Early Structural Valve Deterioration of Mitroflow Aortic Bioprosthesis: Mode, Incidence and Impact on Outcome in a Large Cohort of Patients

Running title: Sénage et al.; Mitroflow aortic valve structural deterioration

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Abstract

**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, the mode and the impact of SVD on outcome in a large series of Mitroflow aortic valve replacement (AVR).

**Methods and Results**—617 consecutive patients (76.1±6.3 years) underwent AVR with a Mitroflow prosthesis (models 12A/LX) between 2002 and 2007. By echocardiography, 39 patients developed early SVD (1.66% per patient-year), mainly on a stenosis mode (n=36). Mean delay to SVD was only 3.8±1.4 years and five-years SVD-free survival was 91.6% [95% CI 88.7-94.7] for the whole cohort, 79.8% [71.2-89.4] and 94.0% [90.3-97.8] for 19 and 21 mm sizes, respectively. Among the 39 SVD, 13 patients (33%) had an accelerated SVD once mean gradient exceeded 30mmHg. Valve-related death was 46.2% in this SVD subgroup. Five-years overall survival was 69.6% [65.7-73.9]. In multivariable analysis SVD was the strongest correlate of overall mortality (HR=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 redo surgery should be discussed in patients with severe SVD even though still asymptomatic.

**Key words:** survival analysis, cardiac valvular surgery, echocardiography, aortic stenosis, bioprosthesis, structural valve disease
Introduction

The number of aortic valve replacements (AVR) performed yearly is estimated at over 200,000 worldwide\(^1\). For the past 10 years, the choice regarding the type of prosthesis has evolved to the advantage of biological over mechanical prostheses due to an aging population and improved hemodynamic performances of the commercially available bioprostheses\(^1\).

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 intra-prosthetic 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 thanks to 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 affect the design or performance of the prosthesis\(^7\). So, both models can be considered as the same bioprosthesis\(^8\).

The major flaw of biological prostheses is the occurrence of structural valve deterioration (SVD) at mid- or long-term, which is variable depending on the type of prosthesis\(^6,9\). The Mitroflow aortic bioprosthesis has been implanted in more than 100 000 patients worldwide\(^10\). Although some studies have presented satisfactory mid- and long-term results\(^11-13\), recent studies
have expressed reservation to the Mitroflow bioprosthesis actual durability, with reports of early SVD within 4 years after implantation. Nevertheless, SVD diagnosis has been often based on surgical re-intervention reports leading to underestimating its current prevalence and its impact on patient survival. In fact, numerous old patients are denied surgery due to the high risk of major adverse events related to the redo surgery.

In view of the potential impact of early SVD in old patients, the present study was thus designed 1) to assess in a large cohort of patients the incidence of SVD for Mitroflow aortic pericardial bioprosthesis (12A/LX) based on echocardiography, 2) to characterize the pattern and the temporal course of SVD, and finally 3) to assess the correlates of SVD and its impact on patients prognosis.

Methods

Patients

Between January 2002 and December 2007, 617 consecutive patients who underwent AVR using 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 Mitroflows (in 617 patients), 1173 Perimount Edwards, 206 Medtronic Mosaïc 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 for Use" manual, with successive rinses of physiological saline solution.
The postoperative anticoagulant treatment consisted of 3 months of therapeutic anticoagulation for non octogenarian patients or because of associated risk factors (treatment by fluindione). Octogenarians without associated risk factors were discharged with antiplatelet treatment (aspirin).

Echocardiography and Structural Valve Deterioration definition

Structural valve deterioration of the bioprosthesis was defined according to the latest recommendations \(^{17}\) and according to precise echocardiographic criteria: progression of aortic transprosthetic gradient \(\geq 30\) mmHg associated with a decreased effective orifice area \(\leq 1\) cm\(^2\), or intraprosthetic aortic regurgitation \(>2/4\). Each case of supposed SVD was carefully assessed and validated after review of medical reports. A severe patient-prosthesis mismatch (PPM) was defined as an effective orifice index area of the aortic prosthesis \(\leq 0.65\) cm\(^2/m^2\).

