

Mid-term durability of the Trifecta bioprosthesis for aortic valve replacement

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► **To cite this version:**

Amedeo Anselmi, Vito Giovanni Ruggieri, Bernard Lelong, Erwan Flecher, Hervé Corbineau, et al.. Mid-term durability of the Trifecta bioprosthesis for aortic valve replacement. *Journal of Thoracic and Cardiovascular Surgery*, Elsevier, 2017, 153 (1), pp.21-28.e1. 10.1016/j.jtcvs.2016.07.080 . hal-01435005

HAL Id: hal-01435005

<https://hal-univ-rennes1.archives-ouvertes.fr/hal-01435005>

Submitted on 13 Apr 2018

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1 **Mid-Term Durability of the Trifecta Bioprosthesis for Aortic** 2 **Valve Replacement**

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20 **Conflicts of interest: None.**

21 **Sources of funding: None.**

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27 **WORD COUNT: 3,947**

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31 **List of Abbreviations.**

32 AVR: Aortic Valve Replacement

33 SVD: Structural Valve Deterioration

34 NSVD: Nonstructural Valve Dysfunction

35 IE: Infective (prosthetic) Endocarditis

36 EOA: Effective Orifice Area

37 iEOA: indexed Effective Orifice Area

38 CPB: Cardio-pulmonary bypass

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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 $98\% \pm 0.9$ (N=6); freedom from reintervention for SVD (N=5) was $98\% \pm 0.9$ (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 $97.7\% \pm 0.7$ (N=12; 6 requiring reoperation). There was one case of late NSVD (5-year freedom: $99.8\% \pm 0.2$). Freedom from hemorrhagic events was $98.6\% \pm 0.5$ (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.

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

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93 Perspective statement

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

99

100 Central Message

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

103

104 Central Picture Legend

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

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113 **Introduction**

114 Bioprostheses are increasingly used for aortic valve replacement (AVR), driven by
115 the continuous improvements in durability and hemodynamic performance during the
116 last decades. The St. Jude Trifecta bioprosthesis (St. Jude Medical Inc., St. Paul,
117 Minn) is a latest-generation stented bioprosthesis, which was introduced into clinical
118 practice in 2007. This device is characterized by a bovine pericardial sheet mounted
119 outside the stent frame. Such feature, associated with the supra-annular design, the
120 ethanol-based anticalcification treatment (proprietary Linx process [1]) and the
121 material properties of the titanium stent, are intended at optimizing its functional
122 behavior and durability. The stent is polyester-covered, and concealed by bovine and
123 porcine pericardium in order to minimize the mechanical stress to the leaflets. The
124 Trifecta valve has demonstrated good hemodynamic performance, both at rest [2, 3,
125 4], during effort [5] and at the three-year follow-up [6]. This characteristic makes it
126 very attractive especially for patients with small aortic annulus. In addition, the
127 Trifecta Durability Study has reported encouraging results during a median 0.9 years
128 follow-up for 1,014 patients (844 patient-years), the freedom from valve explant at 2
129 years being 99.4% [7]. In the same experience, there was only one case of explant
130 due to structural valve deterioration (SVD), suggesting good durability of this device
131 in the initial follow-up.

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

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

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140 **Patients and Methods**

141 Our center started implanting the Trifecta valve in 2008, and participated in the
142 Trifecta Durability Study. In January 2015, we retrospectively reviewed the electronic
143 records of patients who received AVR using this bioprosthesis until December 31st,
144 2014. The performance of any concomitant procedure at the time of AVR, as well as
145 the history of previous cardiac surgery, was not an exclusion criterion. Pre-, intra- and
146 early postoperative data were prospectively collected within an electronic database at
147 the time of patients' discharge as previously described [8]. The database includes all
148 patients receiving cardiac surgery at our Institution; it is managed by research nurses
149 and regularly checked for completion and consistency under the supervision of the
150 surgical team. For the purposes of the present study, a retrospective clinical follow-up
151 was performed between January and May 31st, 2015. Practitioners (referring
152 cardiologists and general medicine doctors) were provided with questionnaires sent
153 through surface mail; questionnaires inquired about the vital status of the patient, the
154 occurrence of any adverse event (both valve- and non-valve-related) and the
155 functional status, as well as the time at which any adverse event had occurred. In
156 case of incomplete or missing information, the patients themselves or their families
157 were contacted; local governmental authorities were asked to confirm the patients'
158 vital status in case of missing data. Valve-related adverse events were defined
159 according to the current guidelines [9], including SVD (changes intrinsic to the device

