Mid-Term Durability of the Trifecta Bioprosthesis for Aortic Valve Replacement

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List of Abbreviations.

AVR: Aortic Valve Replacement

SVD: Structural Valve Deterioration

NSVD: Nonstructural Valve Dysfunction

IE: Infective (prosthetic) Endocarditis

EOA: Effective Orifice Area

iEOA: indexed Effective Orifice Area

CPB: Cardio-pulmonary bypass

Abstract

Objectives. To clarify the mid-term durability of the Trifecta bioprosthesis for aortic valve replacement (AVR).

Methods. We retrospectively analyzed the prospectively collected data of 824 consecutive implants of the Trifecta valve at a single Institution. A 100% complete follow-up was available (average duration: 2.2 ± 1.3 years; range: 0.03 to 6.9; 1,747.6 patient/years). Echocardiography data at discharge were prospectively noted.

Results. Operative mortality was 3.8% (2.7% in patients receiving isolated AVR). There were five valve-related early reoperations (1 for prosthetic endocarditis and 4 due to NSVD). Global rate of severe patient-prosthesis mismatch was 1.26%. Overall 5-years survival was 74.9%; freedom from valve-related death was 97.8%. The majority of deaths attributed to the valve were due to unknown causes. We observed 6 SVD events 3.4 ± 1.6 years after surgery. At 5 years, actuarial freedom from SVD was 98% ± 0.9 (N=6); freedom from reintervention for SVD (N=5) was 98% ± 0.9 (including transcatheter valve-in-valve, N=2); freedom from open reoperation for SVD was 98.9 ± 0.6. Five-year freedom from prosthetic endocarditis was 97.7% ± 0.7 (N=12; 6 requiring reoperation). There was one case of late NSVD (5-year freedom: 99.8% ± 0.2). Freedom from hemorrhagic events was 98.6% ± 0.5 (86% occurring in patients on anticoagulants); there were no thromboembolic events at follow-up.

Conclusions. The Trifecta bioprosthesis is a reliable device for AVR. We confirm excellent immediate hemodynamic properties and very low rate of patient-prosthesis mismatch. The absolute number of SVD cases observed herein remains limited. Nevertheless, their timing, their pathologic characteristics and clinical presentation require continued follow-up.

KEY WORDS: Aortic valve replacement; Trifecta; Durability; Outcomes

Perspective statement

Durability is a pivotal characteristic for modern bioprostheses. In the present mid-term follow-up of 824 implants, the Trifecta valve showed excellent hemodynamic properties and consistent durability. Few SVD events were observed, characterized by peculiar timing, pathophysiology and clinical presentation. Continued follow-up is required.

Central Message

The Trifecta bioprosthesis is a reliable device for aortic valve replacement. Continued surveillance for SVD events is needed.

Central Picture Legend

Study workflow and 5-year freedom from valve-related adverse events.

Introduction

Bioprostheses are increasingly used for aortic valve replacement (AVR), driven by the continuous improvements in durability and hemodynamic performance during the last decades. The St. Jude Trifecta bioprosthesis (St. Jude Medical Inc., St. Paul, Minn) is a latest-generation stented bioprosthesis, which was introduced into clinical practice in 2007. This device is characterized by a bovine pericardial sheet mounted outside the stent frame. Such feature, associated with the supra-annular design, the ethanol-based anticalcification treatment (proprietary Linx process [1]) and the material properties of the titanium stent, are intended at optimizing its functional behavior and durability. The stent is polyester-covered, and concealed by bovine and porcine pericardium in order to minimize the mechanical stress to the leaflets. The Trifecta valve has demonstrated good hemodynamic performance, both at rest [2, 3, 4], during effort [5] and at the three-year follow-up [6]. This characteristic makes it very attractive especially for patients with small aortic annulus. In addition, the Trifecta Durability Study has reported encouraging results during a median 0.9 years follow-up for 1,014 patients (844 patient-years), the freedom from valve explant at 2 years being 99.4% [7]. In the same experience, there was only one case of explant due to structural valve deterioration (SVD), suggesting good durability of this device in the initial follow-up.

Nonetheless, longer-term follow-up is of paramount importance to understand the performance of this valve device, and guide the choice of prosthesis in clinical practice. In the present investigation, our primary purpose was to show our single-center experience and follow-up (average 2.2 years, 1,647.8 patient-years, up to 6.9

years) with 824 Trifecta implants for AVR. As a secondary objective, we present the immediate postoperative hemodynamic performance of the Trifecta valve in the entire study cohort (N=824).

Patients and Methods

Our center started implanting the Trifecta valve in 2008, and participated in the Trifecta Durability Study. In January 2015, we retrospectively reviewed the electronic records of patients who received AVR using this bioprosthesis until December 31st, 2014. The performance of any concomitant procedure at the time of AVR, as well as the history of previous cardiac surgery, was not an exclusion criterion. Pre-, intra- and early postoperative data were prospectively collected within an electronic database at the time of patients' discharge as previously described [8]. The database includes all patients receiving cardiac surgery at our Institution; it is managed by research nurses and regularly checked for completion and consistency under the supervision of the surgical team. For the purposes of the present study, a retrospective clinical follow-up was performed between January and May 31st, 2015. Practitioners (referring cardiologists and general medicine doctors) were provided with questionnaires sent through surface mail; questionnaires inquired about the vital status of the patient, the occurrence of any adverse event (both valve- and non-valve-related) and the functional status, as well as the time at which any adverse event had occurred. In case of incomplete or missing information, the patients themselves or their families were contacted; local governmental authorities were asked to confirm the patients' vital status in case of missing data. Valve-related adverse events were defined according to the current guidelines [9], including SVD (changes intrinsic to the device

