterioration.

3.2. Survival

At 10 and 15 years, the overall survival rate was 89.6 ± 5.2% and 81.5 ± 9.1%, respectively (Fig. 2,A). Five deaths (6.8%; 0.9% per valve-year) were reported, at a median time of 8.3 (IQR: 5.7 to 8.5) years. None of them were associated with SVD. Three patients died for cancer/neurologic degenerative disease diagnosed prior to bAVR, while cardiovascular death occurred in 2 patients (1 myocardial infarction, 1 stroke). Thus, by excluding from the analysis the three mentioned patients with a reduced life-expectancy at the time of original bAVR, the 15-year mortality rate was 2.74%.

Table 3
Surgical data and discharge medications.

Variables	All patients (n = 73)	No SVD (n = 61)	SVD (n = 12)	p Value
Concomitant procedures	23(31.1)	18(29.5)	5(41.7)	0.41
CABG	2(2.7)	2(3.3)	0	0.73
Ascending aorta replacement	13(17.8)	11(18.0)	2(16.7)	0.91
Mitral valve replacement/repair	8(10.9)	5(8.2)	3(25)	0.08
Previous aortic valve repair/replacement	7(9.6)	6(9.8)	1(8.3)	0.87
Bioprosthesis choice				
Patient's preference	62(85.0)	55(90.2)	7(58.3)	
Desire for pregnancy	3(4.1)	2(3.3)	1(8.3)	
Agonist athletes	3(4.1)	3(4.9)	0	
OAT absolute controindication	2(2.7)	0	2(16.7)	
Cancer/degenerative disease at surgery	3(4.1)	1(1.6)	2(16.7)	
Bioprosthesis type				
Carpentier-Edwards Perimount/Magna	66(90.4)	57(93.5)	9(75)	0.08[a]
Mitroflow Sorin	3(4.1)	1(1.6)	2(16.7)	
St.Jude Medical Trifecta	1(1.4)	0	1(8.3)	
Edwards Intuity	3(4.1)	3(4.9)	0	
Bioprosthesis size, mm				0.07
19	7(9.6)	3(5.0)	4(33.3)	0.02
21	15(20.6)	13(21.3)	2(16.7)	0.72
23	22(30.1)	21(34.4)	1(8.3)	0.09
25	20(27.4)	15(24.6)	5(41.7)	0.29
27	8(10.9)	8(13.1)	0	0.34
29	1(1.4)	1(1.6)	0	1.00
Bioprosthesis size ≤21 mm	22(30.1)	16(26.2)	6(50)	0.16
Moderate/severe PPM	1(1.4)	0	1(8.3)	0.12
Discharge medications				
VKA	20(27.4)	13(21.3)	7(58.3)	0.008
APT	52(71.2)	48(78.7)	4(33.3)	0.002
VKA + APT	1(1.4)	0	1(8.3)	0.023

Values are n (%), median (interquartile range).
APT = antiplatelet therapy; AVR = aortic valve replacement; CABG = coronary artery bypass graft; OAT = oral anticoagulation therapy; PPM = prosthesis-patient mismatch; SVD = structural valve deterioration; VKA = vitamin K antagonist.
[a] vs. non-Carpentier-Edwards.

3.3. Structural valve deterioration

SVD was reported in 12 patients (16.4%; 2.3% per valve-year) during follow-up, none within first 5 years after surgery. SVD occurred at a median time of 8.2 (IQR: 6.0 to 9.9) years after bAVR. The cumulative event-free survival from SVD was 73.5 ± 8.2% and 41.9 ± 18.9% at 10 and 12.5 years, respectively (Fig. 2,B). Patients with SVD were significantly younger (median age 36 [IQR: 26 to 44] years, p = 0.013). At follow-up evaluation, a significant higher rate of patients in New York Heart Association (NYHA) functional class I was observed in the no SVD group (93.4% vs. 41.6%, p < 0.01), while no patients in NYHA class III/IV were observed in both groups. Detailed characteristics of the patients with SVD are analyzed in Supplemental Table 1.