Follow-up

A postoperative echocardiography was performed before patient discharge. Long-term follow-up was ensured through controls carried out by the personal patients 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 of the local Ethics Committee (Institutional Review Board) and were recorded in a computerized database (authorization CNIL no.1456630v1). An informed consent was obtained.

Morbidity and mortality were analyzed taking into account the recommendations of the ATTS-STS-EACTS\(^{18}\). 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 redo-surgery or death was taken into account for echocardiography follow-up.
Statistics

Quantitative data is expressed as mean ± standard deviation. Non-parametric two-sided tests such as Fisher's 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 the surgery and the SVD (death-censored). The analyses of long-term outcomes were carried out by using the Kaplan-Meier estimator. A first selection of covariates was performed by using the Log-rank test (p<0.20). Then, a Cox model was estimated respecting a backward procedure performed manually variable-by-variable by using a Wald test (p<0.05). This procedure allows the identification of possible confounding factors (variation of regression coefficients higher than 20%). Hazards proportionality was checked by plotting log-minus-log survival curves and by testing the scaled Schoenfield residuals. Time-dependent coefficients were used for non-proportional covariates. In the analysis of the time-to-death, the SVD was considered as a time-dependent covariate by using 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), gender, body mass index (BMI), family history, high blood pressure history, diabetes, dyslipidemia, obesity, tobacco history, aortic valve disease (stenosis, insufficiency, mixed disease, endocarditis, prosthetic endocarditis), New-York Heart Association class (NYHA), pulmonary edema, syncope, atrial fibrillation, chronic obstructive pulmonary disease (COPD), forced expiratory volume in 1 second (FEV1) <50%, peripheral vascular disease, renal failure (creatinine >200 μmol/L or Cockcroft-Gault creatinine clearance < 60mL/min), preoperative dialysis, cerebral vascular
accident (CVA), carotid stenosis > 50%, myocardial infarction < 30 days, coronary stenosis > 50%, left ventricular ejection fraction (LVEF < 50% and LVEF < 30%), systolic pulmonary arterial pressure (sPAP) > 60mmHg, aortic insufficiency > 2/4, elective cases, urgent or emergency case, and finally SVD.

The proportional hazards assumption was violated for COPD, which was analyzed as a time-dependant variable: the related hazard ratio was assumed different for the first 3 years and afterwards.

The following possible correlates of SVD were considered: dyslipidemia, patient-prosthesis mismatch (PPM), gender, high blood pressure, diabetes, operative age > 70 years, chronic renal failure and thyroid disorder.

Statistical analyses were performed using version 2.15.0 of the 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 old: 54.1% (n=334) of the patients had between 70 and 80 years old and 32.2% (n=199) were octogenarians. 54.8% (n=338) of the patients were females. The indication for surgery was aortic valve stenosis in 82.3% of patients and 30.5% (n=188) of patients presented NYHA class III or IV dyspnea. The proportion of redo 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 and/or tricuspid surgery in 6.3% (n=39) and ascending aorta procedure in 1.6% (n=10). A Cox-Maze IV procedure was performed in 4.4% of interventions (n=27). Cardio-pulmonary bypass and aortic cross-clamping time were
92±39 min and 70±30 min, respectively.

**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%, with 2.3% (n=14) of CVA, 0.6% (n=4) of seizure and 9.8% (n=61) of 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 AV 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), while 9.6% (n=59) received a larger prosthesis (25 or 27 mm). The 19 mm prosthesis was more frequently implanted in the octogenarians compared with the non-octogenarian 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 mostly with sizes 19 and 21 mm (Table 2).