causing dysfunction, evident at echocardiography, reoperation or autopsy), nonstructural valve dysfunction (NSVD; any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation or hemolysis, evident at echocardiography, reoperation or autopsy) and operated valve endocarditis (IE). Valve thrombosis and embolic events (either cerebral or non-cerebral embolic events) were presented in an aggregate form as thrombo-embolic complications. Hemorrhagic complications were reported in the overall population and stratified according to the administration of anticoagulant therapy. Reinterventions were reported both in aggregate form and stratified according to type (either open reoperative surgery or interventional catheter-based procedures). Valve-related mortality was death consequent to any of the above adverse events or to reoperation on the index valve. Causes of death were determined by review of hospital records and instrumental data. All complications and fatal events for which no demonstrated non-valvular cause was known (including sudden death), were considered as valve-related events. Mortality resulting from cerebrovascular events during the follow-up was also assumed to be valve-related. Concerning early complications, we distinguished among perioperative stroke (defined as new focal neurological deficit or coma evident immediately after resolution of anesthesia), which was considered to be non-valve-related, and postoperative stroke (defined as new focal neurological deficit or coma which became evident after a normal awakening from anesthesia), which was considered to be valve-related unless otherwise demonstrated. Such ‘conservative’ approach was used in compliance with guidelines on data reporting, and should be kept in mind while interpreting the results. Adverse events were categorized as either early (when occurring during the hospitalization in which the operation was performed, even if after 30 days and including patients transferred to other acute care facilities, or when

185 occurring after discharge from the hospital, but before the end of the 30th
186 postoperative day) or late in all other cases.

187 Since all patients' data were managed anonymously, and since the study did not
188 entail any modification to the standard treatment protocols, patients' informed
189 consent for inclusion was waived. The study database was declared to the CNIL
190 online database (Commission Nationale de l'Informatique et des Libertès [National
191 Committee for Informatics and Freedom]) under the dossier number 1207754, in
192 accordance with the French law.

193

194 *Surgical technique*

195 For all cases included in the present study, the Trifecta bioprostheses were
196 implanted through full median sternotomy and mildly hypothermic cardio-pulmonary
197 bypass (CPB). Myocardial protection was achieved through cold crystalloid
198 cardioplegia or isothermic hyperkalemic blood cardioplegia. Valves were implanted
199 according to the supra-annular technique, using interrupted, noneverting, U-shaped
200 stitches. Video 1 displays the implantation of a Trifecta GT device (improved model of
201 the Trifecta valve now in clinical use). Particular care needs to be devoted to valve
202 sizing even at the supra-annular level (in order to avoid valve deformation within
203 narrow sino-tubular junction anatomies) and to aortotomy suturing in order to avoid
204 leaflet impingement into sutures. Particular features of the Trifecta GT device with
205 respect to the previous model include an improved sewing ring (facilitating suture
206 passing and sliding as well as valve seating into the annulus) and a modified valve
207 holder (to facilitate handling without risk of stent deformation during parachuting). It is

208 also characterized by increased stent radiopacity to assist valve-in-valve in case of
209 SVD.

210

211 *Postoperative management*

212 All patients underwent transthoracic echocardiography before discharge. At this
213 time, data about valve function were prospectively collected (including peak and
214 mean transvalvular gradient, degree and topography of regurgitation, left ventricular
215 ejection fraction, crude and indexed effective orifice area – EOA and iEOA). A team
216 of experienced in-house cardiologists performed echocardiograms; data were
217 prospectively collected as part of our electronic database. Patient-prosthesis
218 mismatch (PPM) was defined as severe (iEOA ≤0.65 cm^2/m^2), moderate (iEOA ≤0.85
219 cm^2/m^2) or absent (iEOA >0.85 cm^2/m^2) [10]. Given the relatively few number of
220 patients receiving 27-mm and 29-mm valves, hemodynamic data for these two sizes
221 were presented in aggregate form. No modifications were made to our postoperative
222 management protocol during the study period. Patients received no oral
223 anticoagulants after surgery (unless otherwise indicated), and were treated by oral
224 acetylsalicylate 160 mg per day. Antiaggregants were maintained after discharge.
225 During the earliest postoperative days, antithrombotic prophylaxis was conducted
226 through subcutaneous administration of low molecular weight heparin (4.000 IU per
227 day) until patients' mobilization.

228

229 *Endpoints*

230 We addressed the early postoperative clinical results (valve-related and non-valve-
231 related events) after implantation of the Trifecta valve for AVR. In follow-up analysis,

we addressed the mid-term overall survival, event-free survival, SVD-free survival and reoperation-free survival after implantation of the Trifecta valve for AVR. Finally, we presented the early postoperative hemodynamic performance of the Trifecta valve in the entire study cohort.

Statistical analysis

Statistical analysis was performed using the SAS software ver. 9.33 (SAS Institute Inc., Cary, NC). Continuous data are presented as mean ± standard deviation and categorical variables as percentages. Normality of data distribution was evaluated through the Kolmogorov-Smirnoff test. Intergroup comparison was performed for the average CPB and aortic clamp time among isolated AVR vs. non-isolated AVR subgroups. We confirmed normal distribution of these variables. Therefore, intergroup comparison was done using the Student's *t* test (continuous variables) All tests were two-tailed, and the alpha level was set at 0.05. A multiple logistic regression model (stepwise selection method) was built in order to identify baseline factors associated with operative mortality. Follow-up analysis was performed using the Kaplan-Meier (actuarial) methodology, and the results were graphically presented as curves of mortality risk. Survival rates were reported in the text. Secondarily, stratified survival analysis at follow-up was performed according to the presence or absence of severe/moderate PPM after surgery.

