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Structural valve deterioration of biosprosthetic aortic valve: an underestimated complication

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36	Abbreviations:
37	AVR: Aortic Valve Replacement
38	COPD: Chronic Obstructive Pulmonary Disease
39	EAO: Effective Orifice Area
40	NYHA: New York Heart Association
41	PPM: Patient-Prosthesis Mismatch
42	SVD: Structural Valve Deterioration
43	TAVI: Transcatheter Aortic Valve Implantation
44	

Abstract (175 words)

Objectives. Structural valve deterioration (SVD) remains a major bioprosthesis-related complication, as recently described for the Mitroflow® valve (model LX/12A). The real incidence of the SVD risk remains unclear, often due to methodological pitfalls by systematically using the Kaplan-Meier estimator and/or the Cox model. In this report, we propose for the first time a precise statistical modelling of this issue.

Methods. 561 patients who underwent aortic valve replacement with the aortic SORIN Mitroflow® valve between 2002 and 2007 were included. We used an illness-death model for interval-censored data. Median follow-up was 6.6 years: 103 cases of SVD were diagnosed.

Results. The 4-year and 7-year SVD cumulative incidences post-first anniversary of the surgery were 15.2% (95%CI from 11.9 to 19.1) and 31.0% (95%CI from 25.8 to 37.2) respectively. Female gender, dyslipidemia, Chronic Obstructive Pulmonary disease (COPD) and severe patient-prosthesis mismatch were significant risk factors of SVD. The occurrence of SVD was associated with a 2-fold increase in the risk of death.

Conclusions. Appropriate statistical models should be used to avoid underestimating the SVD complication associated with worse long-term survival.

Introduction

More than 200,000 aortic valve replacement (AVR) procedures are performed yearly worldwide (1). Due to enhanced tissue durability, the choice of prosthesis has changed in favour of biological prostheses. Structural valve deterioration (SVD), however, remains a major bioprosthesis-related complication, with significant heterogeneity between the types of prosthesis (2, 3). Among bovine pericardial prostheses, the SORIN Mitroflow® valve, available since 1982, was designed to improve prosthesis hemodynamic performance, especially in small aortic roots thanks to its lower bulk (4). More than 100,000 AVR procedures have been performed with this valve worldwide since its first implantation.

It is reasonable to assume that SVD incidence is currently underestimated. The main reason for this is the macroscopic or histological definition of SVD often used in the literature (5, 6), while high-risk octogenarian patients are referred to surgery less frequently following SVD diagnosis (7, 8). In agreement with recent recommendations (9), we therefore studied the SVD risk based on echocardiographic criteria in a cohort of patients who underwent AVR with the SORIN Mitroflow® bioprosthesis (12A/LX models) (10). By using the usual Kaplan-Meier estimator, we estimated the 5-year cumulative incidence of diagnosed SVD at 8.4% (95% CI from 5.3 to 11.3). Moreover, using a Cox model with time-dependent covariates, we estimated a 7.7-fold higher risk of death after SVD diagnosis (95% CI from 4.4 to 13.6). Our study was one of the first to report this health issue.

We believe however, that the true incidence of SVD is still underestimated. Firstly, the time-to-SVD was interval-censored. There are therefore two types of incomplete data: (i) for patients with SVD, the time-to-SVD between the last normal echocardiogram and the first abnormal echocardiogram is unknown; and (ii) for patients who died without SVD diagnosis, the SVD may have occurred after their last normal echocardiogram. Ignoring this interval-

censored process by considering death as right-censoring may also result in an overestimated mean time-to-SVD and an incorrect estimation of the relationship between SVD incidence and the risk of death (11). Secondly, the median follow-up time was 4.1 years whereas SVD is a long-term event.

The aim of the present study was thus to more accurately estimate the incidence of SVD for patients who underwent an AVR with SORIN Mitroflow® bioprosthesis, along with its impact on patient mortality. For that purpose, we updated the patients' follow-up from our previous study (10) in order to better appraise long-term outcomes. We also developed an original statistical method to deal with interval censoring, i.e. a semi-Markov illness-death model.

Material and Methods

Patients

Between January 2002 and December 2007, 617 consecutive patients underwent AVR with a SORIN Mitroflow® bioprosthesis (12A and LX models) in the Nantes University Hospital (France). The SORIN valve was prepared preoperatively as indicated in the user manual (12). SVD is unlikely to occur during within the first-year post-surgery: we observed no event during this period. In order to study the incidence of SVD and its impact on mortality, the baseline of our study was defined as the first anniversary of the surgery. Five hundred sixty-one patients alive without SVD at 1-year post-surgery were included. More precisely, the 26 patients who died in hospital and the 30 patients discharged from hospital but who died before the first anniversary of surgery were non-included. In case of redo-surgery or TAVI occurring

during the follow-up, with or without diagnosis of SVD, the data were censored at the time of the procedure.

Data Collection

Perioperative data were collected prospectively while echocardiograms and vital signs were retrospectively collected. The long-term follow-up of the patients included in this cohort was ensured by their own cardiologists. Clinical and echocardiographic data were collected by the Clinical Investigation Centre at the Nantes University Hospital after authorization by the local ethics committee (institutional review board) and the CNIL (Commission Nationale Informatique Libertés –, authorizations #1456630v1 and #910300). Morbidity and mortality were analysed taking into account the recommendations of the AATS-STS-EACTS (American Association for Thoracic Surgery, the Society of Thoracic Surgery and European Association for Cardio-Thoracic Surgery) (9).

The following preoperative data were collected: age, sex, body mass index (BMI), family history, high blood pressure history, diabetes mellitus, dyslipidemia, obesity, history of smoking, aortic valve disease (stenosis, insufficiency, mixed disease, endocarditis, prosthetic endocarditis), New York Heart Association (NYHA) classification, pulmonary oedema, syncope, atrial fibrillation, chronic obstructive pulmonary disease (COPD), second forced expiratory volume, peripheral vascular disease, renal failure (creatinine $>200\text{ }\mu\text{mol/L}$ or Cockcroft-Gault creatinine clearance $<60\text{ mL/min}$), preoperative dialysis, stroke, carotid or coronary stenosis, myocardial infarction, left ventricular ejection fraction, systolic pulmonary arterial pressure $>60\text{ mm Hg}$, and elective, urgent or emergency procedure. Severe prosthesis-patient mismatch (PPM) was defined as an effective orifice index area of the aortic prosthesis

140 $\leq 0.65 \text{ cm}^2/\text{m}^2$ (13), based on the *in-vivo* effective orifice area (EOA) given by the
141 manufacturer (12).

142 The following explicative variables were studied: Severe prosthesis-patient mismatch (PPM),
143 body mass index (BMI), age at time of surgery, sex, dyslipidemia, COPD, diabetes mellitus,
144 left ventricular ejection fraction, atrial fibrillation, peripheral vascular disease, and isolated
145 AVR.

148 **SVD Definition**

149 The SVD definition we used was defined based on several international recommendations
150 (14). Indeed, until very recently, no standardized definition was available. We therefore used
151 in this study an *ad-hoc* definition: progression of aortic transprosthetic gradient $\geq 30 \text{ mmHg}$
152 associated with a decrease in effective orifice area $\leq 1 \text{ cm}^2$ and aortic cusp alteration, or intra-
153 prosthetic aortic regurgitation $> 2/4$. Long-term patient follow-up was performed by these
154 latter's own personal cardiologists (outside our institution where the surgeries were
155 performed). The echocardiography times were not planned for our study, we only observed
156 real-life practices. Each case of SVD was carefully assessed and validated following a review
157 of medical reports. In cases where SVD was suspected on echocardiography but not
158 ascertained, patients were referred to our institution.