3.4. Echocardiographic results

There was no significant difference in the baseline and pre-discharge echocardiographic characteristics of the study population stratified according to SVD (Tables 2 and 4). Presence of SVD led to a decrease in left ventricular (LV) ejection fraction (EF) as well as an increase in LV volumes, and pulmonary artery systolic pressure (PASP) at follow-up

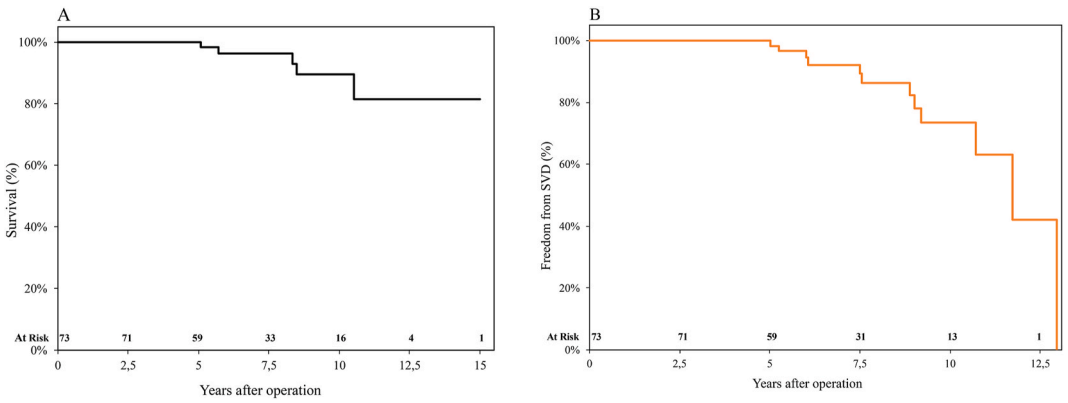

Fig. 2. Primary endpoints. Overall survival after bAVR (A), and Kaplan-Meier freedom from structural valve deterioration (SVD).

Table 4
Echocardiographic assessment at pre-discharge and follow-up.

Variables	No SVD (n = 56)		SVD (n = 12)		p Value				
	Pre-discharge	Last follow-up	Pre-discharge	Last follow-up	P1[a]	P2[b]	P3[c]	P4[d]	P5[e]
LVEDVi (mL/m^2)	58(44.5–72.5)	59(50–77.5)	54(38–84)	59(54.5–88)	0.07	0.027	0.11	0.41	0.84
LVESVi (mL/m^2)	23(16.5–31)	22.5(19–31)	23.5(21–45)	29.5(23–37.5)	0.68	0.047	0.044	0.06	0.79
LVEF (%)	57(54–62.5)	62(58–66)	55(49–60)	56.5(51–62.1)	<.0001	0.93	0.18	0.042	0.28
LA area (cm^2)	21.5 (17–24.5)	20.5 (18–24)	21 (19–23)	25 (20–27)	0.91	0.29	0.28	0.24	0.83
IVS (mm)	11.5 (10–14)	11 (10–12)	12 (11–13)	12 (11–13)	0.25	1.00	0.60	0.18	0.92
AVA index (cm^2/m^2)	1.04(0.82–1.33)	0.87(0.77–1)	0.87(0.72–0.94)	0.43(0.41–0.63)	0.002	0.001	0.15	<.0001	0.014
Mean pressure gradient (mmHg)	15(11–21)	15(11–21)	15.5(10–20.5)	39.5(32–54)	0.49	0.002	<.0001	<.0001	0.83
Peak velocity (m/s)	2.5 (2.3–2.9)	2.65(2.2–3)	2.85(2.5–3.05)	4.2 (3.45–4.45)	0.91	0.011	0.001	<.0001	0.18
Central Aortic Regurgitation ≥2+	0	0	0	4(33.3)				0.007	
PVL	5(8.9)	4(7.1)	0	0				0.51	0.42
trace/mild	4(7.1)	3(5.3)							
≥ moderate	1(1.8)	1(1.8)							
Aortic Stenosis	0	0	0	7(58.3)				<.001	
Moderate/severe PPM	0	0	1(8.3)	1(8.3)				0.13	0.13
Mitral regurgitation ≥2+	0	1(1.8)	0	2(16.7)				0.08	
PASP (mmHg)	29 (25–33)	27 (23–31)	28 (22–29)	38 (29–41.5)	0.24	0.007	0.001	0.003	0.19
Need for reoperation	0	3(5.4)	0	8(66.7)				<.0001	
Time at reoperation (years)		3.4(1.6–7.7)		10.0(8.9–11.9)				0.025	
Follow-up time (years)		6.6(5.1–8.8)		9.9(8.4–13.1)				0.001	

Values are n (%), median (interquartile range).
PVL = paravalvular leak; other abbreviations as in Tables 2–3
[a] P1, p Value of delta1 (Follow-up vs. Pre-discharge) in the No SVD group.
[b] P2, p Value of delta2 (Follow-up vs. Pre-discharge) in the SVD group.
[c] P3, p Value between delta1 and delta2.
[d] P4, p Value for Follow-up between No SVD and SVD group.
[e] P5, p Value for Pre-discharge between No SVD and SVD group.