**Structural valve deterioration (SVD)**

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 echocardiography criteria. Two failure modes were observed: the main was calcified prosthetic stenosis (Figure 1) in 36 patients (92.0%) while moderate to severe intra-prosthetic 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 to the death for all patients. The 1-, 2- and 5-years cumulative probability of SVD were 0.2% [95% 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 as a significant correlate of SVD. Patient-prosthesis mismatch was a significant correlate of SVD (HR=1.95, p=0.047). Female gender (HR=2.16, P=0.044) and preoperative dyslipidemia (HR=2.01, p=0.037) were also found as correlates of SVD.

**Accelerated SVD**

Among the 39 cases of SVD, 13 patients had an accelerated or "explosive" SVD defined by an increase greater than 25 mmHg of the mean transprosthetic gradient over a short period of time of 12 months (Figure 2). In these patients the mean gradient increased from 22±11 mmHg to 61±16 mmHg in only 1 year. The mean age of this subgroup of patients was 73.7±7.8 years and 30.8% were male, with a prosthesis diameter of 19 mm 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 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.

**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; 14.5%). In the SVD group, 16 patients (41.1%) died and SVD was considered as the direct cause of death in 12 patients (11 cases of untreatable heart failure and 1 death after redo surgery). Four patients with SVD (10.3%) underwent a second AVR. The 35 other patients did not undergo any surgery at 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-years survival rate 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: COPD (only the hazard ratio after the third year was significant - HR=3.91, p=0.001), preoperative respiratory insufficiency (HR=2.75, p=0.006), NYHA class III-IV (HR=1.51, p=0.007), redo surgery (HR=1.85, p=0.014) and myocardial infarction in the previous 3 months (HR=2.76, p=0.008). Elderly patients (≥80 years old),
mellitus diabetes and preoperative poor LV function were not found as significant correlates. Structural valve deterioration 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 statistically found between SVD and patient-prosthesis mismatch.

**Discussion**

Structural valve deterioration remains a concern for using bioprostheses. The objectives of the present study were to assess the incidence, the mode of SVD and its impact on outcome in aortic Mitroflow models 12A/LX. Despite satisfactory early hemodynamics results after implantation, 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. Structural valve deterioration consists mainly of progressive stenosis with an unexpected and unpredictable life-threatening accelerated pattern in one third of SVD patients. The SVD occurrence (especially for the accelerated pattern) has a significant impact on patient outcome and translates in a reduced overall survival in patients developing SVD (HR for mortality=7.7). With respect to the large use of Mitroflow bioprosthesis (>100 000 implantation worldwide), one can expect an epidemic of SVD requiring redo surgery or leading to death in these patients. Hence, early SVD in the Mitroflow bioprosthesis imposes an annual echocardiography from the first year after implantation in all patients and even a closer follow-up once 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 bioprosthesis stenosis is severe, even in asymptomatic patients.

**Mitroflow durability**

Apart from specific situations, current guidelines recommend bioprosthesis use in patients older
than 65 years old in the aortic position. However, with a 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 a 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, non-calcific degeneration, fibrosis or cusp tear.

Progressive cusp stiffening and calcification eliciting stenosis is the main mode of SVD in the present study, as previously reported in Mitroflow or other types of commercially available bioprostheses.

