Early Structural Valve Deterioration of Mitroflow
Aortic Bioprosthesis

Mode, Incidence, and Impact on Outcome in a Large Cohort of Patients

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Background—Structural valve deterioration (SVD) is a major flaw of bioprostheses. Early SVD has been suspected in the last models of Mitroflow bioprosthesis. We sought to assess the incidence, mode, and impact of SVD on outcome in a large series of Mitroflow aortic valve replacement.

Methods and Results—Six hundred seventeen consecutive patients (aged 76.1±6.3 years) underwent aortic valve replacement with a Mitroflow prosthesis (models 12A/LX) between 2002 and 2007. By echocardiography, 39 patients developed early SVD (1.66% per patient-year), with stenosis as the main mode (n=36). Mean delay to SVD was only 3.8±1.4 years, and 5-year SVD-free survival was 91.6% (95% confidence interval [CI], 88.7–94.7) for the whole cohort and 79.8% (95% CI, 71.2–89.4) and 94.0% (95% CI, 90.3–97.8) for 19- and 21-mm sizes, respectively. Among the 39 patients with SVD, 13 patients (33%) had an accelerated SVD once the mean gradient exceeded 30 mm Hg. Valve-related death was 46.2% in this SVD subgroup. Five-year overall survival was 69.6% (95% CI, 65.7–73.9). In multivariable analysis, SVD was the strongest correlate of overall mortality (hazard ratio=7.7; 95% CI, 4.4–13.6).

Conclusions—Early SVD is frequent in Mitroflow bioprosthesis (models 12A/LX), especially for small sizes (19 and 21 mm), and reduces overall survival. An unpredictable accelerated pattern of SVD constitutes a life-threatening condition. In view of the large number of Mitroflow valves implanted worldwide, one can expect an epidemic of SVD and valve-related deaths, which represents a major public health issue, especially in the elderly. Hence, a close follow-up with yearly echocardiography after Mitroflow implantation is advisable. An urgent reoperation should be discussed in patients with severe SVD even though they are still asymptomatic. (Circulation. 2014;130:2012-2020.)

Key Words: aortic stenosis ■ bioprosthesis ■ cardiac valves ■ echocardiography ■ survival analysis

The number of aortic valve replacements (AVRs) performed yearly is estimated at >200000 worldwide.1 For the past 10 years, the choice regarding the type of prosthesis has evolved to the advantage of biological over mechanical prostheses because of an aging population and improved hemodynamic performances of the commercially available bioprostheses.1

Editorial see p 1997

Clinical Perspective on p 2020

Among bovine pericardial prostheses, the Mitroflow valve, available since 1982,2 was designed to improve prosthesis hemodynamic performance. Results of the first Mitroflow (Sorin Group Inc) models (11A) have nevertheless been marked by the occurrence of pericardial tears due to leaflet abrasion through abnormal contact with the polyester (Dacron)-covered frame, eliciting severe intraprothetic aortic insufficiency.3,4 The subsequent prosthesis model, the Mitroflow 12A, introduced in 1992, rectified this flaw but did not integrate any anticalcification treatment in its fabrication. The main theoretical advantage of the 12A model relies on its hemodynamic profile, which is particularly adapted to a small aortic annulus because of its lesser bulk.5 However, the absence of anticalcification treatment is an intrinsic weakness and has been associated with early structural failure in other type of bioprostheses.6 More recently, in 2006, the LX model replaced the 12A model. The LX model is a variation of the 12A model with minor manufacturing modifications; the material components remain the same. These manufacturing process improvements for the LX model did not substantially change the performances of the commercially available bioprostheses.1

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Mitroflow Aortic Valve Structural Deterioration

Morbidity and mortality were analyzed with the recommendations of the American Association for Thoracic Surgery/Society of Thoracic Surgeons/European Association for Cardio-Thoracic Surgery taken into account.15,16 Cardiac and valve-related deaths were recorded following these recommendations. In case of suspicion of SVD by echocardiography, patients were referred to our university center. The last available cardiac echocardiography performed in our institution or outside before repeat surgery or death was taken into account for echocardiographic follow-up.

