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Porcine Bioprostheses for SAVR: Very Long-Term Performance of a 3rd Generation Device

Running head: Epic© Bioprosthesis for SAVR

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Abstract

Aims. We aimed at investigating the long-term durability of the Epic© bioprosthesis for SAVR in a single-center series of 888 implantations (2001-2018), expanding previous evaluations with shorter follow-up.

Methods. We retrieved prospectively collected in-hospital data and performed a systematic follow-up focusing on valve-related events (SVD, Structural Valve Deterioration; PPM, Patient-Prosthesis Mismatch; Reoperation) (Kaplan-Meier and Competing Risks methods). We distinguished between SVD (permanent changes in valve function due to evolutive structural deterioration, ≥ 10 mmHg average gradient vs. reference echocardiography) and PPM.

Results. Average age at SAVR was 75.4 ± 7 years; 855 (96.3%) bioprostheses entered the follow-up and 396 (46.4%) were alive at last assessment. Follow-up was 99.9% complete, median duration was 7.7 years (entire cohort) and 9.9 years (survivors). At 10 years, overall survival was $50\% \pm 1.9$, freedom from SVD was $99.3\% \pm 0.4$ (Kaplan-Meier) and $99.4\% \pm 0.3$ (competing risks) (7 SVD events after 8.1 ± 4.3 years). Freedom from SVD at 15 years was $95.6\% \pm 2.7$ (Kaplan-Meier) and $98.4\% \pm 0.8$ (competing risks). Prevalence of severe PPM was higher in 19-mm (6.5%) and 21-mm (10.2%) size cohorts. PPM (severe or moderate/severe) had no significant impact on overall survival (log-rank $p=0.27$ and $p=0.21$, respectively). Freedom from any reintervention (reoperation or TAVI Valve-in-Valve) for SVD at 10 years was $99.3\% \pm 0.4$ (Kaplan-Meier) and $99.4\% \pm 0.3$ (competing risks); freedom from any valve-related reintervention was $96.9\% \pm 0.7$ (Kaplan-Meier) and $97.4\% \pm 0.6$ (competing risks).

Conclusions. The Epic© bioprosthesis for SAVR is limited by non-negligible rates of PPM, which has nonetheless no impact on late survival. This device shows excellent durability and low rates of adverse valve-related events.

KEY WORDS: SAVR; Bioprostheses; Durability; Outcomes

Introduction

Bioprostheses for surgical aortic valve replacement (SAVR) are evaluated under both the profiles of durability over time and hemodynamic performances. These are major parameters, alongside ease of implantation, to be considered in decision-making. The Epic© valve for SAVR, a porcine 3rd generation device, is diffuse in global practice; it has been the object of regulatory evaluations and of large series reporting very good durability in the mid- to long-term [1, 2, 3]. Nonetheless, with the current evolutions in the population of SAVR candidates, entailing reduction of average age and increased life expectancy due to the migration towards TAVI in older patients irrespective to the class of operative risk, the appreciation of long- to very long-term durability of bioprostheses acquires a growing importance. For these patients, the projected very late clinical outcomes need to be considered in decision-making, in addition to the immediate valve performance. Our purpose was to evaluate the long-term performance of the Epic bioprosthesis for SAVR in a large single-center series with uniform surgical and investigational protocols, adding to previous literature with an important duration of follow-up available for analysis, in order to support decision-making in an evolving patients' population.

Patients and Methods

Ethical Statement

This observational study was based on a prospective database approved, according to compliance regulations and to the French law, by the CNIL (*Commission Nationale de l'Informatique et des Libertés* – National Committee for Informatics and Freedom) under the number 1207754. Patients provided written informed consent to the management of personal data and to their use for research purposes.

Patients' selection and management of Data.

