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Long-Term outcomes and durability of the mitroflow aortic bioprosthesis

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Abstract

Background. This study aims to determine the incidence and causes of structural valve deterioration (SVD) among all models of Mitroflow bioprostheses (A12/LX/DL), as well as to define their long-term clinical and hemodynamic performance.

Methods and Results. We retrospectively reviewed a series of 1023 patients who underwent aortic valve replacement with Mitroflow bioprostheses between 2001 and 2014. A small aortic root was found in 22.4% of patients. There were two cases of severe patient-prosthesis mismatch. Only 31 patients developed SVD. The rate of incidence was 8.1 cases per 1000 patient-years. Cumulative incidence of SVD was 1.4% and 3% at five and 10 years, respectively. Freedom from SVD was 97.4% and 88.2% at five and 10 years, respectively. Anticalcification phospholipid reduction treatment (PRT) for model DL was a protective factor for SVD. Multivariable analysis confirmed age <70 years and use of 19 mm valve as independent predictors of SVD. Cumulative survival was 76.6% at five years and 42.3% at 10 years (mean follow-up 3.8 ± 3.1 years). In multivariable analysis, neither the use of small aortic prosthesis ($p = 0.18$) nor the occurrence of SVD ($p = 0.85$) was found to be independent predictors of long-term survival.

Conclusions. Mitroflow valves demonstrate an acceptable rate of SVD and satisfactory long-term hemodynamic performance, particularly in patients with small aortic roots, age >70 years, and cases with severe left ventricular hypertrophy. PRT might contribute to improved long-term durability.

The Mitroflow bioprosthesis (Sorin Group, Milan, Italy) was designed to optimize its hemodynamic profile, which is particularly useful in patients with a small aortic annulus because of its generous geometric orifice area and small sewing ring. These features may be of greatest importance in patients at high risk for developing patient-prosthesis mismatch (PPM), which may result in higher postoperative transvalvular gradients, limited left ventricular (LV) mass regression, and increased early and late morbidity and mortality.[1, 2]

However, recent studies[3-6] have reported early structural valve deterioration (SVD) of Mitroflow prostheses.[7] The aim of this study was to determine the incidence of SVD among all models of the Mitroflow valve (A12/LX/DL) as well as to identify potential causal factors of SVD. This study also seeks to define the Mitroflow bioprosthesis hemodynamic performance in terms of long-term LV mass reduction and transvalvular gradients and to describe its early and late clinical outcomes.

PATIENTS AND METHODS

Study population and data source

Between January 2001 and June 2014, 1023 consecutive patients underwent aortic valve replacement (AVR) with a Mitroflow bioprosthesis at our institution. During the same period, 2162 patients underwent an AVR with a bioprosthesis: 1023 Mitroflow, 718 Carpentier–Edwards, and 421 miscellaneous bioprostheses.

The three available models of the Mitroflow valve (A12/LX/DL) were analyzed. The Mitroflow bioprosthesis model DL was released in December 2012.

Mitroflow model DL valves are treated with an anticalcification phospholipid reduction treatment (PRT), which has been associated with a reduction in phospholipid content in pericardial tissue.[8, 9]

Demographic, clinical, and echocardiographic data collection was accomplished using linked clinical and administrative databases through the Department of Information Technology of our institution. Only adult patients (>18 years old) were considered for the study. The Institutional Review Board approved this study based on retrospective data retrieval, waiving individual patient consent.

Echocardiography

Echocardiography was performed as previously reported[10, 11] according to the American Society of Echocardiography (ASE) recommendations.[12] The effective orifice area (EOA) was calculated using the continuity equation.[13]

A small aortic root has been defined as an indexed aortic root diameter <1.5 cm/m^2.[14]

The preoperative projected EOA of each prosthetic size was provided by the manufacturer and also confirmed by other authors.[15] Additionally, EOA was indexed (indexed effective orifice area, iEOA) in all cases to each patient's BSA.

The threshold for PPM in the aortic position was defined as an EOAi ≤0.85 cm^2/m^2 with values between 0.65 and 0.85 cm^2/m^2 being classified as moderate PPM and those <0.65 cm^2/m^2 as severe PPM.[2, 16]

The LV mass was calculated using the formula by Devereux et al.[17] LV mass was categorized as a sex-specific variable. LV hypertrophy was defined as an indexed LV mass ≥88 g/m^2 in women or indexed LV mass ≥102 g/m^2 in men.[14] Severe LV hypertrophy was defined as ≥122 g/m^2 in women or ≥149 g/m^2 in men in accordance with the ASE recommendations.[14] LV mass reduction was expressed as a percentage of the basal LV mass in order to adequately compare the results between patients.

Surgical technique

The sizing of the aortic annulus was standardized in all cases according to the institution protocol and performed with a cylindrical sizer provided by the Sorin Group with Mitroflow valve sets. A bioprosthesis one size larger than the diameter of the sizer that tightly passed through the aortic annulus was selected in all cases. This sizing technique is designed to to implant the bioprosthesis in a truly supraannular position, thus maximizing its actual EOA. Prostheses were implanted using 2–0 pledgeted mattress sutures with the pledgets placed on the ventricular site of the aortic annulus. No coronary ostia obstruction was reported in this series. No aortic annulus enlargement was performed in this series.