160 **Statistical Analysis**

161 The median follow-up time was estimated using the reverse Kaplan-Meier method (15). We
162 used a semi-Markov illness-death model. This model allowed us to study the SVD as an

interval-censored event before death (16, 17). This interval censoring is important when dealing with an event that is known to occur within an interval instead of being observed exactly. For our cohort, the event date for patients with SVD was known to have occurred between the last normal echocardiogram and the diagnostic echocardiogram. Similarly, patients who died without SVD diagnosis may have developed the SVD after their last normal echocardiogram. Note that the illness-death model we propose aims to estimate the probability of SVD before death. Indeed, our aim was to estimate the properties of the valve in a real-life setting: one can accept that a valve may deteriorate, but SVD must occur after the patient's death. Compared to non-parametric approaches, this approach presents the advantage of requiring fewer parameters with a smaller sample size, estimating an adjusted hazard ratio due to covariates, and allowing us to model the distribution of the time-to-transition from the illness to death state.

Patients who underwent repeat aortic valve replacement unrelated to SVD were right-censored at the time of the new surgery (n=7). The generalized Weibull distribution was tested for the three transition-specific baseline hazard functions, and the model was secondarily simplified without unnecessary parameters (an exponential distribution was chosen for the transition from SVD to death). The assumption of proportional hazards was graphically assessed. Risk factors were initially selected from univariable models (Wald test, $p < 0.25$). A multivariable model was then estimated with a backward procedure performed manually, variable by variable, for each transition (Wald test, $p < 0.05$). The illness-death model was used to estimate: the cumulative incidence of SVD and the Hazard Ratio (HR) of death related to SVD incidence by combining bootstrapping and simulations (for each bootstrap sample, the times-to-event were simulated according to the final multivariable model and the observed baseline characteristics of the patients and the HR was estimated from a time-dependent Cox model) (18).

The description of the semi-Markov model is presented in the supplemental material. The Non-parametric Turnbull estimator for interval-censored data and the Kaplan Meier method were used to estimate the cumulative incidence of SVD and compared with the results from the illness-death model (Figure 2).

To illustrate the need for appropriate methods, we completed the evaluation of our model regarding the competing risk analysis and the interval censoring with comparisons of results obtained by different methods. We compared the CIFs of SVD obtained by i) the proposed SM illness-death model, ii) the same model without taking into account interval-censoring, iii) the Aalen and Johansen estimator (19) (Figure 2 of Supplemental Material), iv) the non-parametric Turnbull estimator for interval-censored data, and v) the Kaplan Meier method. (Figure 2). To obtain data with no interval-censoring, we considered the time-to-SVD as the mean between the lower and the upper bounds of the interval. Patients without SVD diagnosis were considered free of SVD at the end of the follow-up.

Time-to-SVD was defined in the middle of the interval between the normal and abnormal echocardiographs. Patients who died with no SVD diagnosis were right-censored at the date of death.

Statistical analyses were performed with R software (version 3.1.1), along with the *multistate* (20) and *relsurv* packages (21).

Results

Baseline cohort characteristics

The preoperative characteristics of the 561 patients are presented in Table 1. The mean age was 76.4 (SD=6.0) years. Fifty-seven percent (n=321) of patients were between 70 and 80

years old and 29% (n=162) were octogenarians. Females represented 56% (n=314) of the patients. The indication for surgery was aortic valve stenosis in 83.6% (n=469) of patients. The proportion of repeat surgery was 5.5% (n=31). Isolated AVR was performed in 362 patients (64.5%). The associated procedures were mainly coronary artery bypass surgery in 30.3% of patients (n=170). A small diameter prosthesis (19 or 21 mm) was implanted in 64.9% (n=364) of patients and 23.4% (n=131) of patients had severe PPM.

Description of the follow-up

The median follow-up time was 6.6 years (ranging from 0 to 10.6) after the first anniversary of surgery. Two thousand one hundred sixty-four echocardiograms were collected. The median number of echo reports by patient was 3, with a maximum of 10. Nine patients were included without echo assessment. The maximum follow-up was 10.6 years after the first anniversary of surgery, with a mean interval between two follow-ups of 458 days (min-max: 5-3280). SVD was diagnosed in 103 patients. More precisely, 298 patients were still alive without SVD diagnosis, 160 patients died without previous SVD diagnosis, 73 patients were still alive after SVD diagnosis, and 30 patients died following SVD diagnosis. Two SVD modes were observed: the main was calcified prosthetic stenosis (Figure 1) in 81 patients, while moderate to severe intra-prosthetic regurgitation was found in 22 patients. Among patients diagnosed with SVD, 35.0% (n=36) were not referred by personal cardiologists, 38.8% (n=40) underwent a repeat AVR (n=31) or TAVI (n=9), 15.5% (n=16) were denied surgery and TAVI after clinical work-up, and 3.9% (n=4) refused the clinical work-up. Four patients (3.9%) died while waiting for repeat surgery. Among the 190 deaths, SVD was one of the main reported causes of death in 10.0% of cases (n=19). The other reported causes (Table 1 in Supplemental Materials) were congestive heart failure (17.9%, n=34), cancer (12.6%,

n=24) and sepsis (9.5%, n=18). The overall survival compared to the valve-related and cardiac-related survival of this cohort is illustrated in Figure 3 of the Supplemental Materials.

Cumulative incidence of SVD

The first SVD was diagnosed 2 months after the first year of surgery (14 months after surgery). As illustrated by Figure 2, the 4- and 7-year cumulative incidences after the first anniversary of surgery were respectively 7.2% (95% CI from 4.8 to 9.5) and 23.4% (95% CI from 18.3 to 28.2) for the Kaplan-Meier estimator, 11.9% (95% CI from 8.3 to 15.5) and 28.3% (95% CI from 22.6 to 36.4) for the Turnbull estimators, and 15.2% (95% CI from 11.9 to 19.1) and 31.0% (95% CI from 25.8 to 37.1) for the semi-Markov model. As expected, by comparing the results obtained using the Kaplan-Meier and Turnbull estimators, ignorance of the interval-censored process leads to an underestimation of the cumulative incidence of SVD. Moreover, by comparing the results obtained by our semi-Markov illness-death model and the Turnbull estimator, one can conclude that ignorance of competing risks could still leads to an underestimation of the mid-term cumulative incidence of SVD.

As listed in Table 2, the illness-death model indicated that the significant risk factors of SVD were female gender (HR=1.6, 95% CI from 1.1 to 2.4), dyslipidemia (HR=1.6, 95% CI from 1.1 to 2.3), severe PPM (HR=1.7, 95% CI from 1.1 to 2.5) and COPD (HR=2.9, 95% CI from 1.6 to 5.4). According to this model, we estimated a 2-fold increased risk of death (95% CI from 1.3 to 2.9) after SVD incidence.

Discussion

We aimed to accurately estimate the incidence of SVD and its relationship with the risk of death in patients who underwent AVR with the SORIN Mitroflow® models 12A/LX. In our previous study (10), the cumulative incidence of SVD reached 8.4% (Kaplan-Meier estimator, 95%CI from 5.3 to 11.3) at 5 years post-surgery. But the usual methods we used failed to handle several specific issues relating to the SVD risk assessment. As recently pointed out by Huebner et al.(22), methodological pitfalls are frequent in the literature, even in prominent medical journals, leading to biased estimations. In this study, we developed an illness-death model, a statistical approach which deals with the competing risk and interval censoring of SVD. The 5-year post-surgery cumulative incidence of SVD was estimated at 15.2% (95% CI from 11.9 to 19.1), underlining a possible underestimation of the incidence of SVD in our previous study. Thanks to an extended follow-up, we also described a cumulative incidence of SVD of 31.0% (95% CI from 25.8 to 37.2) at 7 years post-first anniversary of the surgery.

Additionally, we highlighted for the first time (as far as we know) that COPD constitutes a significant risk factor of SVD. Its prevalence was 5.9% in our cohort. The mechanism seems unclear, but inhalation exposures, as in COPD, can lead to local and general inflammatory responses, which increase with disease severity. Moreover, respiratory infections are more frequent in patients with COPD and can also increase the systemic inflammatory response. Thus, repetitive inflammatory responses could increase the immune response, which has been reported to potentially increase the SVD process (23). This hypothesis needs to be confirmed, but it could pave the way for preventing SVD.