Results

Early results

During the study period, 824 patients received AVR using a Trifecta valve and were included; their baseline demographics are summarized in Table 1. Predominant stenosis was the most frequent modality of native valve dysfunction; in fact, patients presenting degenerative calcified aortic stenosis composed the majority of the present population. The rate of baseline comorbidities was limited, as it is underlined by the average value of logistic EuroSCORE I. There were few non-elective cases (1.6%) and the rate of concomitant procedures was 7.3% (perioperative characteristics are reported in Table 2). Average CPB and aortic cross-clamp time were significantly greater if a concomitant procedure had been performed ($p<0.001$ both). Conversely, average CPB and aortic clamp time were limited (48.1 min ± 14.9 and 38 min ± 11.3, respectively) in case of isolated AVR. Figure 1 reports the distribution of the sizes of the implanted valves. The 23-mm size was most frequently used (36.4%), followed by the 21-mm size (29.2%).

Overall operative mortality was 3.8% (N=31); mortality-rate was 2.7% in patients receiving isolated AVR and 8.1% in patients receiving combined surgery ($p=0.0013$).

Causes of operative mortality were extracardiac in 15 instances (1.8%), and cardiac non-valvular in the remaining 16 cases (1.9%). No operative death was due to valvular causes. The details of early postoperative (30-days) complications are given in Table 3. There were a total of 9 valve-related early complications (1.1%), including 4 cerebral strokes (among these, only 1 was permanent). We observed 1 case of early IE (requiring reoperation) and 4 cases of NSVD. Among the NSVD cases, 2 presented severe transvalvular regurgitation at echocardiography; at reoperation, this was due to engagement of the bioprosthesis' non-coronary leaflet into the suture of the oblique aortotomy. At reoperation, these two cases were managed through section of the suture without need for valve re-replacement. These two bioprostheses showed normal function at the last available follow-up. One further early NSVD case consisted in severe transvalvular regurgitation evident on echocardiography; at reoperation, this was due to valve oversizing (27-mm device) in a patient with relatively narrow sino-tubular junction. This resulted in deformation of the upper valve stent and consequent leaflet malcoaptation. This patient was treated by replacement of the device with a new 23-mm Trifecta valve. The last NSVD case was characterized by elevated transvalvular gradients at follow-up echocardiography in a patient who had received AVR with a 19-mm Trifecta valve plus septal myectomy for aortic stenosis and obstructive cardiomyopathy. At reoperation, persisting subvalvular stenosis and valve oversizing were noted; the patient was treated by iterative septal myectomy and valve replacement with a 17-mm mechanical valve prosthesis. There were no early SVD cases. We observed 4 additional reoperations which were not valve-related. The rate of early valve-related reoperation was 0.6% (with no cases of associated mortality); the average time interval after primary surgery was 7.6 ± 6.9 days. Multiple logistic regression identified advanced age, renal insufficiency,

coexisting neoplasm and left heart failure as significant predictors of operative mortality.

Table 4 reports the hemodynamic findings obtained at transthoracic echocardiography immediately before discharge. Mean average transvalvular gradient was lower than 10 mmHg in all valve sizes except for the 19-mm subgroup. Severe PPM was observed only in the 19-mm, 21-mm and 23-mm size cohorts, although its rate was considerably low (5%, 1% and 1%, respectively).

Follow-up results.

We obtained data for all the 793 patients who were discharged alive from the hospital and entered the follow-up (100% follow-up completeness). Average follow-up was 2.2 ± 1.3 years (range: 0.03 to 6.9 years; median: 2 years); a total of 1,747.6 patient/years were available for analysis (Figure 2). During the follow-up, we observed 54 late deaths (6.8% of the patients who were discharged alive) occurring at an average 1.8 ± 1.3 years after surgery, while 739 patients were alive at the end of the follow-up (93.2% of the patients who were discharged alive). Causes of late death were extracardiac in 33 cases (61.1% of late deaths), cardiac non-valvular in 12 (22.2%) and valve-related in 9 (16.7%, including 7 deaths of unknown cause and 2 fatal outcomes due to prosthetic valve endocarditis). At the 5-years follow-up, the overall survival in the entire population was 74.9% ± 8.5, and the freedom from valve-related death was 97.8% ± 0.9. Figures 3A and 3B depict the risk of death due to any cause and to valve-related causes, respectively. During the present follow-up we observed 6 SVD events, occurring at an average 3.4 ± 1.6 years after valve implantation. The 5-year Kaplan-Meier survival free from SVD was 98% ± 0.9 (Figure 4A depicts the risk of death or SVD). Among these SVD events, 5 required reintervention and 1 was managed by medical treatment only (Case 5). The freedom

from reintervention (any type) for SVD was 98% ± 0.9 at 5 years (Figure 4B depicts the risk of death or any reintervention for SVD, including Valve-in-Valve). Reinterventions were open redo surgery in 3 instances (Cases 3, 4 and 6), and transcatheter Valve-in-Valve procedure in 2 (Cases 1 and 2). The 5-year freedom from open redo surgery for SVD was 98.9 ± 0.6 at 5 years (Figure 4C depicts the risk of death or open redo surgery for SVD). Modalities of SVD were severe intravalvular regurgitation presenting with rapid onset of heart failure in 4 cases (Cases 1 to 4); moderate intravalvular regurgitation presenting with progressive dyspnea (Case 5); and severe valve stenosis presenting with worsening dyspnea (Case 6). At reoperation, non-calcified leaflet tear with leaflet disinsertion from one stent post was disclosed in Cases 3 and 4; diffuse tissue thickening and calcification without tear was disclosed in Case 6. Abstinence from reintervention in Case 5 was decided on the basis of the non-severe degree of valve dysfunction, moderate symptoms in an elderly patient with reduced physical activity due to several comorbidities, and of the risks associated with both redo surgery and transcatheter therapy.