Follow-up

Clinical and echocardiographic follow-up was complete in all surviving patients after hospital discharge. Data collected included the following: in-hospital mortality, preoperative hemodynamic characteristics, survival, event-free survival, as well as early and late postoperative hemodynamic characteristics. In the study protocol, we decided to include three echocardiographic studies per patient, namely the preoperative echocardiogram and two postoperative echocardiographic controls. Given that the number of postoperative follow-up echocardiograms was not consistent and depended on different referral clinicians, we selected the two postoperative controls that were closest to one-year (mean 174.1 ± 107.4 days) and five-year (mean 1673.2 ± 421.4 days) follow-up after the AVR.

All the adverse events have been defined as recommended by the guidelines of EACTS/STS/AATS.[18] In particular, we include dysfunction or deterioration as determined by reoperation, autopsy, or clinical investigation (e.g., periodic echocardiographic surveillance). Substantially increased regurgitation or stenosis of the operated valve over time was reported. The term SVD refers to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components of a prosthetic valve.[18]

Statistical analysis

Data are expressed as mean and standard deviation or median and rank, when appropriate. For bivariate analysis, proportions were compared with contingency tables by means of chi-square test. Student's *t*-test or Wilcoxon rank-sum test was used to compare means. One-way analysis of variance (one-way ANOVA) was used to determine potential differences in several quantitative variables among the different valve sizes, as well as differences in the follow-up time between the three Mitroflow models analyzed in the study. A p-value of less than 0.05 was considered significant.

Stepwise forward binary logistic regression analysis was used to confirm or reject variables suggested by bivariate analysis as risk factors for in-hospital mortality. Adjusted odds ratio, 95% confidence intervals, and p-values were derived.

Actuarial estimates of survival were accomplished with Kaplan–Meier methods. Differences in the probability of survival between groups were analyzed with the log rank (Mantel–Cox) test.

Cox regression analysis was used to confirm independent predictors of long-term survival and of SVD, which had been previously suggested by bivariate analysis. Adjusted hazard ratio, 95% confidence intervals, and p-values were derived.

The Kolmogorov–Smirnov showed that iEOA and indexed LV mass regression did not present a normal distribution. Thus, Spearman's rank correlation analysis was used to test the potential correlation between de iEOA and different postoperative hemodynamic parameters.

The study adheres to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) initiative.[19]

The SPSS statistical program for Windows version 17.0 (SPSS, Chicago, IL, USA) was used to perform data analysis.

RESULTS

Clinical results

Demographic data and clinical risk factors of all patients are shown in Table 1. There were 520 women (50.8%) and 503 men (49.8%). Mean age was 75.6 ± 5.6 years, with 898 patients (87.8%) over 70 years of age. The indication for surgery was aortic valve stenosis in 76.8% of patients ($n = 786$). Mean logistic euroSCORE was $10.4\% \pm 10.8\%$.

Operative data are shown in Table 1. The smallest diameter prosthesis (19 mm) was implanted in 9.4% of patients ($n = 96$). The implanted valve models were the A12 in 195 patients (19.1%), the LX in 426 patients (41.6%), and the DL in 398 patients (38.9%).

The 19-mm prosthesis was more frequently implanted in women (95.8% vs. 4.2%; $p < 0.001$); in patients older than 70 years (94.8% vs. 5.2%; $p = 0.02$), and in cases of isolated AVR (92.7% vs. 7.3%; $p = 0.02$). Mean BSA in the 19 mm group was $1.63 \pm 0.14\ m^2$. On the other hand, mean BSA was $1.71 \pm 0.18\ m^2$ in 21 mm group, $1.63 \pm 0.14\ m^2$ in 23 mm group, and $1.83 \pm 0.17\ m^2$ in the 25 mm group ($p < 0.001$).

There were 54 patients (5.3%) who had undergone a previous cardiac surgery. An additional procedure at the time of the AVR was performed in 384 patients ($n = 37.5\%$). The associated procedures are summarized in Table 1. An aortic cross-clamp time >90 minutes was found in 35.9% (138/384) of patients undergoing a concomitant procedure ($p < 0.001$) and in 29.6% (16/54) of patients with a previous cardiac surgery ($p = 0.039$).

Overall in-hospital mortality was 6.7% ($n = 69$), while overall in-hospital mortality for isolated AVR was 5% ($n = 32$).

Table 1. Demographics, Clinical Risk Factors, and Surgical Data

Characteristics	Overall Valves (n, %)
Gender (female)	520 (50.8%)
Age (years) (mean ± SD)	75.6 ± 5.6
Age >70 years	898 (87.8%)
Height (cm) (mean ± SD)	155.5 ± 18.6
Weight (kg) (mean ± SD)	75.8 ± 21.3
BSA (m^2) (mean ± SD)	1.77 ± 0.18
BMI (mean ± SD)	28.7 ± 4.6
BMI >30	365 (35.7%)
Aortic valve disease	
Aortic stenosis	786 (76.8%)
Aortic regurgitation	80 (7.8%)
Hypertension	619 (60.5%)
Diabetes mellitus	233 (22.8%)
COPD	124 (12.1%)
Chronic kidney disease	74 (7.2%)
Peripheral vascular disease	62 (6.1%)
Previous stroke	35 (3.4%)
Coronary artery disease	327 (32%)
Previous infective endocarditis	33 (3.3%)
Previous cardiac surgery	54 (5.3%)
Additional procedures at the time of AVR	384 (37.5%)
Associated CABG	294 (28.7%)
Associated MV surgery	55 (5.4%)
Associated aortic surgery	44 (4.3%)
Associated TV surgery	18 (1.8%)
Logistic euroSCORE (%) (mean ± SD)	10.4% ± 10.8%
Implanted valve sizes	
19 mm	96 (9.4%)
21 mm	434 (42.4%)
23 mm	378 (37%)
25 mm	115 (11.2%)
Implanted valve model	
A12	195 (19.1%)
LX	426 (41.6%)
DL	398 (38.9%)
Cardiopulmonary bypass time (min) (mean ± SD)	88 ± 30.6
Aortic cross-clamp time (min) (mean ± SD)	69.2 ± 23.3
Aortic cross-clamp time >90 minutes (%)	178 (17.4%)
ICU days (mean ± SD)	3.9 ± 8
In-hospital mortality (%)	69 (6.7%)