In early 2021, we performed a retrospective recall of all recipients of an Epic© and Epic Supra© xenograft for SAVR and who were operated on at our Institution during the April 2001 – December 2018 period. The completeness and consecutiveness of the series was ensured by a prospective collection of in-hospital data of each cardiac surgery recipient at our center. Such database comprises an array of variables per patient including the pre-, intra- and early postoperative domains.

Grounded on an 'all comers' inclusion strategy, all etiologies of aortic valve disease were included, and irrespective to the performance of SAVR as an isolated or combined, primary or reoperative intervention. The surgical technique was uniform across the dataset, and was based on a supra-annular implantation technique using noneverting, U-shaped interrupted stitches, after both intra- and supra-annular sizing. The interrogation of the database yielded a total of 888 eligible SAVR operations with Epic© in 885 patients. We performed a systematic follow-up of all the included patients; the referring practitioners were sent a questionnaire inquiring about the patients' vital

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status, the occurrence of any adverse event since hospital discharge, their timing, and the last echocardiographic parameters of the aortic valve as well. In case of missing or incomplete information, the patients themselves or their families were contacted. Three included patients were reoperated and received a new Epic© bioprosthesis; in such circumstances, the day of reoperation was considered to be the last in the follow-up of the initial valve and the first in the follow-up of the second prosthesis.

Outcomes and Definitions.

All adverse events during follow-up, as well as causes of death, were adjudicated by the investigators, and in accordance with the referring practitioners, as either valve-related or non-valve-related with respect to their relationship with the index aortic bioprosthesis. As a general rule, non-lethal events (such as stroke) were considered to be valve-related unless proof of the contrary could be demonstrated. Similarly, causes of death were classified as either valve-related or non-valve-related. Unknown causes of death were frequently encountered in this series (entailing numerous elderly patients and operations performed >10 years before last follow-up); this needs to be considered in the interpretation of survival rates as a factor overestimating the rate of valve-related deaths. For the definition of non-lethal valve-related events, we were compliant with the Akins recommendations [4], as previously indicated [5], as well as with the more recent consensus document [6]. Structural Valve Deterioration (SVD) was any dysfunction or deterioration involving the prosthesis in any of its parts (exclusive of infection or thrombosis) as determined by reoperation, autopsy, or clinical investigation, and independently on need for reintervention. SVD could present as meaningful ($\geq 2/4$) intraprosthetic aortic regurgitation, or as significant stenosis, or as a combination of the two. Recently published documents [6, 7] have entailed the

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definition of SVD as a >10 mmHg increase in average transprosthetic gradient compared to baseline, or the demonstration of a >20 mmHg during the follow-up irrespective to the value of this parameter at the moment of hospital discharge. In compliance with previous literature and with the characterization of SVD as an event entailing a pejorative and permanent change over time in valve function (associated with alterations in the structure of the valve: leaflets, stent etc.), we considered that elevated transvalvular gradient without significant (<10 mmHg) change with respect to the reference postoperative period, and in absence of echocardiographically documented structural changes, did not constitute an SVD event. SVD could present as either significant stenosis or intraprosthetic regurgitation. Therefore, we herein distinguish between SVD and patient-prosthesis mismatch (PPM), referred to as an inadequacy between the prosthesis' Effective Orifice Area, EOA, and the patients' body surface area and metabolic needs, and observed at discharge echocardiography immediately after index surgery without evidence of morphological valve dysfunction. PPM was categorized as severe when the indexed Effective Orifice Area (iEOA) was $\leq 0.65 \text{ cm}^2/\text{m}^2$, moderate ($iEOA \leq 0.85 \text{ cm}^2/\text{m}^2$), or absent ($iEOA > 0.85 \text{ cm}^2/\text{m}^2$) [8]. Similarly, these events were exclusive of valve thrombosis. Other outcome measures were Nonstructural Valve Dysfunction (NSVD, which embraced valve thrombosis, periprosthetic leakage and hemolysis) and Prosthetic Infective Endocarditis (IE). We also distinguished between SVD and reintervention for SVD, and between reoperation and Valve-in-Valve TAVI within the domain of reinterventions for SVD. Early (operative) complications and mortality were defined as occurring within the 30th postoperative day, or later if during the index hospitalization. Early postoperative neurological events comprised stroke, coma, or transient ischemic attack (TIA). Stroke was a new focal neurological deficit (or coma) associated with computed tomography