160 causing dysfunction, evident at echocardiography, reoperation or autopsy),
161 nonstructural valve dysfunction (NSVD; any abnormality not intrinsic to the valve itself
162 that results in stenosis or regurgitation or hemolysis, evident at echocardiography,
163 reoperation or autopsy) and operated valve endocarditis (IE). Valve thrombosis and
164 embolic events (either cerebral or non-cerebral embolic events) were presented in an
165 aggregate form as thrombo-embolic complications. Hemorrhagic complications were
166 reported in the overall population and stratified according to the administration of
167 anticoagulant therapy. Reinterventions were reported both in aggregate form and
168 stratified according to type (either open reoperative surgery or interventional catheter-
169 based procedures). Valve-related mortality was death consequent to any of the
170 above adverse events or to reoperation on the index valve. Causes of death were
171 determined by review of hospital records and instrumental data. All complications and
172 fatal events for which no demonstrated non-valvular cause was known (including
173 sudden death), were considered as valve-related events. Mortality resulting from
174 cerebrovascular events during the follow-up was also assumed to be valve-related.
175 Concerning early complications, we distinguished among perioperative stroke
176 (defined as new focal neurological deficit or coma evident immediately after
177 resolution of anesthesia), which was considered to be non-valve-related, and
178 postoperative stroke (defined as new focal neurological deficit or coma which
179 became evident after a normal awakening from anesthesia), which was considered to
180 be valve-related unless otherwise demonstrated. Such 'conservative' approach was
181 used in compliance with guidelines on data reporting, and should be kept in mind
182 while interpreting the results. Adverse events were categorized as either early (when
183 occurring during the hospitalization in which the operation was performed, even if
184 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 Libertés [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 cm²/m²), moderate (iEOA ≤ 0.85
219 cm²/m²) or absent (iEOA > 0.85 cm²/m²) [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,

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

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237 Statistical analysis

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

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260 **Results**

261 Early results

262 During the study period, 824 patients received AVR using a Trifecta valve and were
263 included; their baseline demographics are summarized in Table 1. Predominant
264 stenosis was the most frequent modality of native valve dysfunction; in fact, patients
265 presenting degenerative calcified aortic stenosis composed the majority of the
266 present population. The rate of baseline comorbidities was limited, as it is underlined
267 by the average value of logistic EuroSCORE I. There were few non-elective cases
268 (1.6%) and the rate of concomitant procedures was 7.3% (perioperative
269 characteristics are reported in Table 2). Average CPB and aortic cross-clamp time
270 were significantly greater if a concomitant procedure had been performed ($p < 0.001$
271 both). Conversely, average CPB and aortic clamp time were limited (48.1 min \pm 14.9
272 and 38 min \pm 11.3, respectively) in case of isolated AVR. Figure 1 reports the
273 distribution of the sizes of the implanted valves. The 23-mm size was most frequently
274 used (36.4%), followed by the 21-mm size (29.2%).

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

277 Causes of operative mortality were extracardiac in 15 instances (1.8%), and cardiac
278 non-valvular in the remaining 16 cases (1.9%). No operative death was due to
279 valvular causes. The details of early postoperative (30-days) complications are given
280 in Table 3. There were a total of 9 valve-related early complications (1.1%), including
281 4 cerebral strokes (among these, only 1 was permanent). We observed 1 case of
282 early IE (requiring reoperation) and 4 cases of NSVD. Among the NSVD cases, 2
283 presented severe transvalvular regurgitation at echocardiography; at reoperation, this
284 was due to engagement of the bioprosthesis' non-coronary leaflet into the suture of
285 the oblique aortotomy. At reoperation, these two cases were managed through
286 section of the suture without need for valve re-replacement. These two bioprostheses
287 showed normal function at the last available follow-up. One further early NSVD case
288 consisted in severe transvalvular regurgitation evident on echocardiography; at
289 reoperation, this was due to valve oversizing (27-mm device) in a patient with
290 relatively narrow sino-tubular junction. This resulted in deformation of the upper valve
291 stent and consequent leaflet malcoaptation. This patient was treated by replacement
292 of the device with a new 23-mm Trifecta valve. The last NSVD case was
293 characterized by elevated transvalvular gradients at follow-up echocardiography in a
294 patient who had received AVR with a 19-mm Trifecta valve plus septal myectomy for
295 aortic stenosis and obstructive cardiomyopathy. At reoperation, persisting subvalvular
296 stenosis and valve oversizing were noted; the patient was treated by iterative septal
297 myectomy and valve replacement with a 17-mm mechanical valve prosthesis. There
298 were no early SVD cases. We observed 4 additional reoperations which were not
299 valve-related. The rate of early valve-related reoperation was 0.6% (with no cases of
300 associated mortality); the average time interval after primary surgery was 7.6 ± 6.9
301 days. Multiple logistic regression identified advanced age, renal insufficiency,