Other risk factors were significantly linked to SVD incidence. In accordance with the literature, we identified dyslipidemia (24, 25) and PPM (26, 27). Flameng et al. (26) assumed that the role of PPM could be due to disturbed flow patterns. Annulus enlargement is thus

currently recommended by some authors in patients with predictable severe PPM (28), but with an increased risk of procedure-related surgical complications (29, 30). The prevalence of PPM in our study was 23.4%, a proportion quite different from the literature. For example, Jamieson et al. (31) reported only 2.9% of severe PPM with 19-mm SORIN Mitroflow® and 0.5% overall. However, the *in-vivo* Effective Orifice Area (EOA) was validated from a small number of patients and was clearly greater than that the pre-specified information provided by the company: for instance, an *in-vivo* EOA of 1.4 cm² for the 19-mm SORIN Mitroflow® versus 1.1 cm² from the SORIN data (12). With similar values, the severe PPM rates in our cohort would have been 0% and 2.4% for the 19 mm and 21mm dimensions, respectively.

In our previous study based on a Cox model (10), SVD diagnosis was associated with a significant 7.7-fold increase in the risk of death (95% CI from 4.4 to 13.6). We additionally proposed a precise appraisal of the impact of SVD on patient survival. Based on the illness-death model, we estimated in the present study a 2-fold higher risk of death after SVD occurrence (95% CI from 1.3 to 2.9). These results are in stark contrast with the studies which described a very low percentage of SVD with the SORIN Mitroflow® valve (5, 6, 32, 33). These differences are likely related to the methodological pitfalls we described. We therefore hope that the methodological framework we propose in this study, i.e. the definition of SVD based on echocardiograms and the illness-death model for interval-censored data and competing events, will be further considered in future AVR-related studies. But as is always the case for observational studies of this kind, several limitations must be underlined. Firstly, we deliberately limited the study to patients alive at 1-year post-surgery, due to the absence of observed SVD within this interval. We definitely believe that deterioration is a continuous process, with a minimum duration necessary to achieve a progression of aortic transprosthetic gradient ≥ 30 mmHg associated with a decrease in effective orifice area ≤ 1 cm² and aortic cusp alteration, or intra-prosthetic aortic regurgitation $> 2/4$. Nevertheless, this first period may not

307 be strictly equal to 1 year and may vary according to the cohort, the studied valve(s), and the
308 SVD definition. Secondly, even though we updated the follow-up of this cohort, the follow-up
309 period still does not allow a precise estimation of long-term SVD cumulative incidence (the
310 curve is still increasing at this maximum time in Figure 1). Thirdly, the echocardiograms were
311 not planned, but were implemented by personal cardiologists, as in real medical practice. We
312 would have preferred scheduled echocardiograms with identical intervals between two
313 follow-up visits. In our real-life study however, variable times between two clinical
314 examinations can be observed. One can suppose a dependence between the follow-ups and the
315 health state of the patients, representing a possible information bias in our results. For
316 instance, a patient presenting with increased dyspnoea or cardiac symptoms would be more
317 likely to visit his/her cardiologist. Consequently, the incidence of SVD may still be
318 underestimated by omitting asymptomatic SVD. However, even for studies with the benefit of
319 regular echocardiograms (for instance every two years), interval-censoring data and
320 competing events will still need to be handled. Fourthly, we did not compare the outcomes of
321 this SORIN Mitroflow® bioprosthesis (models 12A and LX with no anticalcification
322 treatment) with another bioprosthesis. A comparison of the efficacy of an alternative
323 bioprosthesis was beyond the scope of this study, which focused on methodological solutions
324 for a precise appraisal of SVD incidence and patient survival after SVD. The results we
325 reported appeal for future randomized clinical trials to evaluate the most effective
326 bioprosthesis. Finally, by exclusively using the Wald test for variable selection, we decided to
327 adopt an explorative approach. There is thus an increase in the first error rate with some
328 possible overfitting issues. Our results need to be confirmed in the future by other studies. We
329 have also completed the evaluation of our model regarding the competing risk analysis with
330 comparisons of results obtained by different methods. As illustrated in the Figure 2 of the

Supplemental Materials, the main conclusion is an underestimation of the CIF by the last two methods, i.e. by ignoring the interval-censoring.

Examination of the literature concerning others bioprostheses reveals that the incidence and definition of SVD are variable, with several large series reporting low rates of SVD in the long-term. Bourguignon et al. (34) evaluated 2758 Carpentier Edwards Perimount prostheses, with no reported SVD (defined as severe aortic stenosis or severe aortic regurgitation) at 15 years of $78.6 \pm 2.2\%$. Cox proportional hazards regression was used to identify risk factors. For the same bioprosthesis, Forcillo et al. (35) reported freedom from SVD of $34 \pm 2\%$ at 15 years, using the Kaplan-Meier method to estimate the SVD survival curve. Another large series, reported by Mohammadi et al (36) in 2012, reported freedom from SVD at 15 years for the Freestyle prosthesis of 82.3%, using a Cox model to assess the risk factors of SVD. Unfortunately, the last two studies failed to precisely report the SVD criteria they used. Overall, our results are difficult to compare because the previous studies did not consider interval-censoring or the competition between death and SVD diagnosis.

The SVD definition we used might be improved. Very recently, Capodanno et al (37) published some standardized definitions of SVD, based on several echographic parameters. Close to our own definition, a combined set of criteria for severe hemodynamic SVD is described: mean gradient above 40mmHg, and/or a 20mmHg change from baseline and/or severe aortic regurgitation. In order to deal with repeated measurements of hemodynamic changes as longitudinal markers, it would have been interesting to use joint modelling, allowing dynamic prediction of the individual risk of death or explant for SVD according to gradient evolution. Interestingly, it considers the variability of the longitudinal marker for a given patient to precisely model its evolution. It should be noted that non-linear marker evolution can be modelled, as previously reported for the gradient evolution (38).

Specifically, such joint models have recently been used in patients who received a human tissue valve in the aortic position (39). Nevertheless, the main limitation of joint models is that they are based on one or two longitudinal markers. In our context, valve deterioration can be defined based on several markers (such as mean aortic gradient, aortic valve area and the presence of aortic regurgitation). We therefore dichotomized echocardiogram-based markers, which appears as a limitation of our approach (40). Introducing these longitudinal measurements in joint models constitutes a future perspective of our work and could represent a solution for developing a dynamic score to help clinicians in their decision to re-operate (41) and in personalizing screening intervals (39). In these models, the baseline of the surgery would be the first postoperative day. At last, although numerous explanatory variables were analyzed, we cannot exclude the possibility that some confounding factors, which were not taken into account in the present study, could have exerted influence.

In conclusion, our study demonstrated an unexpected high incidence of SVD with models 12A and LX of the SORIN Mitroflow® valves. This issue may have been underestimated due to methodological pitfalls: the SVD definition based on histological criteria, the insufficient follow-up period and the use of traditional statistical approaches for time-to-event data (Kaplan-Meier curves and/or Cox regression) which ignore interval-censoring and competition between events. Our results have an immediate impact for patients implanted with the SORIN Mitroflow® valve: we highly recommend annual follow-ups, especially for patients with SVD risk factors such as severe PPM, dyslipidemia or COPD. We also hope that our results will encourage clinical trials and other cohort-based studies to describe/compare the outcomes of other bioprotheses. This literature is crucial in order to avoid such an underestimation of post-AVR complications.

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Legends

Figure 1: Mitroflow bioprosthesis (21 mm) structural failure characterized by commissural calcifications and global thickening of the 3 cusps just before reoperation. A, Transesophageal echocardiography showing thickening and calcification of the bioprosthesis. B, Mitroflow during explantation showing calcified nodules, particularly in the commissural regions, and diffuse cusp infiltration. Left indicates left cusp, and Right, right cusp.