**Echocardiography assessment of SVD**

Several studies have presented satisfactory results with the Mitroflow bioprosthesis and alleged a low SVD rate, but SVD rate nevertheless frequently reached 20% after 10 years. For instance, in a series of 1516 patients 5-year and 10-year SVD-free survival rates were 99% and 82%, respectively. Moreover, SVD diagnosis was determined in most studies only at reoperation, excluding de facto patients denied for redo surgery. This definition of SVD based exclusively on macroscopic assessment in the operative room and on histologic 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 redo surgery with high operating risk in old patients as well as occurrence of severe and rapid heart complications in SVD patients partly explain the low rate of reoperation. Our results thus confirmed the work of Alvarez et al. which found in a cohort of 491 Mitroflow a 5-year SVD free survival rate of 95% based on histologic diagnosis compared with only 85% by echocardiography. In the same way, Flameng et al. reported a 10-year SVD free survival of
86% based on ultrasound diagnosis, compared with 96% SVD free survival when histologic
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 of underestimation
especially in old 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 around 0.1 cm$^2$ with an increase in mean gradient of 8 mmHg$^{31}$ but
some patients have a more rapid rate of progression of the disease$^{32}$. In our cohort of patients,
beyond the threshold of 30 mmHg, the rate of increase in mean gradient through the Mitroflow
bioprosthesis was above 25 mmHg per year in those who developed an 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 SVD$^{9, 21}$ and has been linked to SVD in Mitroflow
bioprostheses$^{14}$. In the present study, multivariable analysis identified female gender,
dyslipidemia and patient-prosthesis mismatch (PPM) as statistically significant correlates of
SVD. However, patient age did not emerge as a significant predictor since most patients are
older than 65 years old. Dyslipidemia and metabolic syndrome have been previously associated with native aortic valve stenosis development but also with progressive SVD of bioprostheses. In our cohort SVD occurred preferentially in small-sized bioprostheses (19 and 21 mm) with higher postoperative gradients and was associated with PPM. Although clinical consequences of PPM on morbidity and mortality after AVR remain a matter of debate, hemodynamic consequences of PPM could have a deleterious influence on bioprosthetic duration. Indeed, Flameng et al. demonstrated that SVD was more frequent in patients with PPM defined by an actual surface area <0.85 cm²/m². By contrast to other types of bioprostheses, 12A/LX Mitroflow was not prepared with a specific anticalcification treatment. Abnormal mechanical constraints related to PPM and the absence of anti-calcification treatment could explain the 12A-LX Mitroflow tendency towards early stiffening and calcification. Indeed, according to Cunanan et al. experimental work the Mitroflow valve is particularly prone to calcification. Ninety days 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 rate of SVD in 12A/LX Mitroflow is therefore likely linked to bioprosthesis structural characteristics and especially the absence of anti-calcification treatment during tissue preparation and fixation.

**Impact of SVD occurrence on patient survival**

Beyond classical 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 12A/LX Mitroflow bioprosthesis. Indeed, SVD stood out as 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 previously highlighted in the Veterans Affairs study, making the high rate of SVD with the Mitroflow a concern. The present study highlights the short durability of 12A/LX Mitroflow bioprostheses in some patients. Since 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 Mitroflow bioprosthesis (models 12A/LX) thus have to 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. As premature SVD risk was considered to be low for all biological valves including the Mitroflow valve, European recommendations advise yearly ultrasound monitoring only after the 5th year. However, early SVD and the accelerated pattern of SVD in some Mitroflow bioprostheses advocate for a closer monitoring from the 1st postoperative year. Based on mean gradients evolution, one would recommend a careful monitoring at least every 6 months when mean gradient is approximately 30 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.

**Limitation of this study**

The main limitation of this study relies on the relative short follow-up that 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 while it might grow slowly in the second hypothesis. Echocardiography follow-up, although in overall agreement with current recommendations, was carried out by personal cardiologists with some variations in data reports and with various interval of time between two follow-ups. Data were thus interval-censored survival data. We choose the middle of the interval between two follow-ups to define the time of SVD. One can notice that such an approach may be associated with an under-estimation of SVD incidence, regarding the possible absence of echocardiography before the death of the patient.

**Conclusion**

Despite satisfactory hemodynamic results early after implantation, SVD is an early and frequent finding in patients implanted with a 12A/LX Mitroflow bioprosthesis in the aortic position particularly for small diameters (19 and 21 mm). Structural valve deterioration 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 and especially the accelerated pattern have a strong impact on patient outcome with a reduced overall survival. In view of the large use of Mitroflow bioprostheses we can expect an epidemic of SVD requiring redo surgery in old patients. Our findings advocate for a yearly echocardiography from the 1st year after 12A/LX
Mitroflow implantation and a careful monitoring once 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), which benefits from an anticalcification treatment, opens better perspectives for the durability of the prosthesis.