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

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

309 Follow-up results.

310 We obtained data for all the 793 patients who were discharged alive from the
311 hospital and entered the follow-up (100% follow-up completeness). Average follow-up
312 was 2.2 ± 1.3 years (range: 0.03 to 6.9 years; median: 2 years); a total of 1,747.6
313 patient/years were available for analysis (Figure 2). During the follow-up, we
314 observed 54 late deaths (6.8% of the patients who were discharged alive) occurring
315 at an average 1.8 ± 1.3 years after surgery, while 739 patients were alive at the end
316 of the follow-up (93.2% of the patients who were discharged alive). Causes of late
317 death were extracardiac in 33 cases (61.1% of late deaths), cardiac non-valvular in
318 12 (22.2%) and valve-related in 9 (16.7%, including 7 deaths of unknown cause and
319 2 fatal outcomes due to prosthetic valve endocarditis). At the 5-years follow-up, the
320 overall survival in the entire population was $74.9\% \pm 8.5$, and the freedom from valve-
321 related death was $97.8\% \pm 0.9$. Figures 3A and 3B depict the risk of death due to any
322 cause and to valve-related causes, respectively. During the present follow-up we
323 observed 6 SVD events, occurring at an average 3.4 ± 1.6 years after valve
324 implantation. The 5-year Kaplan-Meier survival free from SVD was $98\% \pm 0.9$ (Figure
325 4A depicts the risk of death or SVD). Among these SVD events, 5 required
326 reintervention and 1 was managed by medical treatment only (Case 5). The freedom

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

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

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

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360 Discussion

361 The St. Jude Trifecta valve has been employed in clinical practice since 2007. As a
362 typical feature, the bovine pericardial tissue is mounted outside the stent frame. This
363 translates into optimized EOA and excellent hemodynamic properties. A considerable
364 body of independent literature beyond the sponsored Trifecta Durability Study has
365 consistently demonstrated low average transvalvular gradients and very low rates of
366 PPM in the immediate postoperative period compared to other valve devices [2, 3,
367 11, 12, 13]. Although a debate exists about the impact of PPM on the long-term
368 patients' outcome [14, 15], the Trifecta valve offers specific advantages in patients
369 with small aortic annulus and high risk of postoperative PPM. Recently, our group
370 has reported for the first time the three-years hemodynamic performance of this
371 device, suggesting that its hemodynamic profile is preserved at the mid-term follow-
372 up [6]. The population analyzed in the above-referenced study [6] is included in the
373 current investigation. Although the three-years hemodynamic results are not available

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

376 The main scope of the present paper is to address the durability of this innovative
377 device. To such purpose, we analyzed the largest single-center population available
378 so far in the literature, and the longest available follow-up (N=824, 1,747.6
379 patient/years, average 2.2 years). Follow-up was facilitated by the propensity of
380 patients treated at our center to remain in the region after surgery, which gives
381 account for the 100% rate of follow-up completeness. Durability is one major
382 requirement for modern bioprostheses, given the growing tendency to use them in
383 younger individuals [16]. Such feature acquires even greater importance in the
384 current era, when the results of surgical AVR are discussed as the benchmark
385 reference compared to transcatheter valve therapy. In our population, we observed a
386 total of 6 SVD events occurring at an average 3.4 ± 1.6 years from valve implantation
387 ($98\% \pm 0.9$ Kaplan-Meier freedom from SVD at 5 years). This freedom from SVD is
388 slightly lower than that documented for other bioprostheses in large, previously
389 published series. The 5-year freedom from SVD was 99.3% (Kaplan-Meier) and
390 99.4% (competing risks methodology) for a third-generation porcine valve in the
391 aortic position [8]. In smaller previous series, the 5-year freedom from SVD for a
392 third-generation pericardial valve was 100% [16], although this study was potentially
393 limited by sample bias. In more recent investigations, the 5-year actuarial freedom
394 from SVD for a third-generation pericardial valve was 99.8% [18]. For a second-
395 generation porcine valve, the 5-year freedom from SVD was 99.2% (Kaplan-Meier)
396 and 99.3% (competing risks) [19]. One previous series focused on the Trifecta valve
397 did not report cases of reoperation for SVD at two years [11], but the rate of non-
398 reoperated SVD cases was not addressed. Although the absolute number of SVD