(Table 4). Predominantly stenosis, as SVD pattern, was identified in 7 patients (4 of which were isolated) and predominantly regurgitation in 4 (one of which was isolated). PPM with severe leaflet calcification was diagnosed in one patient. Echocardiographic evaluation of valve performance during follow-up is shown in Supplemental Fig. 1.

3.5. Predictors of SVD

Younger age resulted associated with higher (hazard ratio, 0.62; 95% confidence interval, 0.39 to 0.99; p = 0.045) risk for SVD in the univariable analysis, but this result was not confirmed in the multivariate model (Table 5). In the overall population, 57.1% aged ≤30 years (n = 4/7), 18.7% aged 31–40 years (n = 3/16) and 10% of patients aged>40 years (n = 5/50) developed SVD. The three age groups being numerically unbalanced, hazard ratio estimates for age groups were not reliable due to wide confidence intervals (Supplemental Fig. 2). Similarly, smaller prosthesis size ≤21 mm was not associated with higher rate of SVD compared to size >21 mm (Table 5, Supplemental Fig. 2).

3.6. Reoperation

Eleven patients (15.1%; 2.05% per valve-year) underwent reoperation, with median interval time since first operation of 9.3 (IQR: 6.9 to 10.5) years. Freedom from all-causes reoperation at 10 and 15 years was 84.2 ± 6.5% and 21.1 ± 17.7%, respectively (Fig. 3,A). Indications were SVD in 8 patients, endocarditis in 2 and moderate paravalvular leak in one. Rate of reoperation was significantly associated with occurrence of SVD (p = 0.04) (Fig. 3,B) and was performed at a median time of 10.0 (IQR: 8.9 to 11.9) years since first intervention and 1.2 (IQR: 1.1 to 1.4) years since first echocardiographic diagnosis of SVD. Freedom from reoperation due to SVD was 71.3 ± 14.1% and 13.6 ± 12.3% at 10 and 15 years, respectively. Linearized rate of reoperation due to SVD was 6.48%/year. For a redo in SVD, a mechanical valve was used in 4 patients, bioprosthesis in 3 and TAVR in 1 (Supplemental Table 1). Survival at 12 months after reoperation (including 30-day mortality) was 100%.

Table 5
Univariate Cox Regression Analyses assessing the association of factors with the development of SVD.

Predictor	Univariate model		Multivariate model	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Age (years)	0.62 (0.39–0.99)	**0.045**	0.78 (0.43–1.39)	0.398
Female	2.59 (0.75–9.01)[a]	0.134		
BSA	0.78 (0.39–1.53)	0.463		
BMI	0.87 (0.41–1.86)	0.718		
NYHA functional class III-IV	1.24 (0.26–5.83)	0.789		
Serum Creatinine	0.62 (0.38–0.99)	**0.048**	0.75 (0.45–1.24)	0.265
Prosthesis size ≤21mm	2.86 (0.86–9.51)[a]	0.086		
Baseline echocardiogram				
LVEF	0.81 (0.43–1.53)	0.520		
AVA	0.60 (0.19–1.95)	0.400		
Mean aortic pressure gradient	0.63 (0.30–1.33)	0.221		
PASP	1.36 (0.77–2.42)	0.290		
Aortic stenosis	1 (0.30–3.31)[a]	0.999		
Aortic regurgitation	3.66 (0.46–29.07)[a]	0.220		
Bicuspid valve	1.64 (0.47–5.67)[a]	0.436		
IVS	0.46 (0.23–0.92)	**0.027**	0.61 (0.28–1.33)	0.214
Pre-discharge echocardiogram				
LVEF	1.17 (0.61–2.25)	0.632		
AVA	0.51 (0.22–1.17)	0.110		
Mean aortic pressure gradient	0.74 (0.37–1.48)	0.392		
PASP	1.01 (0.50–2.06)	0.979		
IVS	0.412 (0.10–1.74)	0.228		

CI = confidence interval; other abbreviations as in Tables 1-2
[a] Non-standardized variable.