Figure 2: Cumulative incidence of SVD after the first anniversary of surgery. The red curve was estimated from the illness-death model handling interval censoring for time-to-SVD and competition with death without SVD. The black curve was estimated with the Kaplan-Meier method. The dotted line was estimated from the Turnbull's Non-parametric Estimator for Interval Censored Data.

Supplemental material:

Text: Description of the semi-markov model used in the manuscript

Table 1: Causes of death for the 190 observed deaths.

Table 2: Significant factors associated with the time-to-SVD after the first anniversary of surgery from the illness-death model (forced age adjustment), for the 561 on the left and for the 552 without the 9 patients missing echo data on the right.

Figure 1: Beta exponential for the quartiles of the indexed IN VIVO surface area, regarding the transition between state 1 (Healthy with an AVR) and state 2 (proved SVD):

Figure 2. Comparison of the cumulative incidence function of SVD, obtained by i) the proposed SM illness-death model, ii) the same model without taking into account interval-censoring, and iii) the Aalen and Johansen (1978) estimator.

Figure 3. Overall, Valve-related and Cardiac-related patient survival

537 **Figure 4.** Optimal multistate model to represent the detailed evolution for a patient following an aortic valve
538 replacement (AVR).

539 **Figure 5.** Number of available data according to the time of follow-up.

540 **Figure 6:** Mean Gradient evolution for the 103 cases of SVD. Line is in grey before the SVD diagnosis time,
541 and black following the SVD diagnosis.

542 **Figure 7:** Cumulative incidence of SVD after the first anniversary of surgery. The red curve was estimated from
543 the illness-death model for the 561 patients. The black curve was estimated from the same model without the 9
544 patients missing echo data.

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547 **Video Legend:** Redo Aortic Valve Replacement (AVR) for Structural Valve Deterioration. (Male
548 patient, 53 years old, first implantation in 2011, redo-AVR in November 2017).

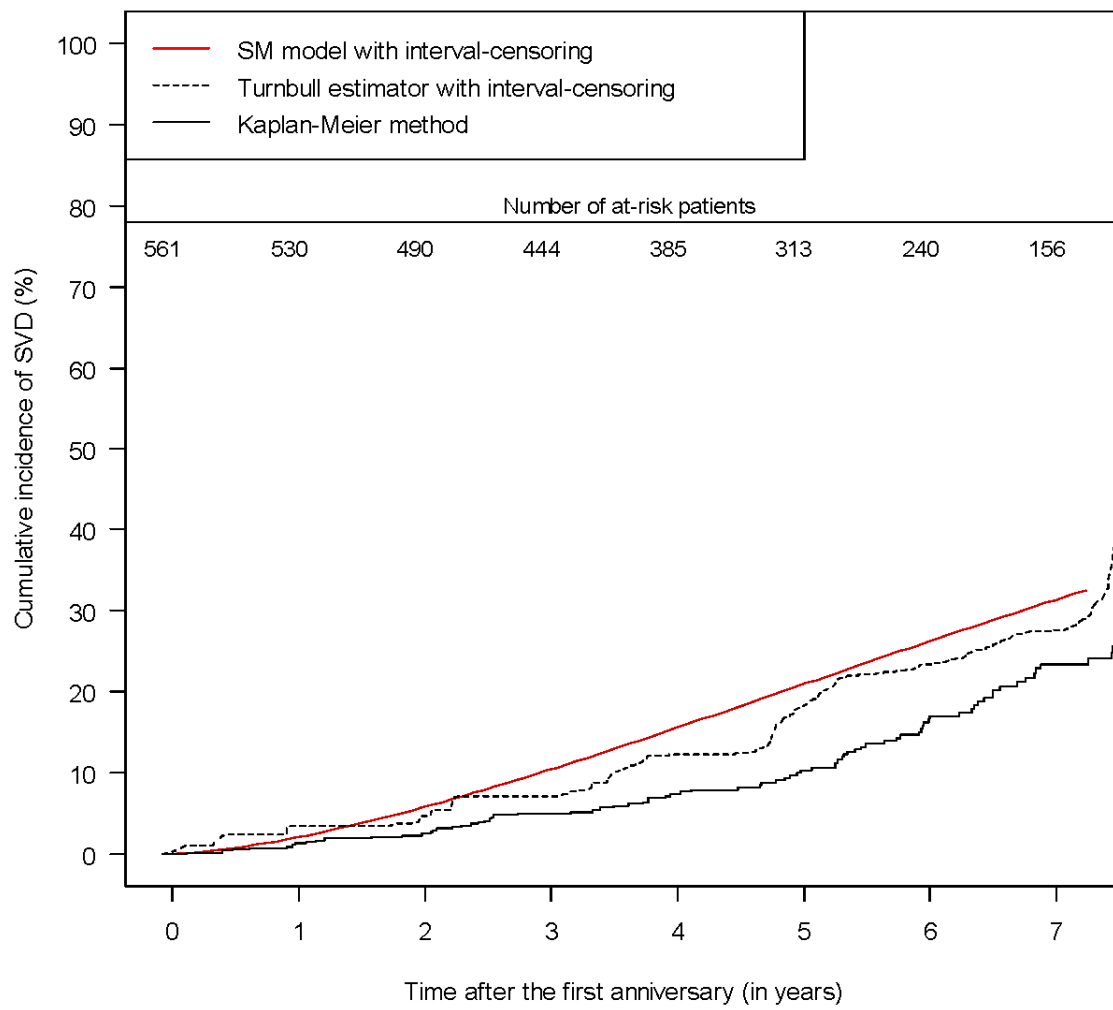
Table 1: Baseline characteristics of the monocentric cohort comprising 561 patients who underwent an AVR with a SORIN Mitroflow® bioprosthesis.