BSA = body surface area; BMI = body mass index; COPD = chronic obstructive pulmonary disease; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MV = mitral valve; TV = tricuspid valve; iEOA = indexed effective orifice area.

The causes of in-hospital death were cardiac related in 36 (52%) patients (cardiogenic shock, 16 cases; hemorrhagic shock, 10 cases; cardiac tamponade, five patients; perioperative myocardial infarction, five cases), and noncardiac related in 33 (48%) patients (multisystem organ failure, 12 cases; septic shock, nine cases; stroke, five cases; mesenteric ischemia, five cases; pulmonary embolism, two cases).

Bivariate analysis suggested age >70 years (2.4% vs. 7.3%; $p = 0.036$); previous cardiac surgery (6% vs. 20.4%; $p = 0.001$); additional procedures at the time of valve replacement (4.9% vs. 9.9%; $p = 0.002$); chronic kidney disease (6.5% vs. 32.7%; $p < 0.001$); pulmonary hypertension (8.8% vs. 27.8%; $p = 0.07$); previous stroke (7.4% vs. 34.8%; $p < 0.001$); peripheral vascular disease (7.3% vs. 22%; $p < 0.001$); infective endocarditis (6% vs. 29.4%; $p < 0.001$); coronary artery disease (5.2% vs. 10.1%; $p = 0.003$); aortic-cross clamp time >90 minutes (5.5% vs. 11.7%; $p = 0.012$) as risk factors for in-hospital mortality. The presence of a small-diameter prosthesis was not a risk factor for in-hospital mortality (6.3% vs. 7.2%; $p = 0.57$).

Logistic regression analysis only confirmed age >70 years (odds ratio [OR], 8.265; 95% confidence interval [CI], 1.405–48.633; $p = 0.02$); previous cardiac surgery (OR, 3.451; 95% CI, 1.369–8.699; $p = 0.009$); additional procedures at the time of valve replacement (OR, 2.183; 95% CI, 1.012–5.394; $p = 0.041$); chronic kidney disease (OR, 3.334; 95% CI, 1.477–7.526; $p = 0.004$); peripheral vascular disease (OR, 3.408; 95% CI, 1.396–8.484; $p = 0.008$), and infective endocarditis (OR, 5.163; 95% CI, 1.658–16.072; $p = 0.005$) as independent risk factors for in-hospital mortality.

Hemodynamic characteristics

Postoperative hemodynamic characteristics were assessed in an early postoperative study (mean 174.1 ± 107.4 days after the surgery) and in a late postoperative study (mean 1673.2 ± 421.4 days after the surgery). Preoperative, early, and late hemodynamic and echocardiographic characteristics are shown in Table 2.

Mean indexed aortic root diameter was 1.79 ± 0.33 cm/m^2. A small aortic root was present in 22.4% ($n = 229$) of patients. In this group of patients with preoperative small aortic roots, 16.5% of the cases received a 19 mm bioprosthesis, 49.6% a 21 mm bioprosthesis, and 33.9% a valve 23 mm or larger ($p = 0.001$).

Overall mean preoperative indexed aortic annulus diameter was 1.49 ± 0.27 cm/m^2.

Mean preoperative indexed LV mass was 156.2 ± 54.6 gm/m^2. Three hundred and fifty-seven patients (34.9%) met criteria of preoperative severe myocardial hypertrophy.

Mean early postoperative iEOA was 1.4 ± 0.2 cm^2/m^2. In the overall population, 29 patients (2.8%) demonstrated PPM and all had received a 19–21 mm bioprosthesis (5.5% vs. 0%; $p < 0.001$). Only two patients (0.2%) demonstrated severe PPM. Both patients were octogenarian females and had received a 19 mm Mitroflow A12 prosthesis. One of the patients, who had undergone combined AVR and CABG, died 96 months after the operation because of pneumonia. The other patient, who had undergone a combined mitral and AVR died five years after the surgery due to acute myocardial infarction.

Mean peak aortic gradients were 24.2 ± 9.9 mmHg and 26.8 ± 13.8 mmHg at early and late studies, respectively. The percentage reductions in indexed LV mass compared with the baseline were $25.3\% \pm 44.6\%$ and $28.1\% \pm 49.5\%$ at early and late studies, respectively. Patients who received a 19 mm bioprosthesis had a smaller reduction in indexed LV mass, although this difference did not reach statistical significance ($15.2\% \pm 36.2\%$ vs. $29.3\% \pm 50.5\%$, $p = 0.13$). The LV mass regression occurred mainly in the first year after AVR.