Statistical Analysis
Quantitative data are expressed as mean±SD. Nonparametric 2-sided tests such as the Fisher exact test and the Mann-Whitney test were used as appropriate. A P value ≤0.05 was considered significant.

The main outcome of this study was the time between surgery and patient death. For this analysis, the few SVD patients (n=4) who underwent a new operation were censored. The second outcome was the time between surgery and SVD (death censored). The analyses of long-term outcomes were performed with the use of the Kaplan-Meier estimator. A first selection of covariates was performed with the log-rank test (P<0.20). Then a Cox model was estimated with a backward procedure performed manually variable by variable with the use of a Wald test (P<0.05). This procedure allows the identification of possible confounding factors (variation of regression coefficients >20%). Hazards proportionality was checked by plotting log-minus-log survival curves and by testing the scaled Schoenfeld residuals. Time-dependent coefficients were used for nonproportional covariates. In the analysis of time to death, SVD was considered a time-dependent covariate with the use of an extended Cox model.

The association between covariates and death was tested. The following preoperative data were considered as possible correlates of death: operative age (years), sex, body mass index, family history, high blood pressure history, diabetes mellitus, dyslipidemia, obesity, history of use of tobacco, aortic valve disease (stenosis, insufficiency, mixed disease, endocarditis, prosthesis endocarditis), New York Heart Association class, pulmonary edema, syncope, atrial fibrillation, chronic obstructive pulmonary disease, forced expiratory volume in 1 second <50%, peripheral vascular disease, renal failure (creatinine >200 μmol/L or Cockcroft-Gault creatinine clearance <60 mL/min), preoperative diuresis, cerebral vascular accident, carotid stenosis >50%, myocardial infarction <30 days, coronary stenosis >50%, left ventricular ejection fraction (<50% and <30%), systolic pulmonary arterial pressure >60 mmHg, aortic insufficiency >2/4, elective cases, urgent or emergency case, and, finally, SVD.

The proportional hazards assumption was violated for chronic obstructive pulmonary disease, which was analyzed as a time-dependent variable. The related hazard ratio (HR) was assumed different for the first 3 years and afterward.

The following possible correlates of SVD were considered: dyslipidemia, PPM, sex, high blood pressure, diabetes mellitus, operative age >70 years, chronic renal failure, and thyroid disorder.

Statistical analyses were performed with the use of version 2.15.0 of R software.

Results
Demographic and Surgical Characteristics
The preoperative characteristics of the cohort are detailed in Table 1. Mean age of the 617 patients was 76.1±6.3 years; 54.1% (n=334) of the patients were aged between 70 and 80 years, and 32.2% (n=199) were octogenarians. In regard to sex, 54.8% (n=338) of the patients were female. The indication for surgery was aortic valve stenosis in 82.3% of patients, and 30.5% (n=188) of patients presented with New York Heart Association class III or IV dyspnea. The proportion of repeat surgery was 6.0% (n=37). An isolated AVR was performed in 391 patients (63.4%). The associated procedures were coronary artery bypass surgery in 30.8% (n=190), mitral or tricuspid valve surgery in

Methods
Patients
Between January 2002 and December 2007, 617 consecutive patients who underwent AVR with the use of a Sorin Mitroflow bioprosthesis (12A and LX models) in the cardiac surgery department of the University Hospital of Nantes were included in the study. During the same period, 2113 bioprostheses were implanted in the aortic position: 621 Mitroflow (in 617 patients), 1173 Carpentier-Edwards PERIMOUNT, 206 Medtronic Mosaic, and 113 miscellaneous bioprostheses. Baseline characteristics were recorded prospectively. For this observational study, the operating techniques and the choice of cardioplegia were left to the operating surgeon’s discretion. In all patients, a surgical approach via median sternotomy was used. The Mitroflow valve was preoperatively prepared according to the directives of the Sorin instruction manual,7 with successive rinses of physiological saline solution.

The postoperative anticoagulant treatment consisted of 3 months of therapeutic anticoagulation for nonoctogenarian patients or because of associated risk factors (treatment by fluindione). Octogenarians without associated risk factors were discharged with antiplatelet treatment (aspirin).