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or magnetic resonance demonstration of new cerebral lesion, becoming evident immediately after awakening from the anesthesia, or occurring later after a normal awakening. Postoperatively, and similar to other aortic bioprostheses in our Institutional policy, patients were treated with antiaggregant (acetylsalicylic acid 160 mg / daily) only unless anticoagulant therapy was indicated due to other reasons than the aortic bioprosthesis itself.

Statistical analysis.

Continuous variables were described as mean \pm standard deviation (SD) if normally distributed, or as median if non-normally distributed. The Kolmogoroff-Smirnoff test was used for assessment of normality. Categorical variables were described as percentages. Time-to-event analyses for non-lethal valve-related events were computed according both the Kaplan-Meier (“actuarial”) and competing risks (“actual”) methodologies, similarly to previous literature [5, 9]. As SVD is a non-lethal event, its description using the “actuarial” (Kaplan-Meier) method alone would provide excessively pessimistic estimations for individual patients’ counseling, since death due to other causes censors the occurrence of SVD. Since the objectives of the present work focused on late valve-related events, the Kaplan-Meier curves were computed after exclusion of the operative mortality cases; confidence intervals were graphically represented as shaded areas. Opposed Kaplan-Meier curves were compared using the log-rank statistics; the alpha level was 0.05. The analyses were conducted using IBM SPSS Statistics 27.0 (IBM Inc., New York, USA) and *survminer* and *cmprsk* packages for R 4.0 (The R Foundation for Statistical Computing Platform, Vienna, Austria).

Results

Early clinical and echocardiographic results.

Table 1 describes the baseline characteristics in the population. Average age at index surgery was 75.4 ± 7 years (range: 37-90). The lesion leading to surgery was in most cases severe calcified aortic stenosis, with a 11.6% rate of bicuspid valve morphology. Table 2 reports the intraoperative details, as well as the early postoperative clinical results. The vast majority of procedures (96.1%) were elective, concordantly with the low rate of infectious endocarditis and other conditions associated with non-elective priority. Conversely, associated procedures were relatively frequent, coronary bypass being performed in 20.2% of cases and thoracic aortic surgery in 4.6% (including three cases where complete root replacement was performed with a composite valved graft constructed by assembling an Epic© bioprosthesis and a Dacron tube). Operative mortality was 3.7%. Of note, the rates of early valve-related complications were contained. More precisely, there were no instances of NSVD, of early infectious endocarditis or of early reoperations associated with the index bioprosthesis. We observed 4 cases (0.5%) of early valve thrombosis, which was managed medically in all instances until resolution, without need for reoperation. There was a total of 14 early neurological complications (1.6%); among these, 6 (0.7%) were permanent. All of these neurological events (embolic strokes and TIAs) were systematically attributed to the index bioprosthesis in absence of proof of cause-effect relationship. The rate of new permanent pacemaker implantation was 2.7%.

Discharge echocardiography data were available for the 855 survivors. The size of the implanted Epic© bioprostheses was 19-mm in 46 patients (5.2%), 21-mm in 206

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patients (23.2%), 23 mm in 376 patients (42.3%), 25-mm in 183 patients (20.6%) and 27/29-mm in 77 individuals (8.7%). Average LVEF in the entire population at that time was $59.7\% \pm 19.4$; the average transvalvular gradient was 16.2 ± 5.9 mmHg. Data about EOA in discharge echocardiography was available for 658 cases only (77% of operative survivors); average EOA was 1.7 ± 0.8 cm². The hemodynamic performances by prosthesis size are summarized in Table 3. As expected, the rates of severe/moderate PPM decreased with increasing the prosthesis' size.