Spearman's rank correlation analysis showed a significant positive correlation of iEOA and percentage reduction of indexed LV mass ($Rho = +0.63$, $p = 0.008$), as well as a significant negative correlation with postoperative peak aortic transvalvular gradient ($Rho = -0.53$, $p < 0.001$). Likewise, there was a negative correlation between postoperative peak aortic transvalvular gradient and percentage reduction of indexed LV mass ($Rho = -0.32$, $p = 0.02$).

Table 2. Pre- and Postoperative Echocardiographic Data

Characteristics	Overall Valves (n, %)
Aortic root diameter (cm) (mean ± SD)	3.13 ± 0.55
Indexed aortic root diameter (cm/m^2) (mean ± SD)	1.79 ± 0.33
Small indexed aortic root (%)	229 (22.4%)
Aortic annulus diameter (cm) (mean ± SD)	2.22 ± 0.36
Indexed aortic annulus diameter (cm/m^2) (mean ± SD)	1.49 ± 0.27
Preoperative peak transvalvular gradient (mmHg) (mean ± SD)	75.9 ± 29.6
Preoperative aortic surface area (cm^2) (mean ± SD)	0.75 ± 0.3
Preoperative LVEF (%) (mean ± SD)	61.3 ± 14.6
Preoperative LVEF <30%	61 (6%)
Preoperative indexed LV mass (g/m^2) (mean ± SD)	156.2 ± 54.6
Preoperative severe myocardial hypertrophy	357 (34.9%)
Preoperative systolic pulmonary arterial pressure (mmHg) (mean ± SD)	43.4 ± 13.9
Preoperative pulmonary systolic pressure >55 mmHg (%)	199 (19.5%)
Preoperative LVEDD (mm) (mean ± SD)	47.4 ± 8.5
Preoperative LVESD (mm) (mean ± SD)	32 ± 9.4
Early postoperative peak transvalvular gradient (mmHg) (mean ± SD)	24.2 ± 9.9
Early postoperative EOAi (cm^2/m^2) (mean ± SD)	1.4 ± 0.2
Early postoperative EOAi < 0.85 cm^2/m^2 (%)	29 (2.8%)
Early postoperative LVEF (%) (mean ± SD)	63 ± 13.8
Early postoperative indexed LV mass (g/m^2) (mean ± SD)	126.9 ± 38.4
Early postoperative indexed LV mass reduction (%) (mean ± SD)	25.3 ± 44.6
Early postoperative LVEDD (mm) (mean ± SD)	45.3 ± 7.4
Early postoperative LVESD (mm) (mean ± SD)	29.4 ± 8.1
Late postoperative peak transvalvular gradient (mmHg) (mean ± SD)	26.8 ± 13.8
Late postoperative EOA (cm^2) (mean ± SD)	1.6 ± 0.3
Late postoperative EOAi (cm^2/m^2) (mean ± SD)	1 ± 0.2
Late postoperative LVEF (%) (mean ± SD)	62.5 ± 14.6
Late postoperative indexed LV mass (g/m^2) (mean ± SD)	125.8 ± 40.8
Late postoperative indexed LV mass percentage reduction (%) (mean ± SD)	28.1 ± 49.5
Late postoperative LVEDD (mm) (mean ± SD)	45.5 ± 7.8
Late postoperative LVESD (mm) (mean ± SD)	29.8 ± 8.8

LV = left ventricle; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; EOAi = indexed effective orifice area.

Mean indexed aortic root diameter was 1.79 ± 0.33 cm/m^2. A small aortic root was present in 22.4% (n = 229) of patients. In this group of patients with preoperative small aortic roots, 16.5% of the cases received a 19 mm bioprosthesis, 49.6% a 21 mm bioprosthesis, and 33.9% a valve 23 mm or larger (p = 0.001).

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statistical significance (15.2% ± 36.2% vs. 29.3% ± 50.5%, p = 0.13). The LV mass regression occurred mainly in the first year after AVR.

Spearman's rank correlation analysis showed a significant positive correlation of iEOA and percentage reduction of indexed LV mass (Rho = +0.63, p = 0.008), as well as a significant negative correlation with postoperative peak aortic transvalvular gradient (Rho = −0.53, p < 0.001). Likewise, there was a negative correlation between postoperative peak aortic transvalvular gradient and percentage reduction of indexed LV mass (Rho = −0.32, p = 0.02).

Long-term survival

Mean follow-up was 3.8 ± 3.1 years (rank 0–12 years). The follow-up times were different between the three Mitroflow models: A12 6.9 ± 3.6 years; LX 4.4 ± 2.4 years; and DL 2.1 ± 0.8 years (p < 0.001). Overall cumulative survival was 88.2% at one year, 76.6% at five years, and 42.3% at 10 years (Fig. 1A). Respiratory diseases were the most common cause of death after hospital discharge, followed by nonaortic valve-related causes (4.6%, n = 47) and cancer diseases (3.8%, n = 39). Table 3 shows the status of the 1023 patients at the end of this study, including perioperative deaths.