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Table 1. Baseline characteristics of the population (n= 617)

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<thead>
<tr>
<th>Clinical Data</th>
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<tbody>
<tr>
<td>Female, n (%)</td>
<td>338 (54.8)</td>
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<td>Age, years</td>
<td>76.1±6.3</td>
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<td>Body Surface Area, m²</td>
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<td>Atrial Fibrillation, n (%)</td>
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<td>High Blood Pressure, n (%)</td>
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<td>Dyslipidemia, n (%)</td>
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<td>Obesity, n (%)</td>
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<td>Tabaco history, n (%)</td>
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<td>NYHA class 3-4, n (%)</td>
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<th>Comorbidities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Vascular Disease, n (%)</td>
<td>78 (12.6)</td>
</tr>
<tr>
<td>Preoperative renal failure, n (%)</td>
<td>47 (7.6)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>25 (4.1)</td>
</tr>
<tr>
<td>Myocardial infarction history, n (%)</td>
<td>42 (6.8)</td>
</tr>
<tr>
<td>Coronary angioplasty, n (%)</td>
<td>31 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EF, %</td>
<td>57±12</td>
</tr>
<tr>
<td>LV EF &lt;50%, n (%)</td>
<td>107 (17.3)</td>
</tr>
<tr>
<td>Aortic surface area, cm²</td>
<td>0.64±0.17</td>
</tr>
<tr>
<td>Mean aortic gradient, mmHg</td>
<td>54±16</td>
</tr>
<tr>
<td>Systolic PAP &gt;60mmHg, n (%)</td>
<td>38 (6.2)</td>
</tr>
<tr>
<td>Aortic stenosis, n (%)</td>
<td>508 (82.3)</td>
</tr>
<tr>
<td>Aortic insufficiency, n (%)</td>
<td>16 (2.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective surgery, n (%)</td>
<td>534 (86.5)</td>
</tr>
<tr>
<td>Urgent or Emergency surgery, n (%)</td>
<td>83 (13.5)</td>
</tr>
<tr>
<td>Logistic Euroscore</td>
<td>10.5±10.1</td>
</tr>
</tbody>
</table>

LV EF: left ventricular ejection fraction, PAP: pulmonary artery pressure
**Table 2.** Echocardiographic parameters at discharge according to prosthesis size.

<table>
<thead>
<tr>
<th>Prosthesis valve area, cm²</th>
<th>LV EF, %</th>
<th>Mean gradient, mmHg</th>
<th>Prosthesis valve area, cm²</th>
<th>PPM, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 mm</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>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>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>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>41.4</td>
<td>9.86±3.67</td>
<td>1.86±0.51</td>
<td>0</td>
</tr>
</tbody>
</table>

PPM: prosthesis patient mismatch

**Table 3.** Correlates of SVD in multivariable analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>2.162</td>
<td>1.021 to 4.577</td>
<td>0.044</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.014</td>
<td>1.045 to 3.880</td>
<td>0.037</td>
</tr>
<tr>
<td>Patient-prosthesis mismatch</td>
<td>1.945</td>
<td>1.010 to 3.743</td>
<td>0.047</td>
</tr>
</tbody>
</table>

**Table 4.** Long-term causes of deaths

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>25</td>
<td>15.7</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>23</td>
<td>14.5</td>
</tr>
<tr>
<td>Sepsis</td>
<td>19</td>
<td>11.9</td>
</tr>
<tr>
<td>Sudden death</td>
<td>13</td>
<td>8.2</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>12</td>
<td>7.5</td>
</tr>
<tr>
<td>Structural valve deterioration</td>
<td>12</td>
<td>7.5</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>8</td>
<td>5.0</td>
</tr>
<tr>
<td>Cerebral Vascular Accident</td>
<td>6</td>
<td>3.8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5</td>
<td>3.1</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Mesenteric ischemia</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td>16.9</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 5. Multivariable Cox model analysis of mid-term survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural Valve Deterioration*</td>
<td>7.7</td>
<td>4.36 -13.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD (after the third year)</td>
<td>3.91</td>
<td>2.02 - 7.55</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction within 3 months before surgery</td>
<td>2.76</td>
<td>1.31 - 5.81</td>
<td>0.008</td>
</tr>
<tr>
<td>Preoperative respiratory insufficiency</td>
<td>2.75</td>
<td>1.33 - 5.67</td>
<td>0.008</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>1.85</td>
<td>1.13 - 3.03</td>
<td>0.014</td>
</tr>
<tr>
<td>NYHA class 3-4</td>
<td>1.51</td>
<td>1.12 - 2.03</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*SVD is modelled as a time-dependent covariate. COPD: chronic obstructive pulmonary disease