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

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

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

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

438 The specific features of the Trifecta valve (namely, the outer position of the
439 pericardial sheet and its globally rectangular shape) have been associated with
440 increased risk of coronary obstruction during transcatheter valve-in-valve procedure
441 [23]. Two patients with SVD in the present series and considered to be at excessive
442 reoperative risk were successfully treated through the valve-in-valve technique
443 without instances of coronary obstruction. Accurate pre-procedural imaging
444 assessment and choice of transcatheter device, as well as precise deployment, are
445 of pivotal importance [24]. Other reports confirm the feasibility of such approach [25].
446 According to recommendations [9], freedom from open redo surgery and from
447 transcatheter reintervention on the index valve was listed here both in aggregate form
448 and separately.

449 Similarly, we underline the importance to define SVD as the occurrence of intrinsic
450 valve changes, irrespective to the performance of any reintervention, in order to avoid
451 any underestimation of the SVD rate [26]. Contrary to previous works, herein we did
452 not present results according to the competing risks methodology, given the limited
453 number of SVD events and the relatively short average follow-up duration. The
454 competing risks ('actual') method has been currently recognized as a key tool for
455 data interpretation in long-term valve durability studies [27, 28, 29]. For the same
456 reasons we did not stratify the results according to the patients' age at surgery.
457 Limitations of the present study include the impossibility to provide EuroSCORE II
458 data, and the lack of complete echocardiographic follow-up at a single center. Video
459 1 reports the implantation of a 19-mm Trifecta GT valve. This improved version of the
460 Trifecta is available in Europe since the second quarter of 2016, and is characterized
461 by facilitated suture gliding through the sewing ring and seating into the native
462 annulus, modified holder to facilitate parachuting and seating, and increased stent
463 radiopacity. The hemodynamic properties are comparable to those observed for the
464 previous version; this device is expected to be the object of future dedicated
465 investigations.

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

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

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484 **References**

- 485 1. Jamieson WR, Lewis CT, Sakwa MP, Cooley DA, Kshetry VR, Jones KW et
486 al. St Jude Medical Epic porcine bioprosthesis: results of the regulatory
487 evaluation. *J Thorac Cardiovasc Surg* 2011 Jun;141:1449-54.
- 488 2. Remadi JP, Levy F, Szymanski C, Nzomvuama A, Zogheib E, Gun M et al.
489 Early hemodynamics results of aortic valve replacement with the new St Jude
490 Trifecta bioprosthesis. *Int J Cardiol.* 2014;174:755-7.
- 491 3. Permanyer E, Estigarribia AJ, Ysasi A, Herrero E, Semper O, Llorens R. St.
492 Jude Medical Trifecta™ aortic valve perioperative performance in 200
493 patients. *Interact Cardiovasc Thorac Surg.* 2013 Oct;17(4):669-72.
- 494 4. Yadlapati A, Diep J, Barnes M, Grogan T, Bethencourt DM, Vorobiof G.
495 Comprehensive hemodynamic comparison and frequency of patient-