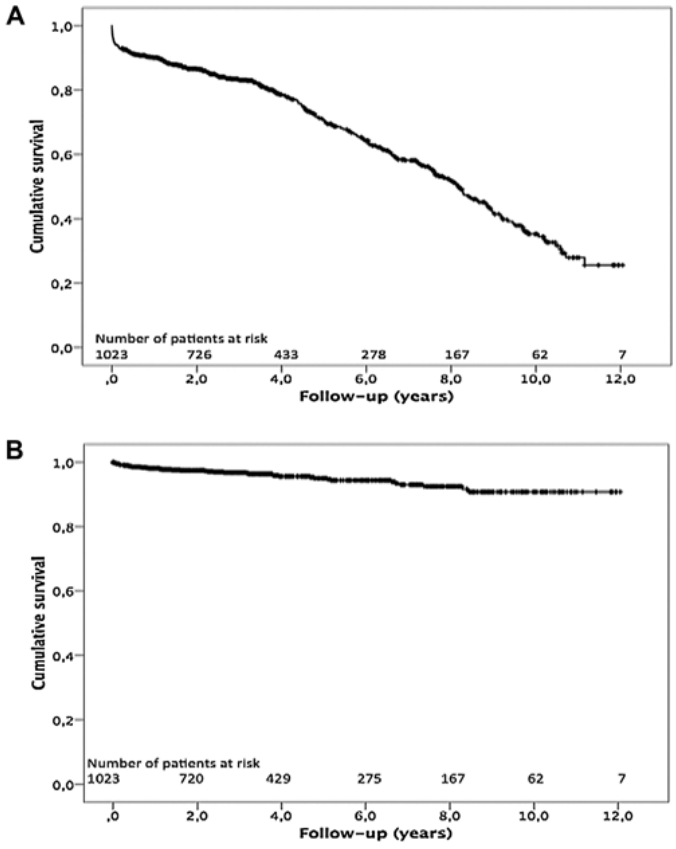

Figure 1. (A) Kaplan–Meier survival curve. (B) Long-term freedom from prosthetic endocarditis.

Table 3. Status of the 1023 Patients at the End of This Study, Including the Perioperative Deaths

Status	Patients (n, %)
Alive	702 (68.6)
Death	321 (31.4)
Perioperative	69 (6.7)
Respiratory diseases	54 (5.3)
Cardiac nonaortic valve related	47 (4.6)
Cancer diseases	39 (3.8)
Infectious cause (nonrespiratory)	33 (3.2)
Stroke	29 (2.8)
Other	25 (2.5)
Unknown	25 (2.5)

Cox regression analysis confirmed previous infective endocarditis (HR, 2.486; 95% CI, 1.342–4.604); preoperative severe LV dysfunction (HR, 1.767; 95% CI, 1.098–2.844); peripheral vascular disease (HR, 1.916; 95% CI, 1.186–3.095); previous stroke (HR, 1.809; 95% CI, 1.071–3.055); previous cardiac surgery (HR, 2.160; 95% CI, 1.367–3.411), and coronary artery disease (HR, 1.435; 95% CI, 1.090–1.899) as independent predictors of long-term survival. The use of a small aortic prosthesis ($p = 0.18$), occurrence of SVD ($p = 0.85$), severe preoperative myocardial hypertrophy ($p = 0.7$), and PPM ($iEOA \leq 0.85$ cm^2/m^2) ($p = 0.23$) were not independent predictors of long-term survival.

Freedom from prosthetic valve infective endocarditis was 97.6% at one year, 95.8% at five years, and 91.9% at 10 years (Fig. 1B). Freedom from thromboembolic events was 99.4% at one year, 96.3% at five years, and 93.1% at 10 years (Fig. 2A).

Structural valve deterioration was detected in 31 patients (3%) during follow-up. Mean follow-up until diagnosis of SVD was 3.8 ± 0.7 years. Cumulative incidence of SVD was 0.5% at one year, 1.4% at five years, and 3% at 10 years. Freedom from SVD was 99.5% at one year, 97.4% at five years, and 88.2%% at 10 years (Fig. 2A). The group of patients with a 19 mm bioprosthesis showed a trend toward lower long-term survival free from SVD (92.8% at five years and 77.3% at 10 years) compared with those patients receiving either a 21 mm (96.9% at five years and 88.2% at 10 years) or a ≥23 mm (98.6% at five years and 90.2% at 10 years) valve ($p = 0.3$).

Differences in peak aortic gradients and indexed LV mass between the group of patients with and without SVD are depicted in Figures 3A and B, respectively. There were no statistically significant differences between patients who did not develop SVD and those with SVD in either preoperative peak aortic gradients (75.7 ± 29.6 mmHg vs. 79.8 ± 28.6 mmHg, $p = 0.77$) or early postoperative peak aortic gradients (23.6 ± 9.7 mmHg vs. 33.1 ± 9.4 mmHg, $p = 0.69$). However, there was a significant difference between groups in late postoperative peak aortic gradients (24.7 ± 10.3 mmHg vs. 58.6 ± 19.4 mmHg, $p < 0.001$). On the contrary, there were no statistically significant differences between groups in preoperative indexed LV mass (156 ± 55.1 g/m^2 vs. 159.4 ± 44.3 g/m^2, $p = 0.8$) and early 126.1 ± 38.8 g/m^2 vs. 137.5 ± 32.2 g/m^2, $p = 0.2$); yet mean late postoperative indexed LV mass tended to be higher in the SVD group (124.6 ± 40.8 g/m^2 vs. 142.8 ± 37.9 g/m^2, $p = 0.05$).