Echocardiography and SVD Definition
SVD of the bioprosthesis was defined according to the latest recommendations and according to precise echocardiographic criteria: progression of aortic transprosthetic gradient ≥30 mmHg associated with a decreased effective orifice area ≤1 cm², or intraprosthetic aortic regurgitation >2/4. Each case of supposed SVD was carefully assessed and validated after review of medical reports. A severe prosthesis-patient mismatch (PPM) was defined as an effective orifice index area of the aortic prosthesis ≤0.65 cm²/m².

Follow-Up
A postoperative echocardiography was performed before patient discharge. Long-term follow-up was ensured through controls performed by the patients’ personal cardiologists. Clinical and echocardiographic data obtained from personal physicians and cardiologists were collected by the clinical investigation center of the University Hospital of Nantes after authorization by the local ethics committee (institutional review board) and were recorded in a computerized database (Commission nationale de l’informatique et des libertés authorization No.1456630v1). Informed consent was obtained.

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Table 1. Baseline Characteristics of the Population (n=617)

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>n (%)</th>
<th>Values are mean±SD unless indicated otherwise. LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; and PAP, pulmonary artery pressure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>338 (54.8)</td>
<td></td>
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<tr>
<td>Age, y</td>
<td>76.1±6.3</td>
<td></td>
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<tr>
<td>Body surface area, m²</td>
<td>1.76±0.2</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>95 (15.4)</td>
<td></td>
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<tr>
<td>High blood pressure, n (%)</td>
<td>380 (61.6)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>121 (19.6)</td>
<td></td>
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<tr>
<td>Dyslipidemia, n (%)</td>
<td>270 (43.8)</td>
<td></td>
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<tr>
<td>Obesity, n (%)</td>
<td>138 (22.4)</td>
<td></td>
</tr>
<tr>
<td>Tobacco use history, n (%)</td>
<td>108 (17.5)</td>
<td></td>
</tr>
<tr>
<td>NYHA class 3–4, n (%)</td>
<td>188 (30.5)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>78 (12.6)</td>
<td></td>
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<tr>
<td>Preoperative renal failure, n (%)</td>
<td>47 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>25 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction history, n (%)</td>
<td>42 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Coronary angioplasty, n (%)</td>
<td>31 (5)</td>
<td></td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>57±12</td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;50%, n (%)</td>
<td>107 (17.3)</td>
<td></td>
</tr>
<tr>
<td>Aortic surface area, cm²</td>
<td>0.64±0.17</td>
<td></td>
</tr>
<tr>
<td>Mean aortic gradient, mm Hg</td>
<td>54±16</td>
<td></td>
</tr>
<tr>
<td>Systolic PAP &gt;60 mm Hg, n (%)</td>
<td>38 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis, n (%)</td>
<td>508 (82.3)</td>
<td></td>
</tr>
<tr>
<td>Aortic insufficiency, n (%)</td>
<td>16 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Surgical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective surgery, n (%)</td>
<td>534 (86.5)</td>
<td></td>
</tr>
<tr>
<td>Urgent or emergency surgery, n (%)</td>
<td>83 (13.5)</td>
<td></td>
</tr>
<tr>
<td>Logistic Euroscore</td>
<td>10.5±10.1</td>
<td></td>
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</tbody>
</table>

Postoperative Complications

The early postoperative mortality was 4.2% (n=26). The main cause of death was cardiogenic shock (n=6). Mean postoperative hospital stay was 14.6±10.3 days, of which a mean of 4.2±7.5 days was spent in the intensive care unit. The proportion of neurological complications was 12.1%, consisting of 2.3% (n=14) cerebral vascular accident, 0.6% (n=4) seizure, and 9.8% (n=61) confusion episodes. Transfusion was needed in 49.6% of patients (n=306). The proportion of postoperative renal failure was 14.1% (n=87), with transient dialysis being necessary in 4.7% of the cases (n=29). Inotropic support was used in 18.5% (n=114) of the patients. The proportion of reoperation was 9.4% (n=58), mainly for pericardial effusion or uncontrolled bleeding. Postoperative atrial fibrillation occurred in 36.3% (n=224) of patients. Finally, 11.7% (n=72) of the patients presented a second- or third-degree atrioventricular block, and 4.9% (n=30) required a pacemaker.