- 496 prosthesis mismatch between the St. Jude Medical Trifecta and Epic
497 Bioprosthetic aortic valves. *J Am Soc Echocardiogr.* 2014;27:581-9.
- 498 5. Levy F, Donal E, Bière L, Szymanski C, Remadi JP, Flécher E et al.
499 Hemodynamic performance during exercise of the new St. Jude Trifecta aortic
500 bioprosthesis: results from a French multicenter study. *J Am Soc*
501 *Echocardiogr.* 2014;27:590-7.
- 502 6. Ruggieri VG, Anselmi A, Chabanne C, Lelong B, Flecher E, Verhoye JP et al.
503 Three-year haemodynamic performance of the St Jude Trifecta bioprosthesis.
504 *Eur J Cardiothorac Surg.* 2015 Jun 18 [Epub ahead of print].
- 505 7. Bavaria JE, Desai ND, Cheung A, Petracek MR, Groh MA, Borger MA et al.
506 The St Jude Medical Trifecta aortic pericardial valve: results from a global,
507 multicenter, prospective clinical study. *J Thorac Cardiovasc Surg.*
508 2014;147:590-7.
- 509 8. Anselmi A, Flécher E, Ruggieri VG, Harmouche M, Langanay T, Corbineau H
510 et al. Long-term results of the Medtronic Mosaic porcine bioprosthesis in the
511 aortic position. *J Thorac Cardiovasc Surg.* 2014;147:1884-91.
- 512 9. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH,
513 Grunkemeier GL et al. Guidelines for reporting mortality and morbidity after
514 cardiac valve interventions. *J Thorac Cardiovasc Surg.* 2008;135:732-8.
- 515 10. Blais C, Dumesnil JG, Baillet R, Simard S, Doyle D, Pibarot P. Impact of valve
516 prosthesis-patient mismatch on short-term mortality after aortic valve
517 replacement. *Circulation.* 2003;108:983-8.
- 518 11. Modi A, Budra M, Miskolczi S, Velissaris T, Kaarne M, Barlow CW et al.
519 Hemodynamic performance of Trifecta: single-center experience of 400
520 patients. *Asian Cardiovasc Thorac Ann.* 2015;23:140-50.

- 521 12. Wendt D, Thielmann M, Plicht B, Aßmann J, Price V, Neuhäuser M et al. The
522 new St Jude Trifecta versus Carpentier-Edwards Perimount Magna and
523 Magna Ease aortic bioprosthesis: is there a hemodynamic superiority? *J*
524 *Thorac Cardiovasc Surg.* 2014;147:1553-60.
- 525 13. Dell'Aquila AM, Schlarb D, Schneider SR, Sindermann JR, Hoffmeier A,
526 Kaleschke G et al. Clinical and echocardiographic outcomes after implantation
527 of the Trifecta aortic bioprosthesis: an initial single-centre experience. *Interact*
528 *Cardiovasc Thorac Surg* 2013;16:112-5.
- 529 14. Tully PJ, Aty W, Rice GD, Bennetts JS, Knight JL, Baker RA. Aortic valve
530 prosthesis-patient mismatch and long-term outcomes: 19-year single-center
531 experience. *Ann Thorac Surg* 2013;96:844-50.
- 532 15. Pibarot P, Dumesnil JG. Prosthesis-patient mismatch: definition, clinical
533 impact, and prevention. *Heart.* 2006;92:1022-9.
- 534 16. McClure RS, McGurk S, Cevasco M, Maloney A, Gosev I, Wiegerinck EM et
535 al. Late outcomes comparison of nonelderly patients with stented bioprosthetic
536 and mechanical valves in the aortic position: a propensity-matched analysis. *J*
537 *Thorac Cardiovasc Surg.* 2014;148:1931-9.
- 538 17. Dellgren G, David TE, Raanani E, Armstrong S, Ivanov J, Rakowski H et al.
539 Late hemodynamic and clinical outcomes of aortic valve replacement with the
540 Carpentier-Edwards Perimount pericardial bioprosthesis. *J Thorac Cardiovasc*
541 *Surg.* 2002;124:146-54.
- 542 18. McClure RS, Narayanasamy N, Wiegerinck E, Lipsitz S, Maloney A, Byrne JG
543 et al. Late outcomes for aortic valve replacement with the Carpentier-Edwards
544 pericardial bioprosthesis: up to 17-year follow-up in 1,000 patients. *Ann*
545 *Thorac Surg.* 2010;89:1410-6.