Interestingly, the detection of severe or moderate PPM immediately after surgery was not associated with significantly different overall survival at follow-up compared to patients without PPM (log-rank p=0.18). Similar findings were obtained for freedom from valve-related death and freedom from SVD (p=0.93 and p=0.5, respectively). There were 12 cases of late IE (5-year actuarial freedom: 97.7% ± 0.7). Reoperation for IE was needed in 6 instances; other cases were managed through medical therapy alone. There was only one NSVD case during the follow-up, which did not require reintervention (5-year freedom: 99.8% ± 0.2). We observed 7 instances of hemorrhagic events; of these, 6 occurred in patients under oral anticoagulants for chronic atrial fibrillation (5-year freedom: 98.6% ± 0.5). There were no thrombo-

embolic events during the available follow-up. Globally, the 5-year actuarial freedom from any valve-related reintervention was 96.9% ± 1 (Figure 3C depicts the risk of death or any valve-related reintervention). Table 5 summarizes the adverse events observed at follow-up.

Discussion

The St. Jude Trifecta valve has been employed in clinical practice since 2007. As a typical feature, the bovine pericardial tissue is mounted outside the stent frame. This translates into optimized EOA and excellent hemodynamic properties. A considerable body of independent literature beyond the sponsored Trifecta Durability Study has consistently demonstrated low average transvalvular gradients and very low rates of PPM in the immediate postoperative period compared to other valve devices [2, 3, 11, 12, 13]. Although a debate exists about the impact of PPM on the long-term patients' outcome [14, 15], the Trifecta valve offers specific advantages in patients with small aortic annulus and high risk of postoperative PPM. Recently, our group has reported for the first time the three-years hemodynamic performance of this device, suggesting that its hemodynamic profile is preserved at the mid-term follow-up [6]. The population analyzed in the above-referenced study [6] is included in the current investigation. Although the three-years hemodynamic results are not available

for the overall cohort presented herein, we confirm the excellent hemodynamic profile of the Trifecta valve at the time of hospital discharge (Table 4).

The main scope of the present paper is to address the durability of this innovative device. To such purpose, we analyzed the largest single-center population available so far in the literature, and the longest available follow-up (N=824, 1,747.6 patient/years, average 2.2 years). Follow-up was facilitated by the propensity of patients treated at our center to remain in the region after surgery, which gives account for the 100% rate of follow-up completeness. Durability is one major requirement for modern bioprostheses, given the growing tendency to use them in younger individuals [16]. Such feature acquires even greater importance in the current era, when the results of surgical AVR are discussed as the benchmark reference compared to transcatheter valve therapy. In our population, we observed a total of 6 SVD events occurring at an average 3.4 ± 1.6 years from valve implantation (98% ± 0.9 Kaplan-Meier freedom from SVD at 5 years). This freedom from SVD is slightly lower than that documented for other bioprostheses in large, previously published series. The 5-year freedom from SVD was 99.3% (Kaplan-Meier) and 99.4% (competing risks methodology) for a third-generation porcine valve in the aortic position [8]. In smaller previous series, the 5-year freedom from SVD for a third-generation pericardial valve was 100% [16], although this study was potentially limited by sample bias. In more recent investigations, the 5-year actuarial freedom from SVD for a third-generation pericardial valve was 99.8% [18]. For a second-generation porcine valve, the 5-year freedom from SVD was 99.2% (Kaplan-Meier) and 99.3% (competing risks) [19]. One previous series focused on the Trifecta valve did not report cases of reoperation for SVD at two years [11], but the rate of non-reoperated SVD cases was not addressed. Although the absolute number of SVD

events reported in our series is limited and may be subjected to population bias, their occurrence underlines the need for continued and exhaustive follow-up of the implanted patients. Calcified SVD occurred in only one case in our series. The Linx® anticalcification treatment has been reported to remove up to 94% of phospholipids from leaflet tissue and has been associated with clinical effectiveness at mid-term follow-up in porcine bioprostheses [1, 20]. On the other hand, 5 out of 6 SVD cases herein presented under the form of noncalcified leaflet tear. This was extended over the height of one stent post (4 instances) or at the bottom of one leaflet (1 instance) without macroscopically overt calcification. Such modality of failure is rather specific with respect to other valve devices. Clinical presentation was also characteristic, involving sudden occurrence of severe dyspnea and heart failure. Conversely, calcified SVD is traditionally considered to be slowly progressive, with sometimes indolent clinical course. Physicians involved in the follow-up of these patients should consider the possibility of rapid onset of clinical manifestation of Trifecta SVD. Interestingly, the Trifecta Durability Study (median follow-up: 0.9 years) reported one case of SVD requiring valve explantation, without finding any significant leaflet calcification. Few similar cases exist in the literature [21], while only one additional instance of early calcific SVD without tear is published [22]. In-depth investigation about valve design and manufacturing is required to clarify the underlying mechanism.

The impact of PPM on patients' outcome is a matter of debate. In the present series, severe/moderate PPM was not associated with increased risk of death from any cause, of valve-related deaths or of SVD at follow-up. The interpretation of PPM and its significance are beyond the scopes of the present paper. Nonetheless, we believe that the expected benefits associated with avoidance of PPM through annular

enlargement procedures should be balanced against the additional operative mortality and morbidity risk which can derive from the application of these technique in such population.