4. Discussion

Depicting our center's attitude in prioritizing the patient's preference over the ever-changing guidelines' recommendations regarding the age threshold, our study aimed to provide data on outcomes, and particularly on the occurrence of SVD, in patients 50 years and younger after bAVR.

Our main findings are: 1) overall survival at 15 years was 81.5%; 2) the incidence of SVD was 16.4% with a median interval time since surgery of 8.2 years; 3) younger age did not result an independent predictor for SVD 4) reoperation for SVD was a common outcome (10.9%), was associated with excellent survival and presented a median delay from the first surgery of 10.0 years.

4.1. Survival

Ruel [11] and recently Schnittman [12] reported similarly high survival rates after biological vs. mechanical AVR in patients 50 years old and younger at 15 years. In patients aged 65 years and younger, mortality rates at 15 years after bAVR with a bovine pericardial valve, were similar to mechanical AVR, suggesting that the choice of valve prosthesis does not affect survival [13]. An overall actuarial survival rate of 65.6% at 15 years after bAVR, in patients aged 60 years or younger, was reported by Bourguignon et coworkers [5]. Kalfa and colleagues [14] reported 15-year actuarial survival rates after the Ross procedure of 90.5%, with perioperative mortality as low as 0.9% in young patients. Similarly, the preliminary results from the group of Ozaki [15], showed encouraging midterm outcomes for aortic valve neocuspidalization. Among these data, our study confirmed that the choice of bioprosthesis does not affect late survival in younger patients.

4.2. Structural valve deterioration

Current data on the durability of bAVR show a non-linear trend with an inflection point beyond 6 years after operation [16]. Studies on valve performance have reported rates of freedom from SVD at 10 years up to 85% [17–20]. Bourguignon and colleagues [5] reported excellent long-term valve durability of 17.6 years, with 15/20 years freedom from SVD of 66.8%/38.1%, for patients aged 60 years or younger (median age 54, IQR: 47–57.5 years). Similarly, Forcillo and colleagues [18] reported a 57% freedom from SVD at 15 years in the same age group. In our study only 12 SVD occurred, at a median time of 8.2 years after surgery.

Age at the time of surgery is one of the main factors associated with SVD following bAVR. Degeneration of biological grafts is attributed to the patient's immunological response to remaining cellular components within the graft tissue. The lower durability in patients with higher immunological competence, such as young population, supports this assumption. Indeed, patients below 50 years of age incur a higher and earlier risk of SVD [21,22]. Despite a higher rate of SVD in the age group ≤30 years, age was not found to be a significant risk factor for SVD, in line with data of Bourguignon and colleagues [5]. However, this trend, though not significant, could be partially explain the lower event-free survival from SVD in our study compared to that showed by Bourguignon et al. also considering the different age distribution in their study.

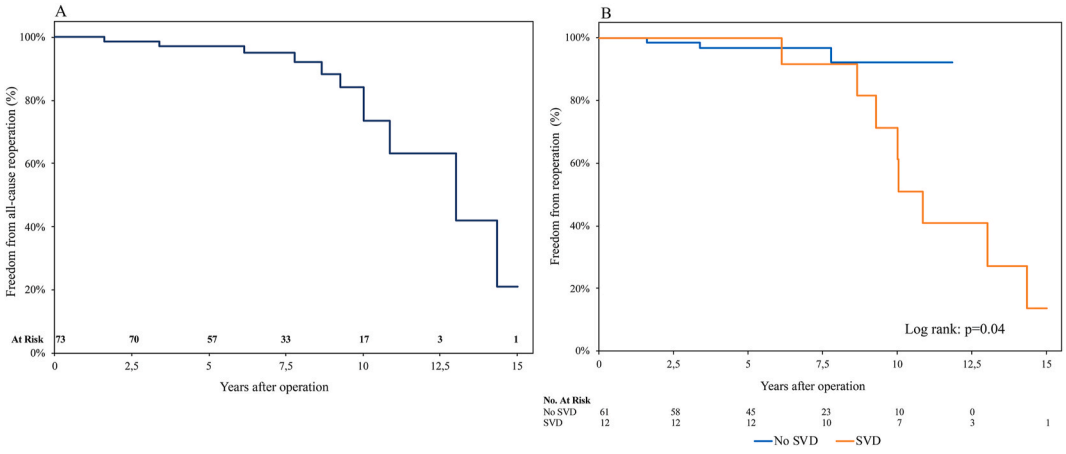

Fig. 3. Kaplan-Meier freedom from reoperation: all causes (A) and SVD vs. No SVD (B).
SVD =
structural valve deterioration.