Implanted Bioprostheses

The different sizes of implanted bioprostheses are reported in Table 2. A small-diameter prosthesis (19 or 21 mm) was implanted in 64.2% of patients (n=396), and 9.6% (n=59) received a larger prosthesis (25 or 27 mm). The 19-mm prosthesis was more frequently implanted in the octogenarian compared with the nonoctogenarian population (27.6% versus 18.7%; P=0.016). Table 2 shows the postoperative gradients and orifice areas according to the size of the implanted prosthesis. Based on the in vivo effective orifice area values given by the manufacturer of the Sorin Mitroflow valve, 23.5% of the patients (n=145) had severe PPM. Severe PPM was observed primarily with sizes 19 and 21 mm (Table 2).

Structural Valve Deterioration

Overall mean follow-up was 3.8±2.0 years, with a median of 4.1 years. During follow-up, 39 cases of SVD occurred according to echocardiographic criteria. Two failure modes were observed: The main mode was calcified prosthetic stenosis (Figure 1) in 36 patients (92.0%), whereas moderate to severe intraprosthetic regurgitation was found in 3 patients (8.0%). Aortic regurgitation was caused by a cusp tear and prolapse in 2 patients and by cusp retraction and calcification in 1 patient. Figure 2 illustrates the progressive evolution of mean transprosthetic gradients from surgery to the end of follow-up or death for all patients. The 1-, 2-, and 5-year cumulative probability values of SVD were 0.2% (95% confidence interval [CI], 0.0–0.6), 0.8% (95% CI, 0.0–1.6), and 8.4% (95% CI, 5.3–11.3; Figure 3). The first SVD was diagnosed only 14 months after surgery in a patient with a 23-mm prosthesis. Univariable analysis demonstrated that small-sized prostheses (19 or 21 mm) were significantly associated with the occurrence of SVD (Figure 4; P<0.001), with 20% and 5% of SVD at 5 years for the sizes 19 and 21 mm, respectively. In multivariable analysis (Table 3), age at the time of surgery was not found to be a significant correlate of SVD. PPM was a significant correlate of SVD (HR=1.95; P=0.047). Female sex (HR=2.16; P=0.044) and preoperative dyslipidemia (HR=2.01; P=0.037) were also found to be correlates of SVD.

Accelerated SVD

Among the 39 cases of SVD, 13 patients had an accelerated or “explosive” SVD, defined by an increase >25 mm Hg in only 1 year. The 1-, 2-, and 5-year cumulative probability values of SVD were 0.2% (95% CI, 0.0–1.6), 0.8% (95% CI, 0.0–1.6), and 8.4% (95% CI, 5.3–11.3; Figure 3). The first SVD was diagnosed only 14 months after surgery in a patient with a 23-mm prosthesis. Univariable analysis demonstrated that small-sized prostheses (19 or 21 mm) were significantly associated with the occurrence of SVD (Figure 4; P<0.001), with 20% and 5% of SVD at 5 years for the sizes 19 and 21 mm, respectively. In multivariable analysis (Table 3), age at the time of surgery was not found to be a significant correlate of SVD. PPM was a significant correlate of SVD (HR=1.95; P=0.047). Female sex (HR=2.16; P=0.044) and preoperative dyslipidemia (HR=2.01; P=0.037) were also found to be correlates of SVD.