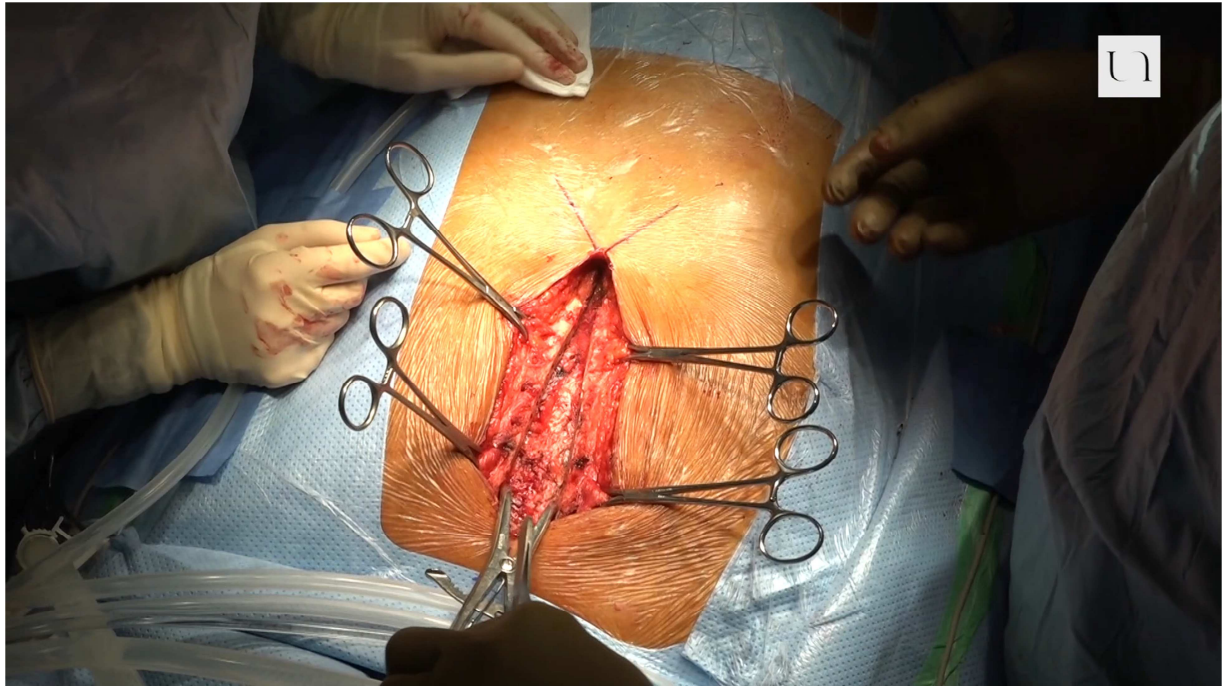
Clinical data	
Female, n (%)	314 (56.0)
Age, years (mean \pm SD)	76.4 \pm 6.0
Body Mass Index, Kg/m ² (mean \pm SD)	26.7 \pm 4.8
Atrial fibrillation, n (%)	86 (15.3)
High blood pressure, n (%)	352 (62.8)
Mellitus diabetes, n (%)	111 (19.8)
Dyslipidemia, n (%)	257 (45.8)
Obesity, n (%)	129 (23.0)
History of smoking, n (%)	91 (16.2)
NYHA classification 3-4, n (%)	167 (29.8)
Comorbidities	
Peripheral vascular disease, n (%)	71 (12.7)
Preoperative renal failure, n (%)	37 (6.6)
Chronic Obstructive Pulmonary Disease, n (%)	33 (5.9)
Stroke, n (%)	18 (3.2)
Myocardial infarction history, n (%)	30 (5.3)
Coronary angioplasty, n (%)	29 (5.2)
Echocardiography	
Left ventricular ejection fraction, percentage (mean \pm SD)	58 \pm 12
Left ventricular ejection fraction < 50%, n (%)	68 (12.1)
Systolic pulmonary artery pressure > 60 mmHg, n (%)	16 (2.9)
Aortic stenosis, n (%)	469 (83.6)
Aortic insufficiency, n (%)	16 (2.6)
Surgical data	
Elective surgery, n (%)	486 (86.6)
Implanted bioprostheses \leq 21 mm, n (%)	364 (64.9)
Severe PPM, n (%)	131 (23.4)
Logistic Euroscore (mean \pm SD)	10.0 \pm 10.1
AVR: Aortic Valve Replacement ; NYHA: New York Heart Association ; PPM: Patient-Prosthesis Mismatch	

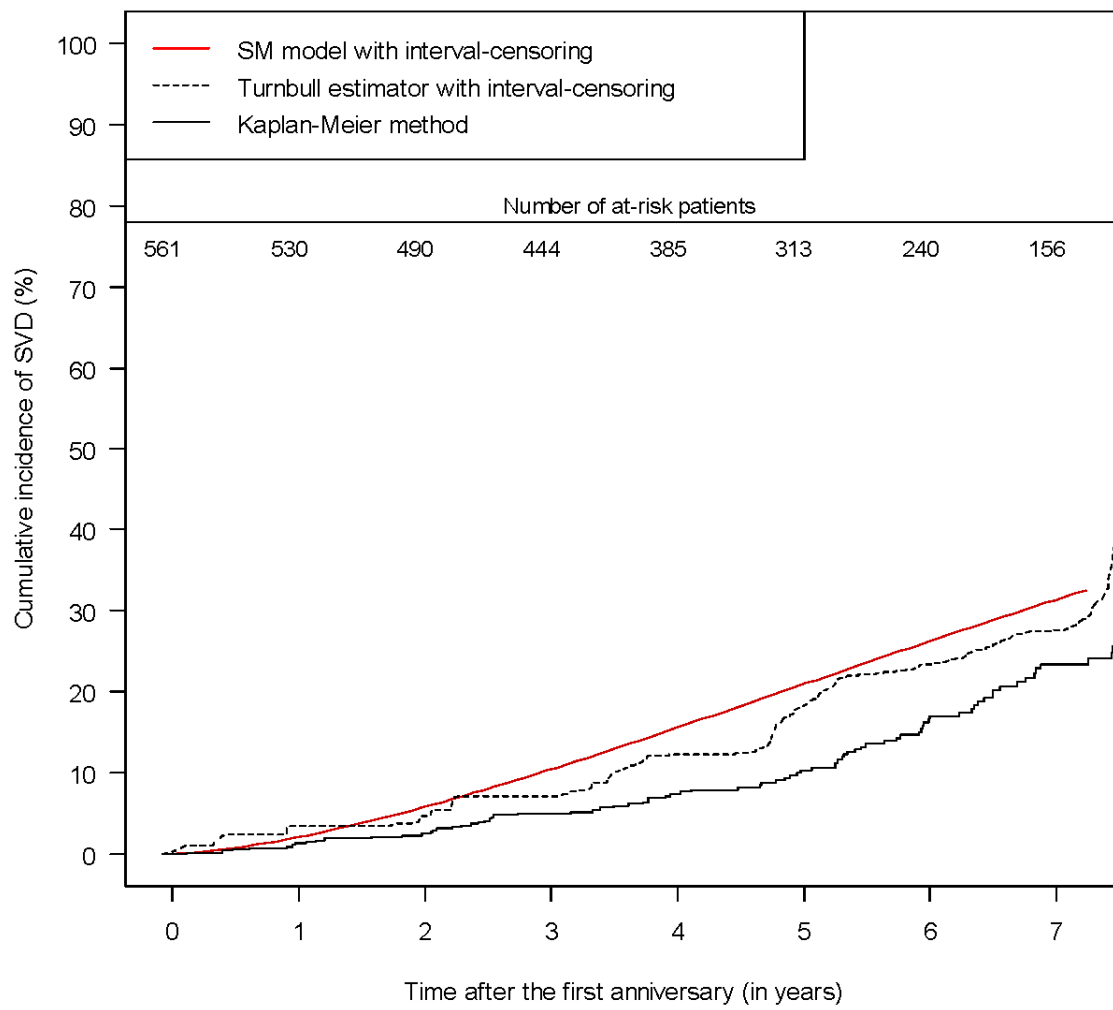
Table 2: Significant factors associated with the time-to-SVD after the first anniversary of surgery in the illness-death model (forced age adjustment – n=561).

	HR	[95%CI]	p-value
Severe Patient-Prosthesis Mismatch (PPM)	1.68	[1.13 – 2.49]	0.010
Female	1.59	[1.06 – 2.38]	0.026
Dyslipidemia	1.56	[1.07 – 2.27]	0.019
Chronic Obstructive Pulmonary Disease (COPD)	2.91	[1.56 – 5.44]	0.001
Under 70 at the time of surgery	1.00		
between 70 and 80 years old	1.05	[0.62 – 1.78]	0.867
Over 80 years old	0.90	[0.47 – 1.72]	0.751









Supplemental material:

Description of the semi-markov model used in the manuscript:

Let T be the chronological time from baseline and S the duration (or sojourn time) in a state. Let \mathcal{Y} be the set of possible clinical states. The stochastic process under consideration is $\{Y_m, T_m, m \in \mathbb{N}\}$, where Y_m is the state of the patient after the m -th transition occurring at time T_m with $T_0 < T_1 < \dots < T_m$ ($T_0 = 0$ and $Y_0 = 1$ by convention). Let ϵ be the set of possible transitions ij with $(i, j) \in (\mathcal{Y}, \mathcal{Y})$, where i represents a transient state with j distinct from i . We use δ_{ij} to denote the indicator function of a transition ij : $\delta_{ij} = 1$ if the transition ij is observed (with the duration time s_{ij} in state i before transition to state j), and $\delta_{ij} = 0$ otherwise. Let X be the vector of patient characteristics at baseline, and X_{ij} the subvector of characteristics specifically associated to the transition ij . In the context of the illness-death model, $\mathcal{Y} = \{1, 2, 3\}$ with $\{Y = 1\}$ the healthy stage, $\{Y = 2\}$ the illness stage, and $\{Y = 3\}$ the death.