Whether SVD after bAVR is influenced by prosthesis type in young patients is still controversial [23–26]. In our study population, all the bioprostheses were stented bovine pericardial valves, and despite well-known different hemodynamic performances among the bioprosthesis types implanted, no association with SVD was found.

Small prosthesis sizes and PPM was associated with the increased incidence of SVD [27,28]. The prosthesis size was not found to be an independent predictor for SVD in our study, similarly to other reports [26].

4.3. Reoperation

According to Forcillo and colleagues [20], younger patients were more likely to undergo reoperation, reporting a 60% freedom from reoperation for patients younger than 60 years, compared with 90% for those 60–70 years. Bourguignon and coworkers [5], reported a 20% probability of reoperation due to SVD after 14.8 years in patients aged 50 years, raising to 30% and 35% in patients aged 40 and 30 years, respectively. In the study of Johnston et colleagues [18] actuarial estimates of explant for SVD at 10 and 20 years were 1.9% and 15% overall, respectively, and in patients younger than 60 years, 5.6% and 46%, respectively. Our rate of reoperation due to SVD was 10.9% with a median interval time of 10.0 years since the first bAVR.

Despite similar survival, bAVR showed higher reoperation rates while mechanical AVR showed higher rates of bleeding and stroke, at 15 years [29,30]. The reported 30-day reoperation mortality of 4.8% by Schnittman [12], was favorably impacting when compared to range of 5.8–12.8% in previous studies [31,32].

NYHA classes III and IV were found to be significant risk factors for redo mortality in one of these studies [31]. Most reports on SVD used reoperation as performance parameter to define valve durability. Our study used thorough echocardiographic follow-up to allow a timely diagnosis and provide long-term data on SVD. Although the SVD group in our study presented decreased LVEF with higher LV volumes and PASP, these changes did not cause severe hemodynamic impairment in most of the cases. None of the SVD patients presented in NYHA III-IV class at the time of reoperation, probably due to a younger age at the first bAVR. This data can explain our zero operative mortality, confirming that it can be significantly reduced by optimizing the timing of reoperation, before the onset of advanced symptoms [32].

The decreasing mortality for reoperation and the development of valve-in-valve transcatheter technology have altered the perception of the bioprosthesis as the “bad guy”. Accordingly, many younger patients may find the risk for SVD reoperation acceptable. Valve choice is a shared decision-making process that must involve a multidisciplinary team to weigh the risks and benefits and the recent guidelines emphasize patients’ preferences over age. In some contexts, the immediate safety profile of bioprosthetic valves may offset the eventual risks of structural valve degeneration and need for reoperation.

4.4. Limitations

This is a single-center study, and a relatively small number of patients were evaluated. Due to the retrospective design, the follow-up echocardiographic examinations were performed during a limited time interval, thus follow-up time intervals among patients and groups differed. For the same reason, the mean follow-up time interval is short compared to larger studies, moreover, a 15-year follow-up time does not capture the lifetime risks of patients in this age group. Larger comparative studies with long terms outcomes yet with limitations regarding accurate presentation of patient level data and echocardiographic follow-up were published. Still, to our knowledge, our study is the first to present granular patient level data including echocardiography depiction of SVD in this age group. Although our data could be regarded as an advantage in terms of consistent management, a center-specific bias cannot be excluded. Immunological competence according to age was not assessed, due to the retrospective nature of our study. Further research should focus on targeting host-mediated mechanisms of SVD development.

5. Conclusions

In our study, the rate and time of SVD occurrence were comparable to those of other studies’ older age groups (<65 years). Therefore, strict echocardiographic monitoring and reporting of valve performance is mandatory to set the appropriate timing of eventual reoperation. This attitude can improve outcomes in the settings of young patient treated with bAVR.

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Author contribution

M. Zanobini and S. Manganiello-study conceptualization; M. Pepi, G. Tamborini, M. Muratori, and S.G. Ali-echocardiographic data collection, echocardiography methodology, writing review and editing; S. Corona-data curation, interpretation and validation, writing original draft and editing; S. Manganiello and M. Naliato-methodology conceptualization, review and editing; N. Capra-formal data analysis; M. Zanobini and F. Alamanni-manuscript drafting, review and supervision.

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Declaration of competing interest

None.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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