Table 2. Echocardiographic Parameters at Discharge According to Prosthesis Size

<table>
<thead>
<tr>
<th>Prosthesis Valve Size</th>
<th>n (%)</th>
<th>LVEF, %</th>
<th>Mean Gradient, mm Hg</th>
<th>Prosthesis Valve Area, cm²</th>
<th>PPM, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 mm</td>
<td>133 (22)</td>
<td>56.4</td>
<td>15.70±7.5</td>
<td>1.14±0.45</td>
<td>46 (35)</td>
</tr>
<tr>
<td>21 mm</td>
<td>263 (43)</td>
<td>55.8</td>
<td>14.04±5.32</td>
<td>1.31±0.33</td>
<td>87 (33)</td>
</tr>
<tr>
<td>23 mm</td>
<td>162 (26)</td>
<td>55.4</td>
<td>12.08±4.44</td>
<td>1.57±0.51</td>
<td>12 (7)</td>
</tr>
<tr>
<td>25 mm</td>
<td>47 (8)</td>
<td>53.8</td>
<td>9.21±3.52</td>
<td>1.57±0.33</td>
<td>0</td>
</tr>
<tr>
<td>27 mm</td>
<td>12 (2)</td>
<td>41.4</td>
<td>9.86±3.67</td>
<td>1.86±0.51</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are mean±SD unless indicated otherwise. LVEF indicates left ventricular ejection fraction; and PPM, prosthesis-patient mismatch.
mean age of this subgroup of patients was 73.7±7.8 years, and 30.8% were male, with a prosthesis diameter of 19 or 21 mm in 76.9% of the cases. The evolution was marked by a valve-related death in 46.2% (n=6) of this subgroup of patients. A mean transprosthetic gradient threshold of 30 mmHg seems to be a divergent point between patients who are developing accelerated and more progressive stenotic SVD. This accelerated form of SVD could be similar to those described by the Boston Children’s Hospital and the Harvard Medical School, with several cases of rapid life-threatening valve deterioration with the Mitroflow prosthesis in young adults.19

Long-Term Survival and Impact of SVD on Mortality
Table 4 shows the causes of death (n=159), dominated by cancer (n=25; 15.7%) and congestive heart failure (n=23;
In the SVD group, 16 patients (41.1%) died, and SVD was considered the direct cause of death in 12 patients (11 cases of untreatable heart failure and 1 death after reoperation). Four patients with SVD (10.3%) underwent a second AVR. The 35 other patients did not undergo any surgery at the date of data extraction (main reason: patient not referred to surgery [51.4%], patient’s refusal of treatment [14.3%], death while on the waiting list [11.4%], and sudden death soon after SVD diagnosis [11.4%]).

The 5-year overall survival rate was 69.6% (95% CI, 65.7–73.9; Figure 5). At 5 years, valve-related and cardiovascular-related survival rates were 88.3% (95% CI, 85.3–91.4) and 81.8% (95% CI, 78.4–85.4), respectively (Figure 5). The 5-year survival rates without stroke or without endocarditis were 93.4% (95% CI, 91.1–95.8) and 94.3% (95% CI, 92.1–96.6), respectively. Thirty-two cases (5.2%) of prosthetic endocarditis were observed (8 of them required a second AVR).

The multivariable Cox model for mortality is shown in Table 5. The final model retained several significant preoperative factors: chronic obstructive pulmonary disease (only the HR after the third year was significant: HR=3.91; \( P=0.001 \)), preoperative respiratory insufficiency (HR=2.75; \( P=0.006 \)), New York Heart Association class III to IV (HR=1.51; \( P=0.007 \)), repeat surgery (HR=1.85; \( P=0.014 \)), and myocardial infarction in the previous 3 months (HR=2.76; \( P=0.008 \)). Elderly patients (aged ≥80 years), diabetes mellitus, and preoperative poor left ventricular function were not found to be significant correlates. SVD emerged as the strongest correlate of mortality, with an increased risk of death of 7.7 after diagnosis of SVD (95% CI, 4.4–13.6). No interaction was found statistically between SVD and PPM.