The semi-Markov (SM) model considers that the transition intensities between two states depend on the time already spent in the current state. The hazard function for transition from state $Y_m = i$ to the state $Y_{m+1} = j$ after a duration s , given patient characteristics $X_{ij} = x_{ij}$ is therefore defined by:

$$\lambda_{ij}(s|x_{ij}) = \lim_{\Delta s \rightarrow 0^+} P(s \leq T_{m+1} - T_m < s + \Delta s, Y_{m+1} = j | T_{m+1} - T_m > s, Y_m = i, x_{ij}) / \Delta s$$

The probability for a patient to spend at least some time s in state i , given its characteristics $X_i = x_i$ at baseline, can be defined as:

$$S_i(s|x_i) = \exp\left(- \sum_{j: ij \in \epsilon} \int_0^s \lambda_{ij}(u|x_{ij}) du\right)$$

The corresponding density function specific to transition ij after duration s can be deduced from the previous equations: $f_{ij}(s|x_i) = \lambda_{ij}(s|x_{ij})S_i(s|x_i)$. Consider a parametric SM model, parameters being estimated by maximizing the log-likelihood. Take a sample of N independent subjects ($h = 1, \dots, N$). Let l_h be the individual contribution to the likelihood for a subject h .

In the illness-death context where time-to-illness is interval-censored, four observed trajectories are possible (Figure X).

Trajectory i) At the time of right-censoring t_{max} , the individual h was alive. The illness was never diagnosed, the patient being illness-free at the time t_{inf} , which corresponds to the last visit with a negative diagnosis. In this situation, the illness may have occurred in-between t_{inf} and t_{max} or the patient can also be illness-free at t_{max} . The probability of observing this trajectory is:

$$l_h = S_1(t_{max}|x_1) + \int_{t_{inf}}^{t_{max}} f_{12}(u|x_1)S_2(t_{max} - u|x_{23}, u)du$$

Trajectory ii) At the time of right-censoring t_{max} , the individual h was alive. The illness was diagnosed at the time t_{sup} . The patient was illness-free at the time t_{inf} , which corresponds to the last visit with a negative diagnosis. The illness have occurred in-between t_{inf} and t_{sup} . The probability of observing this trajectory is:

$$l_h = \int_{t_{inf}}^{t_{sup}} f_{12}(u|x_1)S_2(t_{max} - u|x_{23}, u)du$$

Trajectory iii) The individual h died at the time t_{max} . The illness was diagnosed at the time t_{sup} . The patient was illness-free at t_{inf} , which corresponds to the last visit with a negative diagnosis. The illness have occurred in-between t_{inf} and t_{sup} . The probability of observing this trajectory is:

$$l_h = \int_{t_{inf}}^{t_{sup}} f_{12}(u|x_1)f_{23}(t_{max} - u|x_{23}, u)du$$

Trajectory iv) The individual h died at the time t_{max} . The illness was never diagnosed, the patient being illness-free at the time t_{inf} , which corresponds to the last visit with a negative diagnosis. The illness may have occurred in-between t_{inf} and t_{max} or the patient may also die without Structural Valve Deterioration (SVD). The probability of observing this trajectory is:

$$l_h = f_{13}(t_{max}|x_1) + \int_{t_{inf}}^{t_{max}} f_{12}(u|x_1)f_{23}(t_{max} - u|x_{23}, u)du$$

In the multivariable SM model and under the proportional hazard (PH) assumption, the hazard function for transition from state $Y_m = i$ to the state $Y_{m+1} = j$ after a duration s , given patient characteristics $X_{ij} = x_{ij}$ was defined as follows:

$$\lambda_{ij}(s|x_{ij}) = \lambda_{0,ij}(s)\exp(\beta_{ij}x_{ij})$$

where $\lambda_{0,ij}(s)$ is the baseline hazard function when all the covariates equal 0 and β_{ij} are the regression coefficients for transition from state $Y_m = i$ to the state $Y_{m+1} = j$. The interpretation of one regression coefficient is possible given that all the other covariates are fixed. The Hazard Ratio (HR) equals the exponential of the regression coefficient.

Parameters of the SM model are estimated by maximizing the log-likelihood, i.e. $\sum_{h=1}^N \log l_h$. We used the R statistical software version 3.0.1 with `optim()` to maximize the log-likelihood function of the SM model and to compute the corresponding Hessian matrix (Nelder and Mead algorithms). The complete methodology has been implemented in the multistate R package available at www.labcom-risca.com or on the CRAN mirrors.

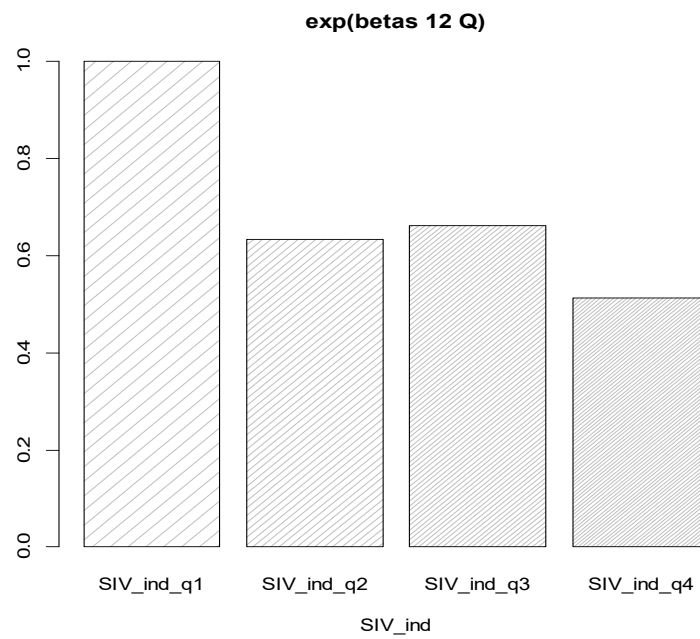
Table 1. Causes of death for the 190 observed deaths.

	Effective	Percentage
Congestive heart failure	34	17,9%
Cancer	24	12,6%
Structural valve deterioration	19	10,0%
Sepsis	18	9,5%
Sudden death	11	5,8%
Respiratory failure	8	4,2%
Cerebral Vascular Accident	7	3,7%
Endocarditis	6	3,2%
Myocardial infarction	6	3,2%
Multi-organ failure	3	1,6%
Thromboembolic event	3	1,6%
Digestive Bleeding	2	1,1%
Cardiogenic shock	2	1,1%
Mesenteric ischemia	2	1,1%
Other	20	10,5%
Unknown	25	13,2%
Total	190	100,0%

Table 2: Significant factors associated with the time-to-SVD after the first anniversary of surgery from the illness-death model (forced age adjustment), for the 561 on the left and for the 552 without the 9 patients missing echo data on the right.

Table1.		
	HR [95%CI]	HR [95%CI]
	(n=561)	(n=552)
Severe Patient-Prosthesis Mismatch (PPM)	1.68 [1.13 – 2.49]	1.70 [1.14 – 2.51]
Female	1.59 [1.06 – 2.38]	1.61 [1.08 – 2.43]
Dyslipidemia	1.56 [1.07 – 2.27]	1.10 [1.59 – 2.31]
Chronic Obstructive Pulmonary Disease (COPD)	2.91 [1.56 – 5.44]	2.99 [1.61 – 5.54]
Under 70 at the time of surgery	1.00	1.00
between 70 and 80 years old	1.05 [0.62 – 1.78]	1.01 [0.59 – 1.72]
Over 80 years old	0.90 [0.47 – 1.72]	0.86 [0.58 – 1.28]

Figure 1: Beta exponential for the quartiles of the indexed IN VIVO surface area, regarding the transition between state 1 (Healthy with an AVR) and state 2 (proved SVD):



SIV_ind_q2 is the beta exponential for the 2nd quartile of the indexed IN VIVO surface area
(1st quartile as reference)

Figure 2. Comparison of the cumulative incidence function of SVD, obtained by i) the proposed SM illness-death model, ii) the same model without taking into account interval-censoring, and iii) the Aalen and Johansen (1978) estimator.