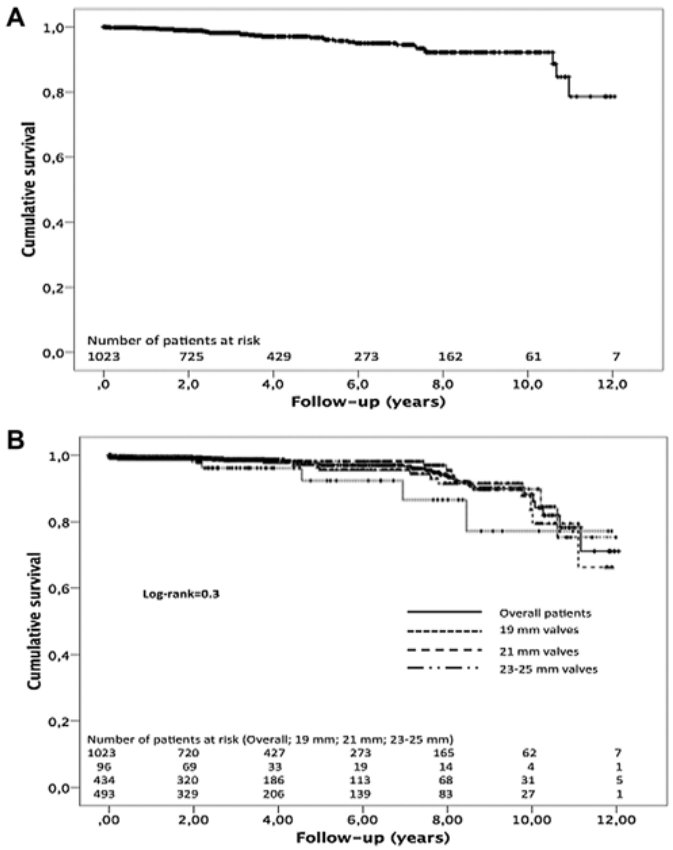

Figure 2. (A) Long-term freedom from thromboembolic events. (B) Actuarial freedom from structural valve deterioration according to AATS/STS/EACTS guidelines [18] for the overall series and for sizes 19 mm, 21 mm, and ≥23 mm. Notice the trend to a lower long-term survival free from SVD in 19 mm valves.

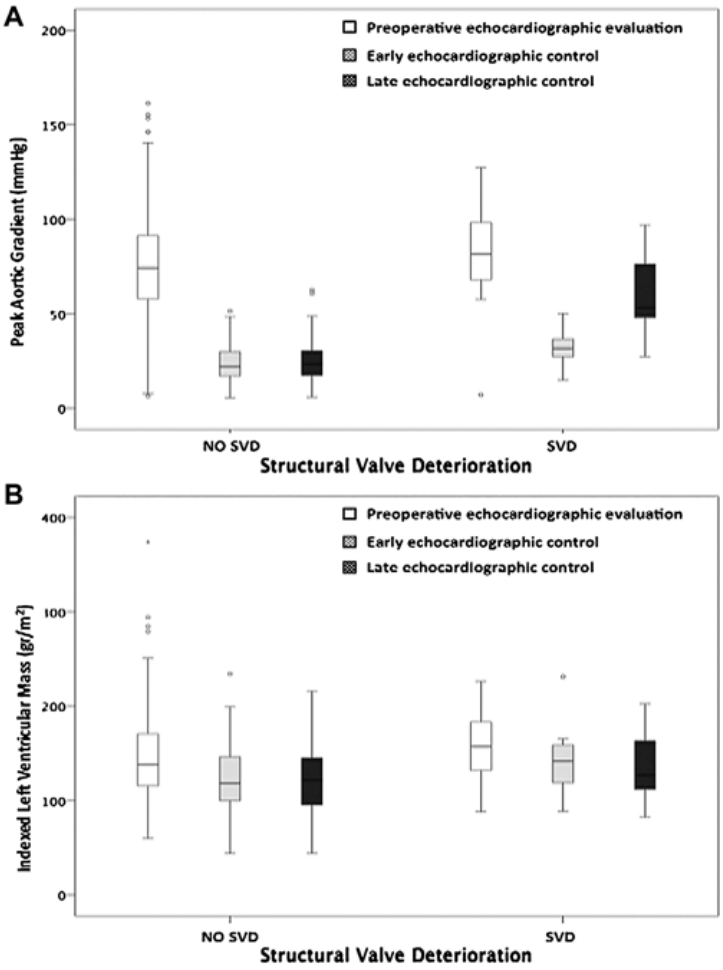

Figure 3. The box plot depicts differences in peak aortic gradients (A) and indexed LV mass (B) between the groups of patients with and without SVD. Notice that there were no significant differences between groups in either peak aortic gradients or indexed LV mass at preoperative and early controls. However, peak aortic gradients were significantly higher beyond the first year after AVR in patients sustaining SVD. On the contrary, although indexed LV mass tended to be higher at late control, this difference did not reach statistical significance.