**Discussion**

SVD remains a concern for the use of bioprostheses.6,12–14 The objectives of the present study were to assess the incidence of SVD, the mode of SVD, and its impact on outcome in aortic Mitroflow models 12A/LX. Despite satisfactory early hemodynamics results after implantation,28 SVD rates in our study reached 8.4% (95% CI, 5.3–11.3) only 5 years after surgery. SVD is therefore an early and frequent finding in patients implanted with a Mitroflow bioprosthesis in the aortic position. SVD consists mainly of progressive stenosis with an
unexpected and unpredictable life-threatening accelerated pattern in one third of SVD patients. The occurrence of SVD (particularly the accelerated pattern) has a significant impact on patient outcome and translates to a reduced overall survival in patients developing SVD (HR for mortality=7.7). With respect to the large use of Mitroflow bioprostheses (>100,000 implantation worldwide), one can expect an epidemic of SVD requiring reoperation or leading to death in these patients. Hence, early SVD in the Mitroflow bioprosthesis necessitates annual echocardiography from the first year after implantation in all patients and an even closer follow-up once the mean gradient reaches 30 mm Hg. Owing to the life-threatening accelerated pattern of SVD in one third of patients, urgent reoperation should be considered once bioprosthesis stenosis is severe, even in asymptomatic patients.

Mitroflow Durability
Apart from specific situations, current guidelines recommend bioprosthesis use in the aortic position in patients older than 65 years. However, with 5-year SVD-free survival of 79.8±4.6% and 94.0±1.9% for sizes 19 and 21 mm, respectively, our present study demonstrates that the Mitroflow bioprosthesis presents an abnormal risk of premature SVD. Up to 8.4% of patients in our series would develop SVD only 5 years after surgery despite the absence of specific factors favoring early degeneration such as young age or renal failure. Primary modes of bioprosthesis failure are calcification, noncalcific degeneration, fibrosis, or cusp tear. Progressive cusp stiffening and calcification eliciting stenosis are the main modes of SVD in the present study, as reported previously in Mitroflow14,23–25 or other types of commercially available bioprostheses.6,22

Echocardiographic Assessment of SVD
Several studies have presented satisfactory results with the Mitroflow bioprosthesis and have alleged a low SVD rate, but the SVD rate nevertheless frequently reached 20% after 10 years.12,26–29 For instance, in a series of 1516 patients, 5- and 10-year SVD-free survival rates were 99% and 82%, respectively.13 Moreover, SVD diagnosis was determined in most studies only at reoperation, excluding patients denied for repeat surgery. This definition of SVD, based exclusively on macroscopic assessment in the operating department and on histological examination, leads to an underestimation of this complication. In our cohort, only 10% (4/39) of patients with SVD were reoperated during the study period, which represents only 0.3% of the overall cohort. Fear of repeat surgery with a high operating risk in elderly patients as well as the occurrence of severe and rapid heart complications in SVD patients partly explains the low rate of reoperation. Our results thus confirm the work of Alvarez et al,14 which found, in a cohort of 491 patients with Mitroflow 12A implantation, a 5-year SVD-free survival rate of 95% based on histological diagnosis compared with only 85% by echocardiography. In the same way, Flameng et al30 reported a 10-year SVD-free survival rate of 86% based on ultrasound diagnosis compared with 96% SVD-free survival when histological diagnosis was considered in different biological valves. Hence, echocardiography should be the reference method for diagnosing and reporting SVD in series of bioprosthetic patients rather than only reoperation, which is a less accurate approach and a clear factor in underestimation, especially in elderly patients.

Life-Threatening Accelerated Pattern of SVD
We observed an accelerated pattern of SVD in approximately one third of patients with SVD, portending a poor outcome. Those patients had a rapid progression of bioprosthesis stenosis leading to severe aortic stenosis in a few months. In native aortic valve stenosis, the annual rate of worsening is normally =0.1 cm², with an increase in mean gradient of 8 mm Hg,31 but some patients have a more rapid rate of progression of the disease.32 In our cohort of patients, beyond the threshold of 30 mm Hg, the rate of increase in mean gradient through the Mitroflow bioprosthesis was >25 mm Hg per year in those who developed accelerated SVD. This accelerated pattern should be known by clinicians and taken into account in the clinical management of these patients. Although the absolute number of patients with an accelerated pattern was relatively small (n=13; 33% of SVD), the high mortality rate of this subgroup is a subject of concern and is an incentive to propose a closer follow-up for patients with a Mitroflow bioprosthesis and to refer patients promptly to surgery once stenosis is severe.