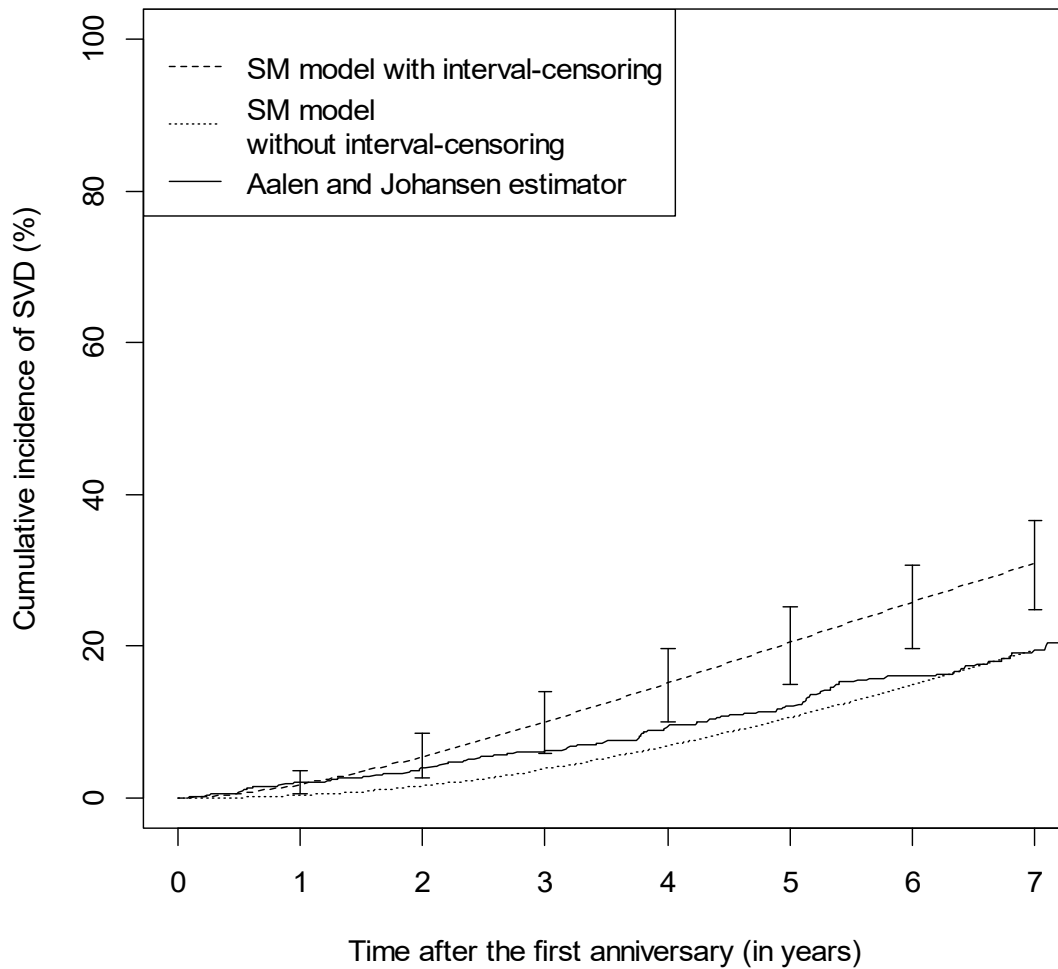


Figure 3. Overall, Valve-related and Cardiac-related patient survival

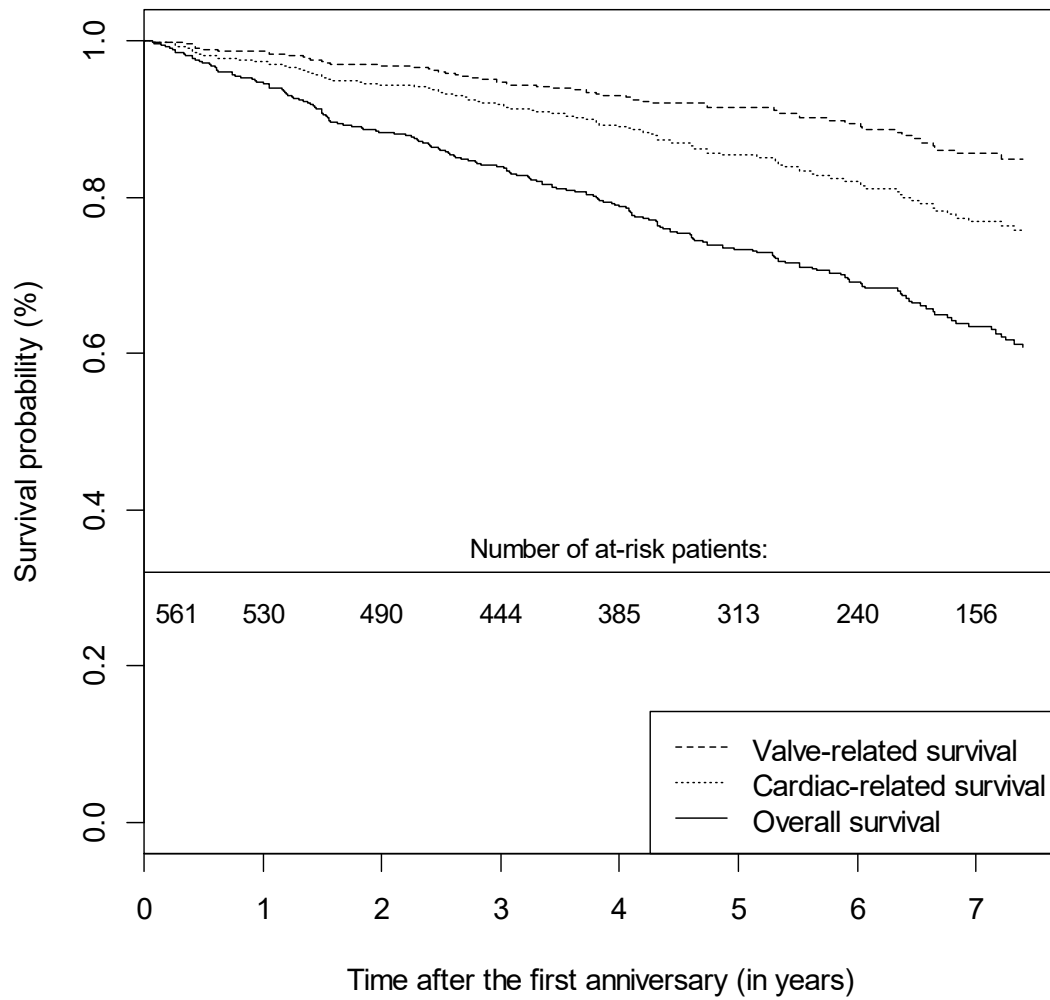


Figure 4. Optimal multistate model to represent the detailed evolution for a patient following an aortic valve replacement (AVR):

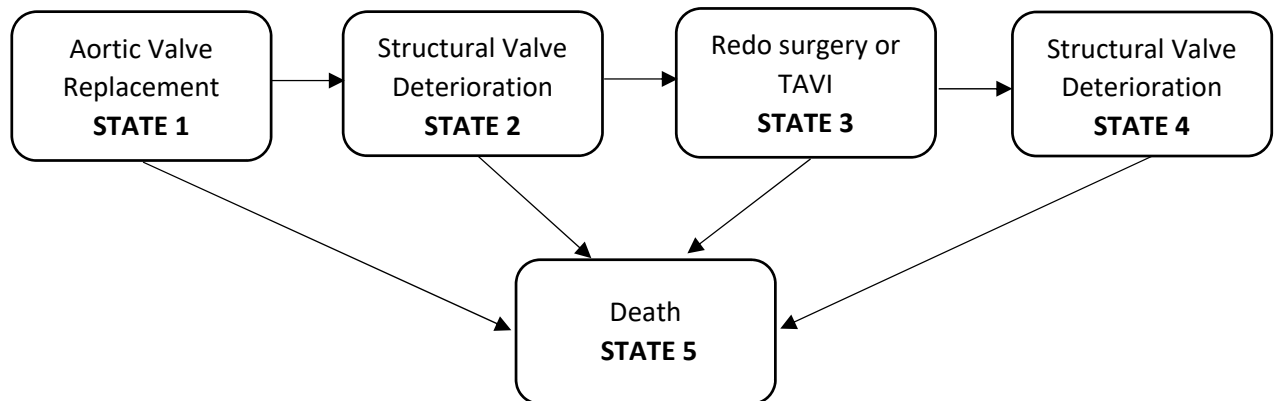


Figure 5. Number of available data according to the time of follow-up.