The present experience also highlights particular precautions to be taken in the sizing and implantation of the Trifecta bioprosthesis. Two early NSVD cases were due to oversizing. As the Trifecta titanium stent is deformable mainly in its upper portion, narrow sino-tubular junction anatomy may determine leaflet malcoaptation through stent deformation. As well, oversizing may explain one instance reported in the literature of late fusion of a valve leaflet into the aortic wall [21]. The specific valve design exposes to the risk of non-coronary leaflet impingement in sutures, mainly if the aortotomy is extended into the non-coronary sinus and supplementary hemostatic stitches are added after release of aortic cross-clamp. Particular attention needs to be devoted to accurate suture of the aortotomy. Coronary obstruction is one additional potential complication which may be due to oversizing.

The specific features of the Trifecta valve (namely, the outer position of the pericardial sheet and its globally rectangular shape) have been associated with increased risk of coronary obstruction during transcatheter valve-in-valve procedure [23]. Two patients with SVD in the present series and considered to be at excessive reoperative risk were successfully treated through the valve-in-valve technique without instances of coronary obstruction. Accurate pre-procedural imaging assessment and choice of transcatheter device, as well as precise deployment, are of pivotal importance [24]. Other reports confirm the feasibility of such approach [25]. According to recommendations [9], freedom from open redo surgery and from transcatheter reintervention on the index valve was listed here both in aggregate form and separately.

Similarly, we underline the importance to define SVD as the occurrence of intrinsic valve changes, irrespective to the performance of any reintervention, in order to avoid any underestimation of the SVD rate [26]. Contrary to previous works, herein we did not present results according to the competing risks methodology, given the limited number of SVD events and the relatively short average follow-up duration. The competing risks ('actual') method has been currently recognized as a key tool for data interpretation in long-term valve durability studies [27, 28, 29]. For the same reasons we did not stratify the results according to the patients' age at surgery. Limitations of the present study include the impossibility to provide EuroSCORE II data, and the lack of complete echocardiographic follow-up at a single center. Video 1 reports the implantation of a 19-mm Trifecta GT valve. This improved version of the Trifecta is available in Europe since the second quarter of 2016, and is characterized by facilitated suture gliding through the sewing ring and seating into the native annulus, modified holder to facilitate parachuting and seating, and increased stent radiopacity. The hemodynamic properties are comparable to those observed for the previous version; this device is expected to the object of future dedicated investigations.

In conclusion, herein we describe the durability of the Trifecta bioprosthesis for AVR (longest follow-up available so far) in the largest published single-center cohort. We confirm the excellent immediate hemodynamic properties of this device. Accurate sizing and implantation technique are important. Durability is consistent, although rigorous follow-up is required during future years given the characteristics and the timing of the few SVD events observed herein. Such SVD events may be linked with the design of this prosthesis and its mechanical behavior. Improvements in this perspective could be achieved by recent evolution of the device. Practitioners need

to be aware of the potential modalities of failure and of their clinical presentation, while dedicated studies are needed to understand their pathophysiology.

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Table 1.

Characteristic	
Age (years)	75.4 ± 7.7
Male gender	461 (55.9%)
NYHA class III or IV	276 (33.5%)
Extracardiac arteriopathy	146 (17.7%)
Renal insufficiency	38 (4.6%)
COPD	106 (12.9%)

Previous stroke	36 (4.4%)
Hypertension	580 (70.4%)
Tobacco	162 (19.7%)
Diabetes	137 (16.6%)
Hematologic disorder	27 (3.3%)
Hepatic insufficiency	6 (0.7%)
Neoplasm	76 (9.2%)
LVEF (%)	60.8 ± 10.9
Native valve dysfunction - Predominant stenosis - Predominant regurgitation	 791 (96%) 33 (4%)
Bicuspid aortic valve	79 (9.6%)
Infective endocarditis	6 (0.7%)
Previous cardiac operation	11 (1.3%)
Logistic EuroSCORE I (%)	8.7 ± 5.6

Patient demographics. COPD: Chronic Obstructive Pulmonary Disease. LVEF: Left Ventricular Ejection Fraction.

Table 2.

Characteristic	
Non-elective priority	13 (1.6%)
<u>Associated procedures</u> - Other valve surgery - Other valve surgery and coronary bypass - Thoracic aortic surgery - Thoracic aortic surgery and coronary bypass - Coronary bypass - Miscellaneous procedures	 11 (1.3%) 1 (0.1%) 30 (3.6%) 2 (0.2%) 2 (0.2%) 14 (1.7%)
<u>CPB time (min)</u>	

- Overall population	56 ± 24.6
- Isolated AVR	48.1 ± 14.9*
- Associated procedure	88.6 ± 29.6*
Cross-clamp time (min)	
- Overall population	44.6 ± 19.7
- Isolated AVR	38 ± 11.3†
- Associated procedure	71.6 ± 23.7†

Perioperative characteristics. CPB: Cardio-pulmonary bypass. *p<0.001. †p<0.001.

Table 3.

Characteristic	**N (%)**
Valve-related complications	
- Stroke	4 (0.5%)
- NSVD	4 (0.5%)
- IE	1 (0.1%)
- Reoperation	5 (0.6%)
- Non-cerebral embolism	None
Early reoperation (NSVD, IE, non valve-related)	9 (1.1%)
Non-valve-related complications	

- Revision for bleeding	21 (2.5%)
- Prolonged ventilation	33 (4%)
- Renal failure (with dialysis)	13 (1.6%)
- Renal failure (without dialysis)	37 (4.5%)
- Reoperation	4 (0.5%)
- Atrial fibrillation	361 (44%)
- Pacemaker implantation	16 (1.9%)

Early postoperative morbidity (within 30 days of surgery).