Correlates of SVD
Age is a well-known risk factor for SVD9,21 and has been linked to SVD in Mitroflow bioprostheses.14 In the present
study, multivariable analysis identified female sex, dyslipidemia, and PPM as statistically significant correlates of SVD. However, patient age did not emerge as a significant predictor because most patients are older than 65 years. Dyslipidemia and metabolic syndrome have been associated previously with native aortic valve stenosis development but also with progressive SVD of bioprostheses.33,34 In our cohort, SVD occurred preferentially in small-sized bioprostheses (19 and 21 mm) with higher postoperative gradients and was associated with PPM. Although the clinical consequences of PPM on morbidity and mortality after AVR remain a matter of debate,35,36 the hemodynamic consequences of PPM could have a deleterious influence on bioprosthetic duration. Indeed, Flameng et al30 demonstrated that SVD was more frequent in patients with PPM defined by an actual surface area <0.85 cm²/m². In contrast to other types of bioprostheses, Mitroflow 12A/LX was not prepared with a specific anticalcification treatment. Abnormal mechanical constraints related to PPM and the absence of anticalcification treatment could explain the Mitroflow 12A/LX tendency toward early stiffening and calcification. Indeed, according to experimental work by Cunanan et al,25 the Mitroflow valve is particularly prone to calcification. Ninety-day subcutaneous valvular prosthetic tissue implants in rats demonstrated a tissue calcium content up to 214 μg/mg for the Mitroflow but only 2.13 μg/mg (P<0.001) for the porcine Carpentier-Edwards and the pericardial PERIMOUNT bioprostheses. Besides patient characteristics and PPM, the early and high rates of SVD in Mitroflow 12A/LX are therefore likely linked to structural characteristics of bioprosthesis and especially the absence of anticalcification treatment during tissue preparation and fixation.

**Impact of SVD Occurrence on Patient Survival**

Beyond the classic factors of postoperative survival such as respiratory or coronary disease and symptoms, SVD emerged as a strong predictive factor of survival after AVR with a Mitroflow 12A/LX bioprosthesis. Indeed, SVD was found to be the strongest correlate of mortality in multivariable analysis (HR=7.7; P<0.001), overwhelming other pejorative prognosis factors. The deleterious effect of SVD on survival was highlighted previously in the Veterans Affairs study,37 making the high rate of SVD with the Mitroflow a concern. The present study highlights the short durability of Mitroflow 12A/LX bioprostheses in some patients. Because SVD portends a poor prognosis, patients need to be followed closely after surgery and referred promptly to surgery according to the severity of SVD.

**Clinical Implications**

Patients with a Mitroflow bioprosthesis (models 12A/LX) thus must face an unusual and quite unpredictable structural and hemodynamic deterioration, with an accelerated worsening in one third of SVD portending a poor outcome under conventional management and a high mortality rate. Because premature SVD risk was considered to be low for all biological valves,9 including the Mitroflow valve,12,27 European
recommendations advise yearly ultrasound monitoring only after the fifth year. However, early SVD and the accelerated pattern of SVD in some Mitroflow bioprostheses advocate for a closer monitoring from the first postoperative year. On the basis of mean gradient evolution, one would recommend a careful monitoring at least every 6 months when mean gradient is \( \approx 30 \text{ mmHg} \). Surgical replacement seems to be the most adapted solution in cases of SVD with small prostheses because the Mitroflow valve is not completely favorable to the “valve in valve” concept. The internal diameter of the size 19 Mitroflow is only 15.4 mm, which does not currently allow the smallest available percutaneous valve to be implanted properly. Furthermore, the Mitroflow prosthesis design, with the pericardial leaflet located outside of the stent, exposes the coronary ostia to an obstruction by the transcatheter valve.\(^\text{29}\)

### Limitation of this Study

The main limitation of this study relies on the relatively short follow-up, which averaged 3.8 years. Further studies are thus warranted to confirm our results regarding early SVD and to extend our findings to long-term durability. Although the absence of anticalcification treatment is the main hypothesis for Mitroflow SVD, we cannot rule out the hypothesis of a sporadic structural defect. In the first hypothesis, SVD rate might continue to grow in an exponential way, whereas it might grow slowly in the second hypothesis. Echocardiographic follow-up, although in overall agreement with current recommendations, was performed by personal cardiologists with some variations in data reporting and with various intervals of time between the 2 follow-ups. Data were thus interval-censored survival data. We chose the middle of the interval between the 2 follow-ups to define the time of SVD. Such an approach may be associated with an underestimation of SVD incidence regarding the possible absence of echocardiography before the death of the patient.