- 546 19. Ruggieri VG, Flécher E, Anselmi A, Lelong B, Corbineau H, Verhoye JP et al.
547 Long-term results of the carpentier-edwards supraannular aortic valve
548 prosthesis. *Ann Thorac Surg.* 2012;94:1191-7.
- 549 20. Lehmann S, Walther T, Leontjev S, Kempfert J, Rastan A, Garbade J et al.
550 Mid-term results after Epic xenograft implantation for aortic, mitral, and double
551 valve replacement. *J Heart Valve Dis.* 2007;16:641-8.
- 552 21. Campisi S, Camilleri L, Innorta A, Azarnoush K. Early failures of Trifecta aortic
553 bioprosthesis. *J Thorac Cardiovasc Surg.* 2014;148:e133-4.
- 554 22. Saxena P, Greason KL, Schaff HV. Early structural valve deterioration of the
555 Trifecta aortic valve biological prosthesis: a word of caution. *J Thorac*
556 *Cardiovasc Surg.* 2014;147:e10-1.
- 557 23. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A et al.
558 Transcatheter aortic valve replacement for degenerative bioprosthetic surgical
559 valves: results from the global valve-in-valve registry. *Circulation.*
560 2012;126:2335-44.
- 561 24. Verhoye JP, Harmouche M, Belhaj Soulami R, Thebault C, Boulmier D,
562 Leguerrier A et al. Feasibility of Valve-in-Valve Procedure for Degenerated
563 St.Jude Trifecta Bioprosthesis. *J Heart Valve Dis* 2015 in press.
- 564 25. Haussig S, Schuler G, Linke A. Treatment of a failing St. Jude Medical Trifecta
565 by Medtronic Corevalve Evolut valve-in-valve implantation. *JACC Cardiovasc*
566 *Interv.* 2014;7:e81-2.
- 567 26. Jamieson WR. Bioprosthetic durability assessment: importance of complete
568 data. *J Thorac Cardiovasc Surg.* 2011;141:596.

- 569 27. Grunkemeier GL, Jin R, Eijkemans MJ, Takkenberg JJ. Actual and actuarial
 570 probabilities of competing risks: apples and lemons. *Ann Thorac Surg.*
 571 *2007;83:1586-92.*
- 572 28. Grunkemeier GL, Takkenberg JJ, Jamieson WR, Miller DC. Reporting "actual
 573 freedom" should not be banned. *J Thorac Cardiovasc Surg.* *2008;135:460-2.*
- 574 29. Grunkemeier GL, Furnary AP, Wu Y, Wang L, Starr A. Durability of pericardial
 575 versus porcine bioprosthetic heart valves. *J Thorac Cardiovasc Surg.*
 576 *2012;144:1381-6.*

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583 **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
<u>Native valve dysfunction</u>	
- Predominant stenosis	791 (96%)
- Predominant regurgitation	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

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

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Table 2.

Characteristic	
Non-elective priority	13 (1.6%)
<u>Associated procedures</u>	
- Other valve surgery	11 (1.3%)
- Other valve surgery and coronary bypass	1 (0.1%)
- Thoracic aortic surgery	30 (3.6%)
- Thoracic aortic surgery and coronary bypass	2 (0.2%)
- Coronary bypass	2 (0.2%)
- Miscellaneous procedures	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*
<u>Cross-clamp time (min)</u>	
- Overall population	44.6 ± 19.7
- Isolated AVR	38 ± 11.3 [†]
- Associated procedure	71.6 ± 23.7 [†]

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

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618 **Table 3.**

Characteristic	N (%)
<u>Valve-related complications</u>	
- 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%)
<u>Non-valve-related complications</u>	

- 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%)

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620 Early postoperative morbidity (within 30 days of surgery).

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629 **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%

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631 Valve hemodynamics at discharge stratified according to valve sizes. EOA and iEOA:

632 crude and indexed Effective Orifice Area. PPM: Patient-Prosthesis Mismatch.

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641 **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	7
- IE	2
Cardiac non-valve-related	
- Heart failure with well-functioning prosthesis	7
- Myocardial infarction	3
- Ventricular arrhythmia	1
- Endocarditis on other valve	1
Non-cardiac	
- Cancer	17
- Suicide	4
- Trauma	2
- Pulmonary failure	2
- Senility	2
- Atherosclerosis	2
- End-organ failure	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.

650 **Figure 2.** Study workflow. PY: Patient/Years. Among 824 patients initially included,
651 739 (89.7%) were alive at the end of the follow-up. A total of 1,747.6 patient/years
652 were available.