Figure Legends:

Figure 1. Mitroflow bioprosthesis (21 mm) structural failure characterized by commissural calcified nodules and global thickening and stiffening of the 3 cusps just before redo surgery.

The Mitroflow was implanted in a 75 year-old woman for severe aortic stenosis. Five years later the patient had a symptomatic calcified SVD with a mean gradient of 75 mmHg and an orifice of 0.7 cm². A. Trans-oesophageal echocardiography showing calcification of the bioprosthesis, B. Transvalvular Mitroflow gradients, C. Diffuse calcification of the Mitroflow bioprosthesis by CT scan, and D. Mitroflow after explantation showing calcified nodules especially in the commissural regions and diffuse cusp infiltration, thickening, and stiffening. Pictures A, C and D are placed roughly in the same orientation for comparison. Right: right cusp, Left: left cusp, Non-coro: non-coronary cusp.

Figure 2. Mean transprothetic gradients changes of patients with no SVD during follow-up (box plots) and representation of each transvalvular gradient changes of SVD patients (red lines).
**Figure 3.** Cumulative incidence of SVD (Kaplan-Meier method). Note the early occurrence of SVD from 1-year after surgery and the high 5-year rate of SVD.

**Figure 4.** SVD-free survival curves according to prosthesis size.

**Figure 5.** Overall, cardiovascular-related and valve-related survival curves.
Figure 1
Figure 3
Figure 4

The Kaplan-Meier survival curves demonstrate the SVD-free survival rates for patients with different lesion sizes. The curves are as follows:

- Dashed line: Size 19
- Dotted line: Size 21
- Solid line: Size >23

The survival rates at 5 years are 96.5%, 94.8%, and 80.6% respectively for the three groups. The P-value is less than 0.001, indicating a statistically significant difference in survival rates among the groups.

The number of patients at-risk at each time point is as follows:

<table>
<thead>
<tr>
<th>Time, years</th>
<th>Size 19</th>
<th>Size 21</th>
<th>Size &gt;23</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>133</td>
<td>263</td>
<td>221</td>
</tr>
<tr>
<td>1</td>
<td>114</td>
<td>225</td>
<td>182</td>
</tr>
<tr>
<td>2</td>
<td>106</td>
<td>210</td>
<td>170</td>
</tr>
<tr>
<td>3</td>
<td>98</td>
<td>192</td>
<td>153</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>142</td>
<td>102</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>46</td>
</tr>
</tbody>
</table>
Figure 5

- Valve-related survival
- Cardiovascular-related survival
- Overall survival

Number of patients at-risk:

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>617</td>
<td>521</td>
</tr>
<tr>
<td>486</td>
<td>443</td>
</tr>
<tr>
<td>314</td>
<td>194</td>
</tr>
</tbody>
</table>

Time, years: 0, 1, 2, 3, 4, 5

Survival rate, %: 100%, 88.2%, 81.7%, 69.4%
Early Structural Valve Deterioration of Mitroflow Aortic Bioprosthesis: Mode, Incidence and Impact on Outcome in a Large Cohort of Patients

Thomas Sénage, Thierry Le Tourneau, Yohann Foucher, Sabine Pattier, Caroline Cueff, Magali Michel, Jean-Michel Serfaty, Hubert François Carton, Christian Perigaud, Antoine Mugniot, Ousama Al Habash, Olivier Baron and Jean Christian Roussel

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