Table 4.

Characteristic	**19**	**21**	**23**	**25**	**27-29**
Average transvalvular gradient (mmHg)	13	9.8	9.4	7.4	6.4
Peak transvalvular gradient (mmHg)	23.9	18.5	18.2	14.3	12.7
EOA (cm^2)	1.5	1.8	2.1	2.4	2.8

iEOA (cm^2/m^2)	0.9	1.1	1.1	1.3	1.5
PPM					
- Severe	5%	1%	1%	0	0
- Moderate	33%	15%	8%	3%	0
- None	62%	84%	87%	97%	100%

Valve hemodynamics at discharge stratified according to valve sizes. EOA and iEOA: crude and indexed Effective Orifice Area. PPM: Patient-Prosthesis Mismatch.

Table 5 (Online inclusion).

Characteristic	
5-year freedom from death (any cause)	74.9% ± 8.5
5-year freedom from valve-related death	97.8% ± 0.9
5-year freedom from SVD	98% ± 0.9

5-year freedom reintervention (any type) for SVD	98% ± 0.9
5-year freedom from redo surgery for SVD	98.9% ± 0.6
<u>Causes of death at follow-up.</u> Valve-related - Unknown cause - IE Cardiac non-valve-related - Heart failure with well-functioning prosthesis - Myocardial infarction - Ventricular arrhythmia - Endocarditis on other valve Non-cardiac - Cancer - Suicide - Trauma - Pulmonary failure - Senility - Atherosclerosis - End-organ failure	 7 2 7 3 1 1 17 4 2 2 2 2 4

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643 Follow-up results and details of causes of death at follow-up.

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647 ## Figure Legends

648 **Figure 1 (Online inclusion).** Distribution of nominal valve sizes; the 23-mm diameter

649 valve was most frequently implanted.

Figure 2. Study workflow. PY: Patient/Years. Among 824 patients initially included, 739 (89.7%) were alive at the end of the follow-up. A total of 1,747.6 patient/years were available.

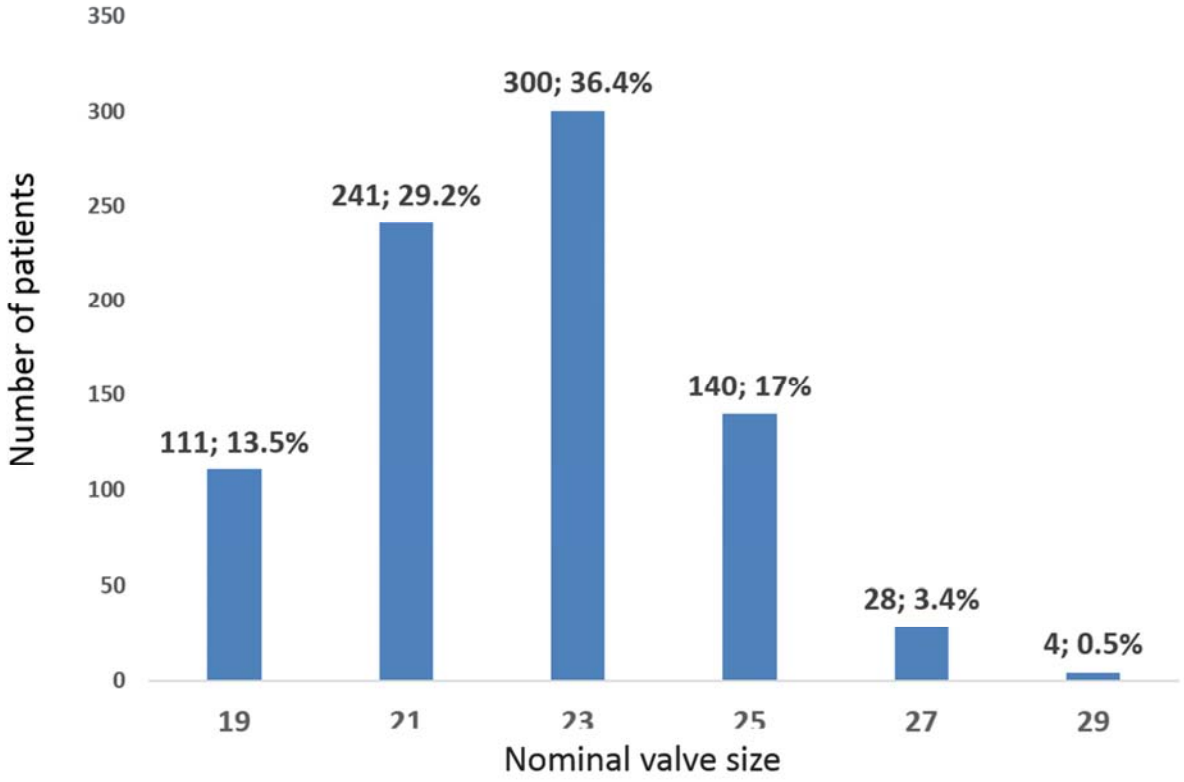
Figure 3. Kaplan-Meier curves of mortality risk in the entire study population. Confidence limits are indicated as area around the curves. A. Risk of death due to any cause. B. Risk of valve-related death. C. Risk of any valve-related reintervention.