Follow-up results.

Eight-hundred fifty-five patients were discharged alive from the hospital and entered the follow-up (Figure 1). One patient was lost, and follow-up data were available for 854 patients (99.9% completeness); the median follow-up duration was 7.7 years (range: 0.1 to 19.2 years) in the overall cohort. A total of 396 patients (46.4%) were alive at the end of the follow-up; among them, the median follow-up duration was 9.9 years. The 'actuarial' overall survival (Figure 2A) was $50\% \pm 1.9$ at 10 years and $19.5\% \pm 2.5$ at 15 years. Table 4 summarizes the freedom rates from major time-dependent outcomes by follow-up timepoint, according to both the Kaplan Meier and competing risks methodologies. Concerning SVD, we accounted for a total of 7 events during the follow-up, occurring at 8.1 ± 4.3 years after index surgery. Freedom from SVD at 10 years was $99.3\% \pm 0.4$ and $99.4\% \pm 0.3$, and at 15 years was $95.6\% \pm 2.7$ and $98.4\% \pm 0.8$ (Kaplan-Meier and competing risks, respectively) (Figure 2B). Of these, 1 required conventional reoperation and one was waiting for the performance of Valve-in-Valve TAVI at the time of closure of the follow-up; the remainders received medical treatment alone, due to either moderate and mildly symptomatic valve dysfunction, or to excessive risk for any reintervention. We observed 17 IE events occurring after 3.7

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± 4.1 years (Kaplan Meier curve for survival free from IE in Figure 2C), and 17 NSVD events occurring 2 ± 2.4 years after surgery (Table 4). We noted a total of 20 valve-related reinterventions during the follow-up (all causes including SVD, IE and NSVD); the freedom from any valve-related reintervention was $96.9\% \pm 0.7$ (actuarial) and $97.4\% \pm 0.6$ (competing risks) at 10 years, and $96.9\% \pm 0.7$ (actuarial) and $97.4\% \pm 0.6$ (competing risks) at 15 years (Figure 2D). The evaluation of freedom from valve-related mortality was hindered by a considerable number of deaths due to unknown reasons (N=271) in the current follow-up (late death was formally ascertained to be valve-related in 19 instances only – 4.1% of all late deaths, N=458). Nonetheless, in order to comply with recommendations over event reporting, we present a $64\% \pm 2$ freedom from valve-related death at 10 years and a $33.8\% \pm 3.6$ freedom at 15 years; such rates need to be interpreted in the light of the important prevalence of deaths due to unknown reasons.

The existence of PPM at discharge was not associated with a decrease in overall survival at follow-up. In fact, stratified Kaplan-Meier survival curves according to either Absent-Moderate-Severe PPM (Figure 3A) or Absent-Any PPM (Figure 3B) did not disclose any statistically meaningful difference in global survival (log-rank $p=0.27$ and $p=0.21$, respectively).

Discussion

The expansion of indications to the use of TAVI for the management of severe aortic stenosis entails major evolutions in the populations of candidates to SAVR. Among these, the younger age of surgical candidates amplifies durability as a main requirement of bioprostheses. The Epic© bioprosthesis, an evolution of the Biocor© valve (itself characterized by very good durability properties [10]), features the ethanol-based Linx© anticalcification treatment, is constituted by a low-profile stent equipped with a pericardial shield for leaflet protection, and three independent porcine aortic leaflets. It is available in the standard and in the supra-annular version mounting a low-profile suture ring (Figure 4). We started implanting this valve in 2001, which allows achieving a considerable follow-up (up to 19.2 years) and most appropriately address the study objectives. We include 888 patients in a single-center experience; few larger series have been previously published with, in example, 1,920 SAVR cases; nonetheless, this study was characterized by a mean 4.5 years follow-up, while we present herein a median 7.7 years (overall) and an about 10 years (survivors) median follow-up period. Similarly, an actualized series of 2,441 SAVRs with Epic© was limited by a 3.04 years median follow-up [3]. Significant sample size and follow-up duration are required to appropriately evaluate aortic valve therapies, in order to support rational decision-making in younger candidates to aortic valve therapies. At 10 years, we report a $99.3\% \pm 0.4$ actuarial freedom from SVD, despite it is defined irrespective to the need for reintervention [3], which compares favorably to the $96.3 \pm 0.6\%$ freedom rate at the same timepoint in one major and larger series [2]. The latter one was nonetheless limited by a small number of patients at risk at 10 years (N=40 vs. N=302 in our investigation), with ensuing consequences on confidence intervals and reliability of this finding. Our 10-year freedom from SVD was comparable to that observed with another