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

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

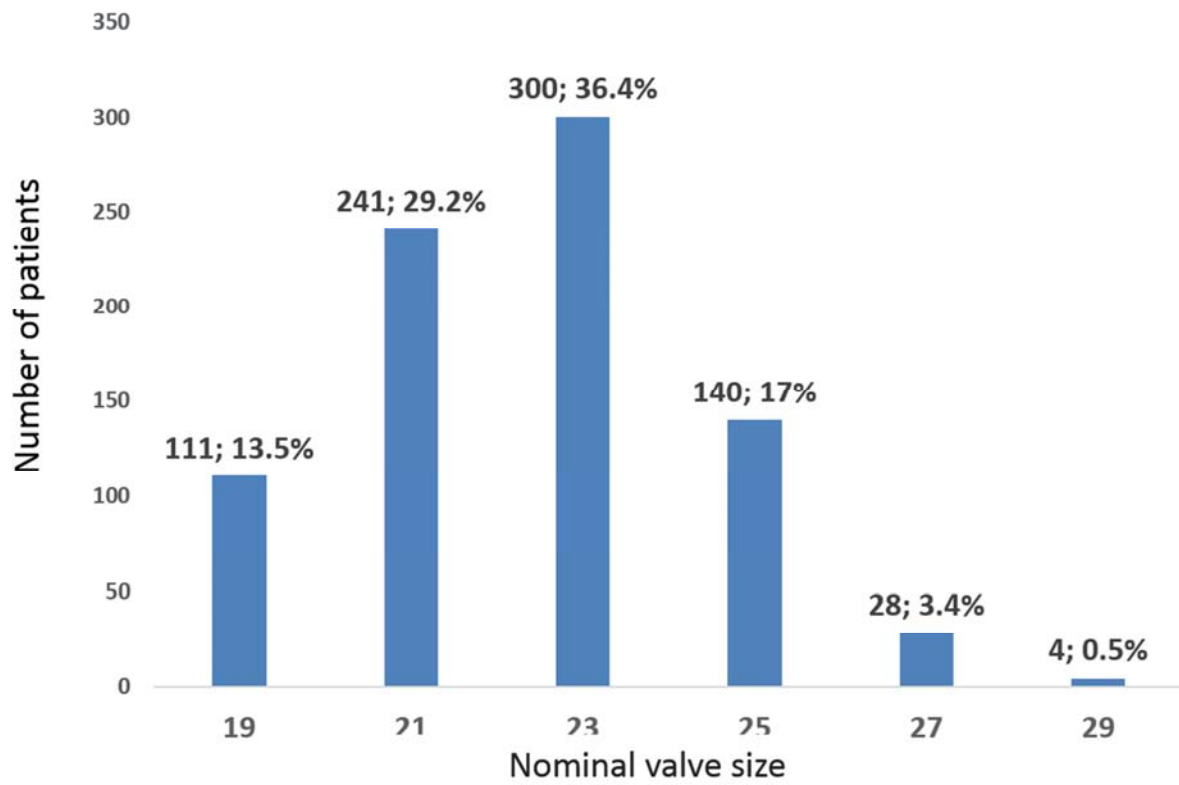
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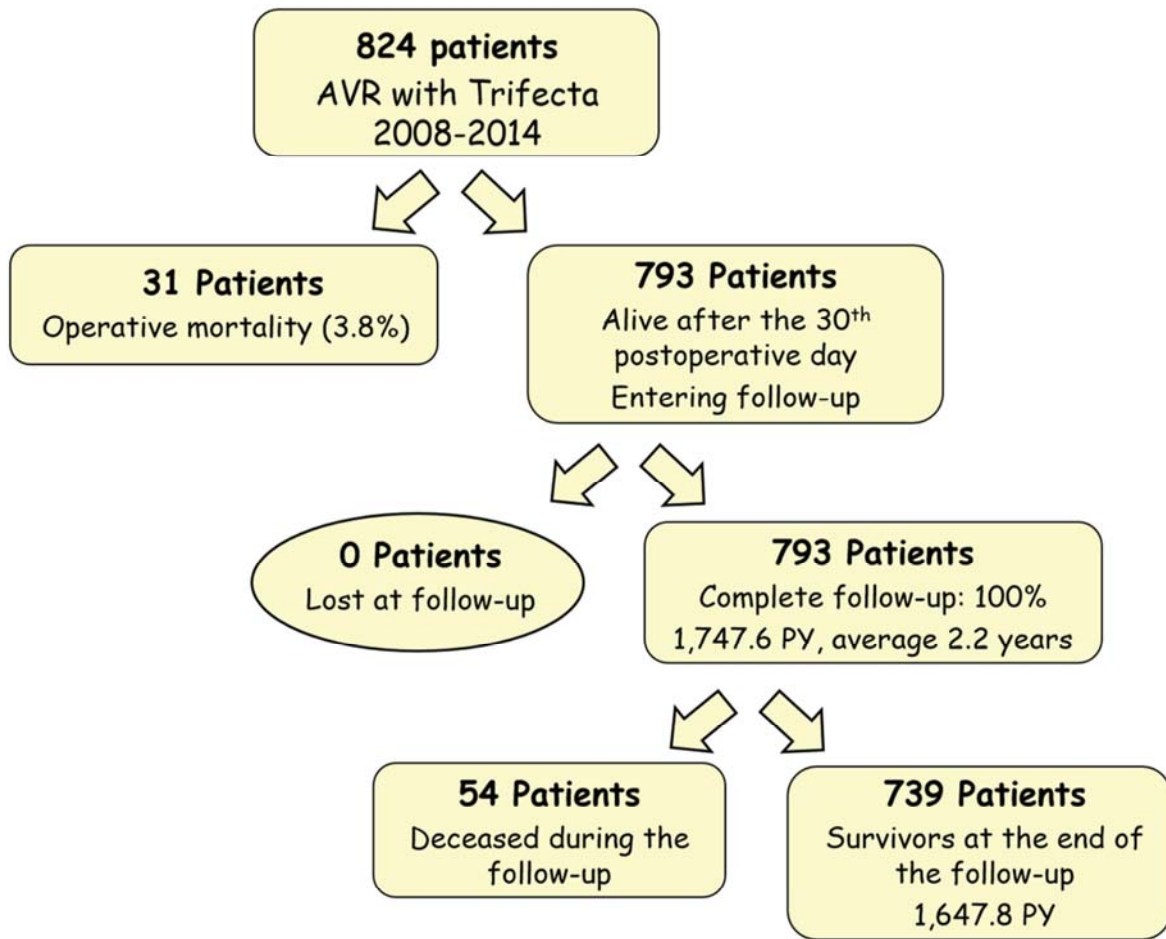
662 **Video Legends**