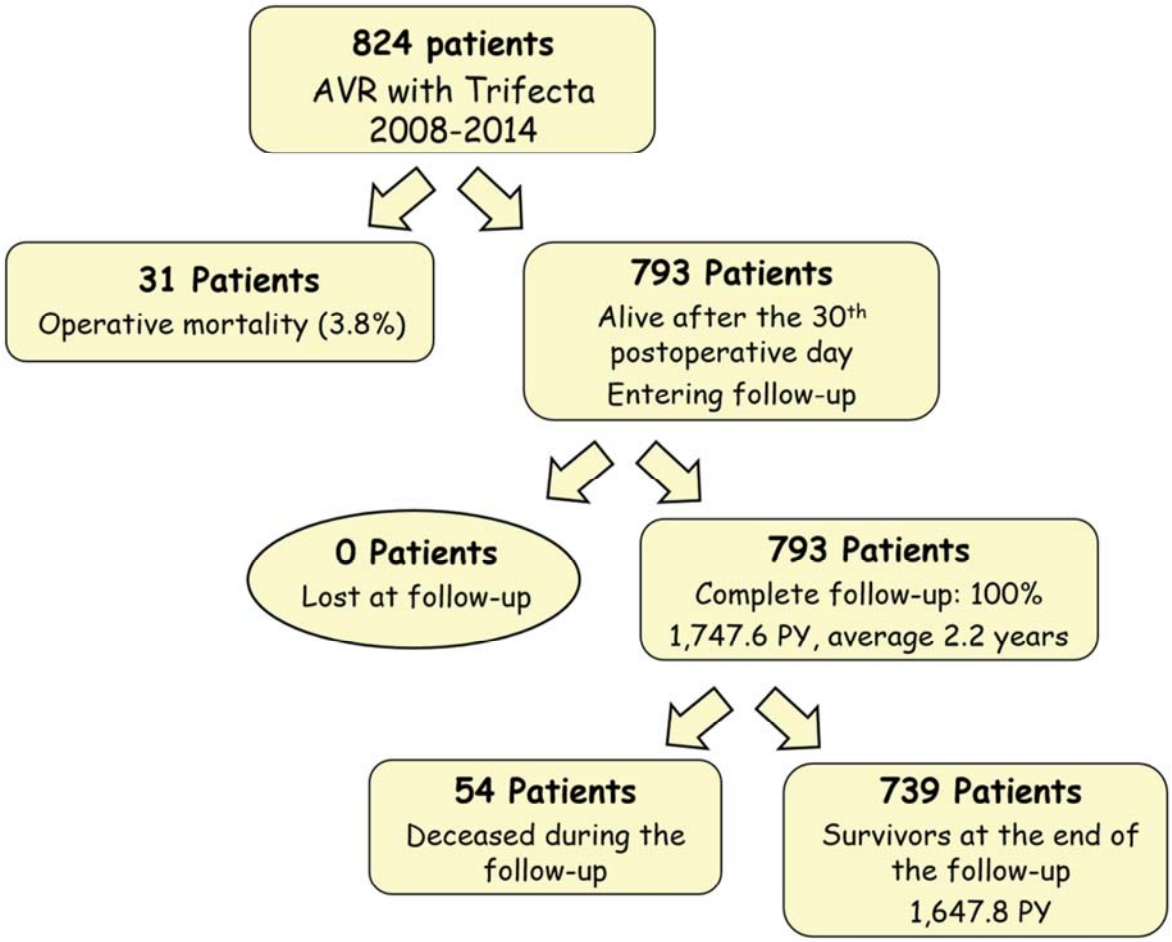
Figure 4. Kaplan-Meier curves of mortality risk in the entire study population. Confidence limits are indicated as area around the curves. A. Risk of death or SVD. B. Risk of death or any reintervention for SVD **(including transcatheter valve-in-valve)**. C. Risk of death or open redo surgery for SVD.