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current porcine bioprosthesis [11]. Other valve-related adverse events, such as IE and NSVD, presented contained rates similar to those seen in competitor valves; the overall rate of valve-related reinterventions (all causes) is also small.

We defined SVD not only independently on the need for reintervention, but also reflecting the concept of SVD as an evolutive decline in valve function over time due to intrinsic failure and demonstrable morphological alterations. The NOTION trial is illustrative of the importance of the definition of SVD in impacting the reported outcomes. This study randomized 280 all-comers patients to either TAVI or SAVR using an array of four different surgical bioprostheses (including porcine and pericardial devices); a significant higher rate of SVD was associated with the SAVR group when the definition of this outcome included the simple demonstration of mean transvalvular gradient >20 mmHg during the follow-up. In fact, TAVI valves are known for good hemodynamic performances [12]. When a modified definition of SVD was used (requiring also a stable >10 mmHg increase in mean transvalvular gradient with respect to discharge echocardiography to qualify SVD), there was no more significant difference in time-dependent occurrence of SVD among groups [13]. SVD should be distinguished from valve thrombosis, which is potentially reversible. More importantly, SVD is a definitely different condition than PPM, with unlike clinical implications. Imaging (echocardiography) demonstration of valve deterioration (abnormalities of leaflets or other valve components) is also a component of the definition of SVD. Porcine bioprostheses are associated with worse hemodynamic characteristics and greater incidence of PPM than pericardial bioprostheses for SAVR [14, 15], particularly with respect to smaller nominal sizes (19-mm to 23-mm). The rates of PPM reported herein for the Epic© valve confirm such conclusion in comparison to both valve models with externally-mounted and internally-mounted pericardium [16, 17]. Concordantly,

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the current 'all-comers' study entailed a relatively low rate of 19-mm and 21-mm valves, which may reflect the tendency of surgeons to implant pericardial bioprostheses in smaller annuli and in patients with larger body surface area, where the likelihood of PPM is greater. PPM has been addressed in various dedicated studies mixing up various valve models. In a randomized investigation, no differences at one year were observed in left ventricular mass regression and survival among subgroups of bioprostheses (including 99 Epic© valves) presenting different hemodynamic performances [18]. Left ventricular mass regression at 6 months has been found to be independent on iEOA in 3rd-generation valves [19]. Such concept was strengthened by the NOTION trial itself, which reported an expected higher rate of PPM in the SAVR group than in the TAVR group; but the existence of severe PPM did not influence the rate of major adverse cardiovascular events, cardiac-related hospitalizations or NYHA class at 2 years after implantation [20]. Herein, we add to this body of knowledge by providing very long-term information about the impact of PPM as well in a large cohort of SAVR with a unique 3rd generation valve. We found no significant impact on overall survival at 10 to 15 years after surgery neither with severe nor with any PPM (Figure 3). Relief of clinically significant aortic stenosis and stability of gradients over years, as it is indicated by the low rate of SVD, likely explain this observation. We also confirm limited rates of new permanent pacemaker implantation in the early postoperative period (2.7%).