Bivariate analysis suggested age <70 years (8.3% vs. 2.3%, $p < 0.001$), use of a 19 mm prosthesis (9.9% vs. 2.3%, $p < 0.001$), and Mitroflow model (8% A12, 3.1% LX and 0.5% DL, $p < 0.001$) were associated with development of SVD, while the presence of PRT (Mitroflow DL model) was associated with a lower rate of SVD (0.5% vs. 4.6%, $p < 0.001$). Nonetheless, Cox regression analysis only confirmed age <70 years (HR, 2.844; 95% CI, 1.324–6.108, $p = 0.004$) and use of a 19 mm bioprosthesis (HR, 4.614; 95% CI, 2.156–9.876, $p < 0.001$) as independent predictors of SVD. The protective effect of PRT did not reach statistical significance in the Cox regression (HR, 0.955; 95% CI, 0.183–4.981, $p = 0.956$).

Among the 31 patients with SVD, 18 patients (58%) are dead. The status of the patients sustaining SVD is shown in Table 4.

Table 4. Status of the 31 Patients Sustaining a SVD at the End of This Study

Status SVD	Patients (%) (n = 31)
Alive	13 (41.9%)
Reoperation	7 (five open/two TAVI)
Waiting list	2 (one open/1 TAVI)
Unfit for surgery	1 (colon cancer stage IV)
Non referred for surgery	3
Death	18 (58%)
Reoperation	3 (open surgery)
Death on waiting list	4 (three open/one TAVI)
Unfit for surgery	3 (two dementia/one severe COPD)
Non referred for surgery	8 (four ICC prosthesis related; four no prosthesis-related deaths : two AMI; one infectious cause; one COPD)

SVD = structural valve deterioration

DISCUSSION

In spite of the excellent postoperative hemodynamic performance of bovine pericardium valves, especially in elder patients, some recent studies[3-6] have cast doubts about their long-term durability and safety. Our study sheds light on the long-term incidence of SVD, its potential causal factors, and hemodynamic outcomes of all the models of Mitroflow bioprosthesis, which nowadays is one of the most frequently implanted bovine pericardium valves in the world.

Our overall cumulative survival was 88.2% at one year, 76.6% at five years, and 42.3% at 10 years. The low 10-year survival is attributed to the average patient age of almost 76 years at implantation in our series, and it is in line with the results obtained in other studies with similar populations.[20] The fact that respiratory and cancer diseases were among the three most common causes of death after hospital discharge further identifies an aging population with a significant number of associated comorbidities. In fact, preoperative expected mortality rose to 10.4% ± 10.8% as estimated by logistic euroSCORE. Conversely, our in-hospital mortality was 6.7% which is in line with that reported in other series with similar high-risk populations.[3, 21]

Mitroflow valves are usually implanted in small aortic roots.[20, 22] It should be emphasized that patients with small aortic roots, particularly those with aortic valve stenosis and severe myocardial hypertrophy, are at high risk of developing PPM, which may result in higher postoperative transvalvular gradients, limited LV mass regression, and increased early and late morbidity and mortality.[1, 2] In this cohort, 29 patients (2.8%) experienced PPM and all had received a 19 or 21 mm bioprosthesis. Moreover, those patients in our series who received a 19 mm bioprosthesis exhibited a marked trend toward a smaller reduction in indexed LV mass, yet this difference did not reach statistical significance. Even in the subgroup of small aortic roots, 49.6% of the patients had a 21 mm bioprosthesis, while 33.9% received a 23 mm or larger valve. This fact highlights the potential of the Mitroflow to be implanted above the tissue annulus resulting in enhanced performance from a relatively larger valve in this supra-annular position.

Another issue of paramount importance is achieving a rapid LV mass regression in the hypertrophied stiff left ventricles of elderly patients with long-standing aortic stenosis. Epidemiological data have shown that the severity of LV hypertrophy is a significant predictor of all-cause mortality and cardiovascular events.[11, 23] LV mass regression occurred mostly in the first year after AVR in our series with a mean reduction in indexed LV mass of 25.3% ± 44.6%.

The implantation of a small valve entails a higher risk of PPM and SVD.[1] In a study of the hemodynamic performance of the Mitroflow valve, Jamieson et al.[22] demonstrated that Mitroflow bioprostheses were specially designed to minimize the incidence of PPM in patients at moderate and severe risk, with durability performance similar to other biological prostheses. In our series, the two cases of severe PPM occurred in patients who had undergone an AVR with a 19 mm bioprosthesis. Furthermore, we found a reduction in LV mass in all valve sizes, though there was a trend toward a lower reduction in smaller sizes. Additionally, correlation analysis demonstrated a marked positive correlation between iEOA and percentage reduction of indexed LV mass, as well as a significant negative correlation

for postoperative peak aortic transvalvular gradient. Those findings support the deleterious long-term effect of receiving a small valve.

Some authors[3-6, 24] have reported leaflet tears and early SVD due to early calcification even in elderly patients, which was a rare event in our series. Our study reflected a low cumulative incidence of SVD 1.4% and 3% at five and 10 years, respectively. We could only detect significant differences between patients without SVD and those who eventually developed SVD in late postoperative peak aortic gradients. This pattern mainly reflects that SVD occurred beyond the first years after AVR, while early hemodynamic patterns could not be used to predict eventual development of SVD.