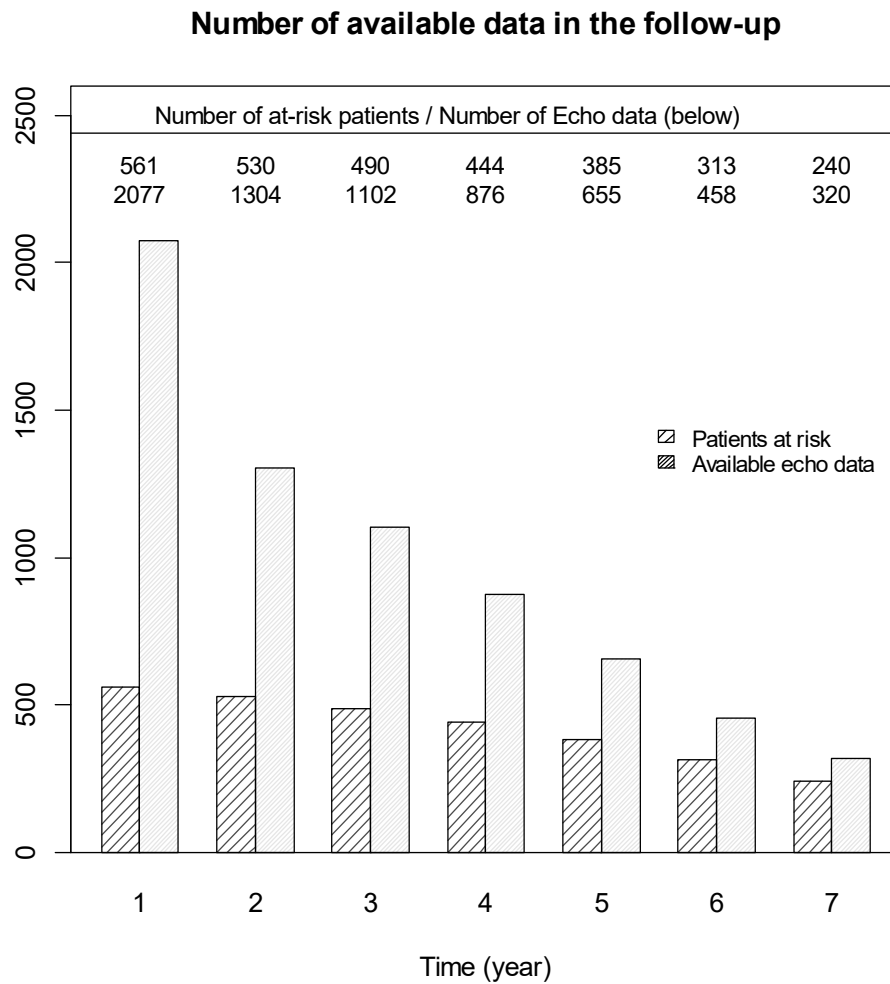


Figure 6: Mean Gradient evolution for the 103 cases of SVD. Line is in grey before the SVD diagnosis time, and black following the SVD diagnosis.

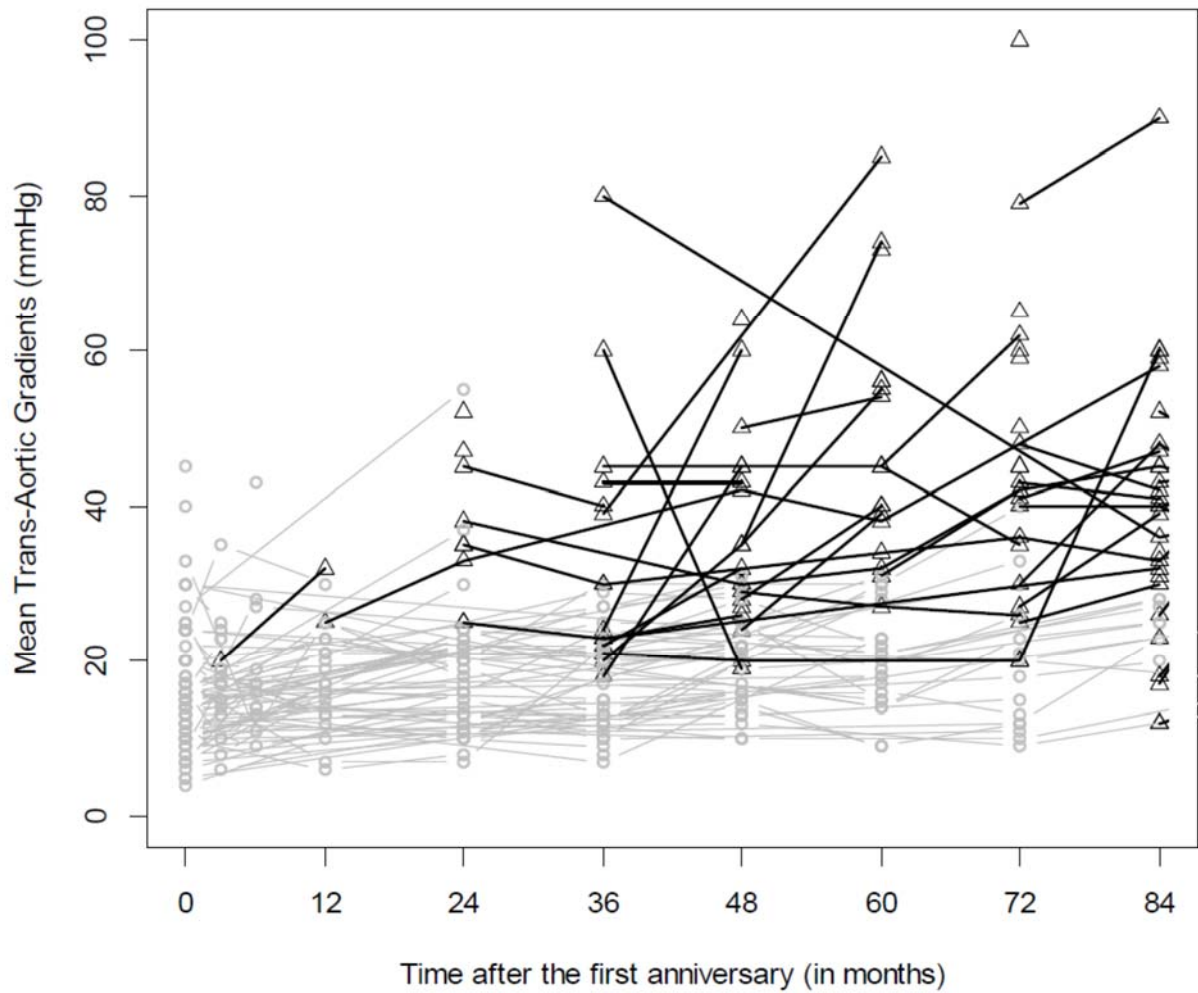


Figure 7: Cumulative incidence of SVD after the first anniversary of surgery. The red curve was estimated from the illness-death model for the 561 patients. The black curve was estimated from the same model without the 9 patients missing echo data.