The completeness of follow-up and the sample size are points of strength of the present series, associated with the tendency of our patients to reside in the same geographical region over time. Nonetheless, the series is limited by a considerable number of unknown causes of death at follow-up, which precludes in-depth evaluation of several valve-related parameters on cardiac-related death. Additionally, follow-up

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echocardiography explorations were not done in-house for all patients; we retrieved latest available information from referring cardiologists during systematic patients' follow-up.

In conclusion, the current data suggest excellent durability of a 3rd generation porcine bioprosthesis for SAVR in the long- and very long-term follow-up. Rates of other valve-related adverse events are contained. These data need to be compared to cohorts of pericardial valves with comparable follow-up duration. This porcine valve is confirmed to present lesser hemodynamic properties than pericardial valves; nonetheless, PPM is less frequent in larger valve sizes and it has no demonstrated impact on survival, facilitating the use of this valve in annuli ≥ 23 mm after consideration of patients' body surface area.

Data Availability Statement

Data contained in the current database are not publicly available, but are available from the corresponding author (AA) upon reasonable request.

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Table 1. Baseline characteristics in the entire study population (N=888 operations).

Characteristic	N (%) or Average (SD)
Age (years)	75.4 ± 7
Gender: Male	650 (73.2%)
NYHA III or IV	328 (36.9%)
Atrial fibrillation	110 (12.4%)
Diabetes mellitus	131 (14.8%)
Obesity	207 (23.3%)
BSA (m ²)	1.8 ± 0.2
Serum creatinine (µmol/L)	89.2 ± 23.4
Renal insufficiency	39 (4.4%)
Hepatic insufficiency	9 (1%)
Previous stroke	37 (4.2%)
COPD	132 (14.9%)
Previous chest radiation therapy	15 (1.7%)
Previous cardiac surgery	29 (3.3%)
LVEF (%)	59.8 ± 11.3
AVA (cm ²)	0.72 ± 0.2
Average transvalvular gradient (mmHg)	50.5 ± 15.3
<u>Modality of native valve dysfunction</u>	
- Prevalent regurgitation	60 (6.8%)
- Prevalent stenosis	783 (88.2%)
- Mixed	45 (5.1%)
Bicuspid valve morphology	103 (11.6%)
Infectious endocarditis (native)	26 (2.9%)
Acute type A aortic dissection	4 (0.5%)

SD: Standard Deviation. BSA: Body Surface Area. COPD: Chronic Obstructive Pulmonary Disease. LVEF: Left Ventricular Ejection Fraction. AVA: Aortic Valve Area.

Table 2. Intraoperative characteristics and early postoperative results in the entire study population (N=888 operations).

Characteristic	N (%) or Average (SD)
Non-elective	35 (3.9%)
Critical perioperative state	5 (0.6%)
<u>Associated procedures</u>	
- Other valve surgery	42 (4.7%)
- Coronary surgery	179 (20.2%)
- Thoracic aortic surgery	41 (4.6%)
- Septal myectomy	7 (0.8%)
- Others	21 (2.4%)
CPB time (min)	65.6 ± 34.3
Aortic cross-clamp time (min)	51.8 ± 26.9
Early (operative) mortality	33 (3.7%)
<u>Valve-related complications</u>	
- NSVD	None
- Thrombosis	4 (0.5%)
- Neurological complications: permanent	6 (0.7%)
- Neurological complications: transient	8 (0.9%)
- Reoperation	None
- Noncerebral embolism	2 (0.2%)
- IE	None
<u>Non-Valve-related complications</u>	
- New Permanent Pacemaker	24 (2.7%)
- Reoperation	4 (0.5%)
- Prolonged ventilation	25 (2.8%)
- Renal failure (with dialysis)	7 (0.8%)
- Renal failure (without dialysis)	70 (7.9%)
- Atrial fibrillation	392 (44.1%)
- Reoperation for bleeding	32 (3.6%)

SD: Standard Deviation. CPB: Cardiopulmonary bypass. NSVD: Nonstructural Valve Dysfunction. IE: Infectious Prosthetic Endocarditis.