Our finding of the incidence of SVD is in line with the published durability of other aortic bioprostheses. Anselmi et al.[25] reported 99% of freedom from reoperation for SVD at 10 years, after a mean follow-up of eight years with the Mosaic aortic bioprosthesis (Medtronic, Inc., Minneapolis, MN, USA). Ruggieri et al.[26] reported actuarial freedom from reoperation for SVD at 10 and 15 years of 95.9% and 85.9% in patients implanted with the Carpentier–Edwards Supra Annular porcine valve (Edwards Life-sciences, Irvine, CA, USA). Recently, Johnston et al.[27] reported an actuarial explant for SVD at 10 and 20 years of 1.9% and 15%, respectively.

A major shortcoming of recent studies[3, 4, 6] claiming an early SVD and high PPM among patients receiving small Mitroflow valves is that those studies reported neither the preoperative aortic root nor annulus diameters. Supraanular valves require a proper sizing technique based on choosing one size larger than the valve sizer that snugly fits into the annulus. That sizing method allows implantation of the valve truly above the aortic annulus, thus avoiding unintentionally undersizing the bioprosthesis, which can be especially devastating in the small aortic annulus.

In a recent publication, Sénage et al.[3] reported a 22% incidence of 19 mm Mitroflow valves ($n = 133$) in a series of Mitroflow implants. The proportion of 19 mm valves in our series was 9.4% ($n = 96$), which is in line with the data from other series using the Mitroflow bioprostheses.[20, 22, 28, 29] Moreover, there were no relevant differences in BSA between Sénage et al.[3] series ($1.76 \pm 0.2\ m^2$) and ours ($1.77 \pm 0.18\ m^2$) that could have suggested a different baseline population. Additionally, these authors[3] found that 19 mm valves were more frequently implanted in octogenarian patients (27.6% vs. 18.7%, $p = 0.016$). Considering that there were 199 octogenarian patients (32.2%) in their series, it is obvious that more than 59% ($n = 78$) of their 19 mm valves were implanted in patients <80 years old ($n = 418$). In our series, the profile of a typical patient receiving a 19 mm aortic bioprosthesis was a woman >70 years old, of small stature (mean BSA $1.6 \pm 0.2\ m^2$) undergoing an isolated AVR because of a severe aortic valve stenosis. In fact, the 91.6% of the patients receiving a 19 mm valve (88/96) fulfilled all these conditions.

In our study, the multivariable analysis revealed that 19 mm valves were associated with a higher likelihood of SVD than larger prostheses. The other independent risk factor for SVD identified in our series by multivariable analysis was patient age <70 years, which has already been highlighted by other authors.[30, 31] Fifty-eight percent of patients suffering SVD died during follow-up, and 44.4% (8/18) of these deaths were SVD related. However, neither the occurrence of SVD nor the use of a small aortic prosthesis was independent predictors of long-term survival in the multivariable analysis.

Another major shortcoming of those studies reporting an abnormal rate of SVD among Mitroflow bioprostheses[3-6, 24] is that none of them included the latest Mitroflow DL model in their series. Our study reports the potential differences in long-term outcomes between the three Mitroflow models (A12/LX/DL). In fact, the rate of SVD was significantly lower in Mitroflow DL models (0.5%) compared with A12 (8%) and LX models (3.1%). This is an issue of utmost importance given the fact that the DL model was the first one incorporating an anticalcification treatment of bovine pericardium (PRT) that may influence the long-term freedom from SVD.[8, 9] In our series, the presence of PRT was associated with a lower rate of SVD than those bioprostheses without it (0.5% vs. 4.6%, $p < 0.001$). Although the Cox regression could not confirm it as an independent protective factor, probably because of the small number of patients suffering SVD in our series, it was close to attaining statistical significance.

Those studies claiming an increased SVD among the Mitroflow valves only considered the A12 and LX models,[3-6, 24] which lacked an anticalcification treatment. Furthermore, the same studies surmised that the absence of anticalcification treatment was the main hypothesis for their findings of an exaggerated Mitroflow SVD.[3-6, 24]

Limitations

This study presents the limitations inherent in any retrospective study. A major limitation is that mean follow-up was only 3.8 ± 3.1 years. The follow-up times were different between the three Mitroflow models, being longer for the A12 model that was the first to be released. It must be bear in mind that the

Mitroflow bioprostheses model DL was released to the market in December 2012, so this model's possible maximum follow-up time was three years. Hence, further studies are warranted to confirm our results regarding the potential benefit in long-term durability of this and other bioprostheses with PRT.

Another limitation is that echocardiographic follow-up studies, although in overall agreement with current recommendations, were not performed precisely at the same time in all the patients. In addition, the timing of echocardiograms performed in each patient was not consistent, due to differences in practices of referring physicians. Thus, we resorted to the arbitrary definition of two postoperative study timepoints, at approximately one and five years after the AVR, and chose the closest available echocardiogram to these timepoints for each patient.

Finally, we could not provide data and follow-up for the other models of bioprostheses used at our institution during this same period, so that we could not compare the incidence of SD with other current bioprostheses.

CONCLUSIONS

Proper sizing of pericardial supra-anular valves is of utmost importance, especially in small aortic annulus, in order to obtain their enhanced effective area derived from its implant position above the aortic annulus. Mitroflow valves present an outstanding performance in small and calcified aortic roots, in patients older than 70 years or with other comorbidities, as well as in those patients in which a rapid regression of LV hypertrophy is mandatory. PRT might play a key role in improved long-term durability.

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