### Conclusions

Despite satisfactory hemodynamic results early after implantation, SVD is an early and frequent finding in patients implanted with a Mitroflow 12A/LX bioprosthesis in the aortic position, particularly for small diameters (19 and 21 mm). SVD consists mainly of progressive aortic stenosis, with cusp stiffening and calcification likely related to the absence of anticalcification treatment of the prosthesis. Approximately one third of patients with SVD experienced an unexpected and unpredictable life-threatening accelerated hemodynamic and structural deterioration of the bioprosthesis. Early SVD, particularly the accelerated pattern, has a strong impact on patient outcome, with a reduced overall survival rate. In view of the large volume of implanted Mitroflow bioprostheses, we can expect an epidemic of SVD requiring reoperation in elderly patients. Our findings advocate for yearly echocardiography from the first year after Mitroflow 12A/LX implantation and careful monitoring once the mean gradient reaches 30 mmHg. Owing to the life-threatening accelerated pattern of SVD in one third of patients, urgent reoperation should be considered once stenosis is severe, even in asymptomatic patients. The replacement of the Mitroflow models 12A/LXA by a new model (DLA with PRT [phospholipid reduction treatment]), which benefits from an anticalcification treatment, offers better perspectives for the durability of the prosthesis.

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### Disclosures

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### References

Structural valve deterioration (SVD) remains a major flaw of bioprostheses. Current recommendations advise yearly echocardiography from the fifth year after surgery with the assumption that SVD would not occur earlier. We retrospectively assessed 617 consecutive patients (aged 76.1±6.3 years) who underwent an aortic valve replacement with a Mitroflow bioprosthesis (12A/LX models) between 2002 and 2007 to evaluate the incidence, mode, and impact of SVD on outcome. The diagnosis of SVD was based not only on reoperation but also on echocardiography. During a follow-up of 3.8±1.4 years, we ascertained 39 cases of SVD (1.66% per patient-year), with stenosis as the main mode (n=36; 92%). The first SVD was diagnosed only 14 months after surgery. The 5-year cumulative probability of SVD was up to 8.4% (95% confidence interval, 4.4–13.6). To conclude, early SVD is an unexpected but frequent finding in Mitroflow bioprostheses.


CLINICAL PERSPECTIVE

Structural valve deterioration (SVD) remains a major flaw of bioprostheses. Current recommendations advise yearly echocardiography from the fifth year after surgery with the assumption that SVD would not occur earlier. We retrospectively assessed 617 consecutive patients (aged 76.1±6.3 years) who underwent an aortic valve replacement with a Mitroflow bioprosthesis (12A/LX models) between 2002 and 2007 to evaluate the incidence, mode, and impact of SVD on outcome. The diagnosis of SVD was based not only on reoperation but also on echocardiography. During a follow-up of 3.8±1.4 years, we ascertained 39 cases of SVD (1.66% per patient-year), with stenosis as the main mode (n=36; 92%). The first SVD was diagnosed only 14 months after surgery. The 5-year cumulative probability of SVD was up to 8.4% (95% confidence interval, 4.4–13.6). To conclude, early SVD is an unexpected but frequent finding in Mitroflow bioprostheses (12A/LX), especially for small sizes (19 and 21 mm), and reduces overall survival. In view of the large number of Mitroflow valves implanted worldwide, one can expect an epidemic of SVD and valve-related deaths. Hence, close follow-up with yearly echocardiography on surgery is advisable in patients with Mitroflow bioprostheses. An urgent reoperation should be discussed in patients with severe SVD in view of the risk of rapid progression and death.
Early Structural Valve Deterioration of Mitroflow Aortic Bioprosthesis: Mode, Incidence, and Impact on Outcome in a Large Cohort of Patients

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