Table 3. Hemodynamic characteristics of the aortic bioprosthesis at discharge by prosthesis size.

Characteristic	19 (N=46)	21 (N=206)	23 (N=376)	25 (N=183)	27-29 (N=77)	p-value**	All (N=888*)
Average transvalvular gradient (mmHg)	18.6 ± 5.3	17.6 ± 6.6	16 ± 5.8	15.8 ± 5.5	12.2 ± 4.1	<0.001	16.2 ± 5.9
Peak transvalvular gradient (mmHg)	33.7 ± 10.8	32.3 ± 11.5	30.3 ± 10.2	29.3 ± 10.3	22.7 7.6	<0.001	30.1 ± 10.7
EOA* (cm ²)	1.3 ± 0.2	1.4 ± 0.2	1.7 ± 0.8	1.9 ± 1.1	2.3 ± 0.4	<0.001	1.7 ± 0.8
iEOA* (cm ² /m ²)	0.79 ± 0.13	0.81 ± 0.16	0.92 ± 0.38	1.02 ± 0.58	1.18 ± 0.35	<0.001	0.94 ± 0.41
PPM*						<0.001	
- Absent	8 (26.7%)	55 (39.9%)	150 (54.9%)	111 (71.6%)	56 (90.3%)		380 (57.8%)
- Moderate	19 (63.3%)	63 (45.7%)	108 (39.6%)	43 (27.7%)	6 (9.7%)		239 (36.3%)
- Severe	3 (10.0%)	20 (14.5%)	15 (5.5%)	1 (0.6%)	-		39 (5.9%)

EOA: Effective Orifice Area. iEOA: Indexed Effective Orifice Area. PPM: Patient Prosthesis Mismatch. *Data available for 658 cases (77% of operative survivors). ** Spearman's test for rank-order correlation.

Table 4. Freedom from major time-dependent outcomes by timepoints of follow-up in the entire population. Kaplan-Meier/'actuarial' or (Competing risks/'actual') freedom rates are provided. Data are in %.

Characteristic	5 years	10 years	12 years	15 years
Overall survival	79.3 ± 1.5	50 ± 1.9	38.7 ± 2	19.5 ± 2.5
Freedom from valve-related mortality*	88.1 ± 1.2	64 ± 2	54.7 ± 2.3	33.8 ± 3.6
Freedom from SVD	(99.7 ± 0.2)	(99.4 ± 0.3)	(99.3 ± 0.3)	(98.4 ± 0.8)
Freedom from NSVD	(98.2 ± 0.5)	(98.0 ± 0.5)	(98.0 ± 0.5)	(98.0 ± 0.5)
Freedom from IE	(98.4 ± 0.4)	(97.9 ± 0.5)	(97.9 ± 0.5)	(97.3 ± 0.8)
Freedom from any valve-related reintervention	(98.2 ± 0.5)	(97.4 ± 0.6)	(97.4 ± 0.6)	(97.4 ± 0.6)

**Including 271 late deaths due to unknown reasons, 19 late deaths only being formally attributed to the index bioprosthesis.*

Figure Legends

Figure 1. Study workflow.

Figure 2. Kaplan-Meier survival curves. **A.** Global survival in the overall population. **B.** Freedom from SVD. **C.** Freedom from IE. **D.** Freedom from valve-related reintervention (any cause including SVD, NSVD and IE).

Figure 3. Kaplan-Meier survival curves. **A.** Global survival stratified by Absent-Moderate-Severe PPM at the time of hospital discharge. **B.** Global survival stratified by Absent-Any PPM at the time of hospital discharge.

Figure 4. The Epic© (left) and Epic Supra© (right) valves for SAVR. Courtesy of Abbott Cardiovascular France.