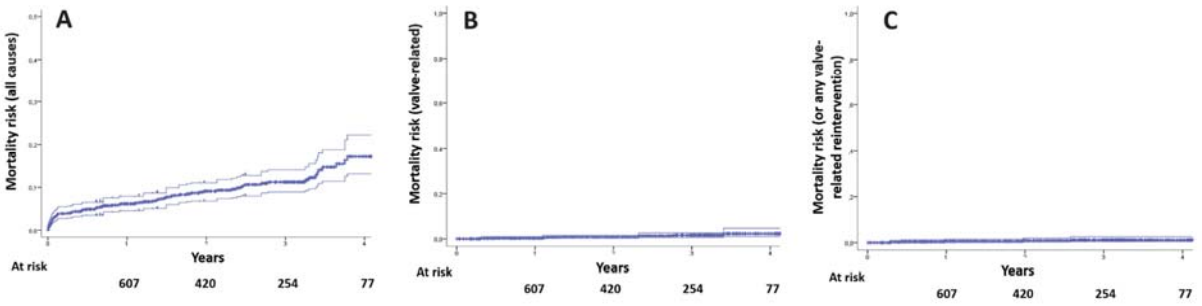
Video Legends

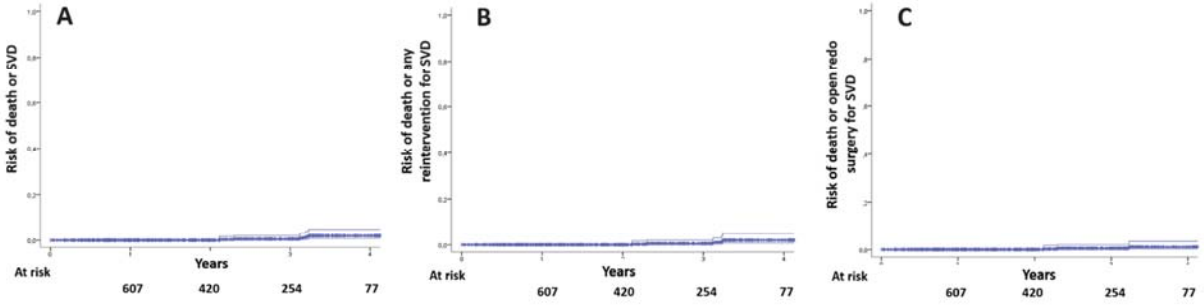
Video 1. Implantation of a 19-mm Trifecta GT valve through full sternotomy for severe aortic stenosis. After aortic cross-clamp and injection of antegrade cardioplegia, an oblique aortotomy is performed and the native valve is excised. This case is characterized by small annular diameter; both intra- and supra-annular sizing are performed in order to anticipate the overall device fit within the aortic root. A supra-annular technique through interrupted U-shaped stitches is employed. Sutures are passed through the prosthetic sewing ring, which features markers at the bottom of each stent post. The sewing ring is designed in order to facilitate suture gliding when the valve is parachuted, and is shaped in order to conform the three-dimensional anatomy of the native annulus. The valve holder is modified to push at the midpoints between stent posts and avoid risk of stent deformation during

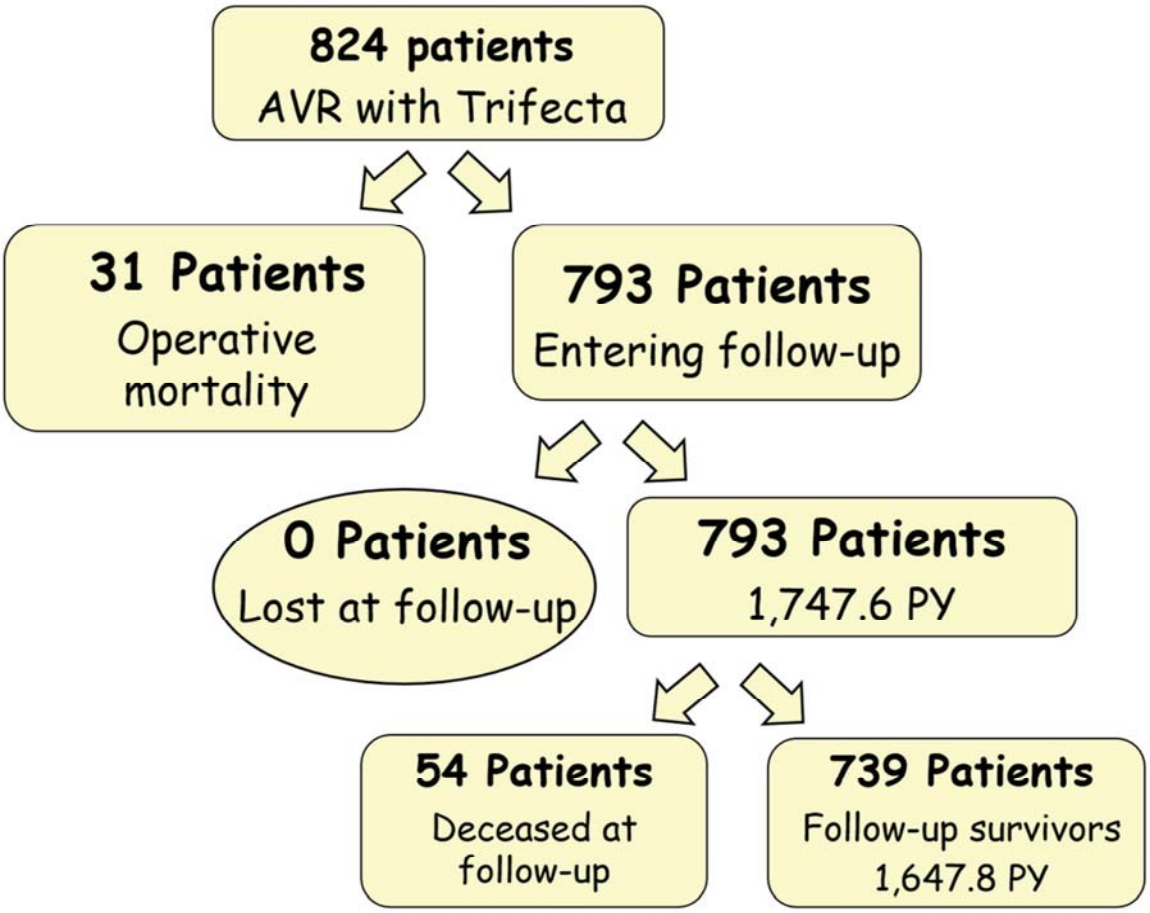
parachuting. Only one suture needs to be divided in order to liberate the valve. After knot tying, the aortotomy is sutured paying attention to avoid leaflet impingement into the sutures.




824 patients
AVR with Trifecta
2008-2014
31 Patients
Operative mortality (3.8%)
793 Patients
Alive after the 30th postoperative day
Entering follow-up
0 Patients
Lost at follow-up
793 Patients
Complete follow-up: 100%
1,747.6 PY, average 2.2 years
54 Patients
Deceased during the follow-up
739 Patients
Survivors at the end of the follow-up
1,647.8 PY



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AVR with Trifecta
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Operative mortality
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Entering follow-up
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Follow-up survivors
1,647.8 PY