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

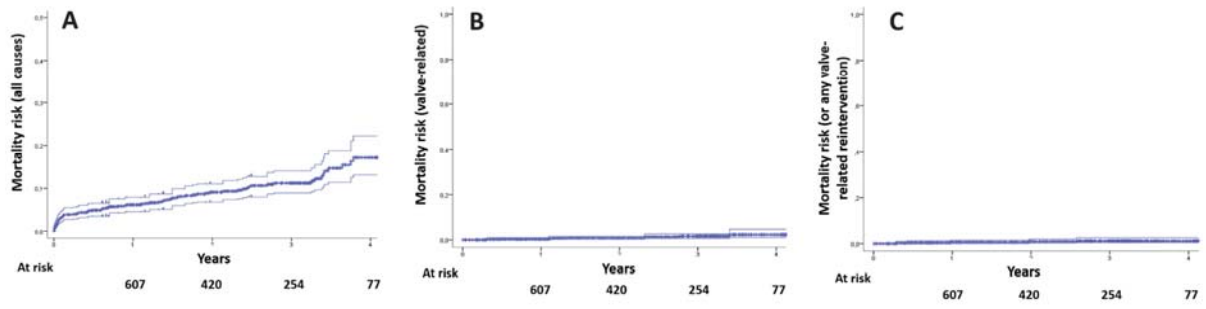
674 parachuting. Only one suture needs to be divided in order to liberate the valve. After
675 knot tying, the aortotomy is sutured paying attention to avoid leaflet impingement into
676 the sutures.

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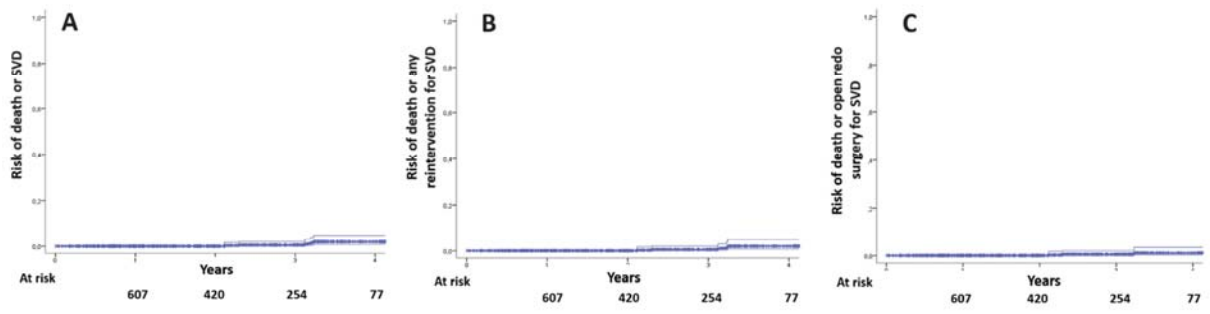


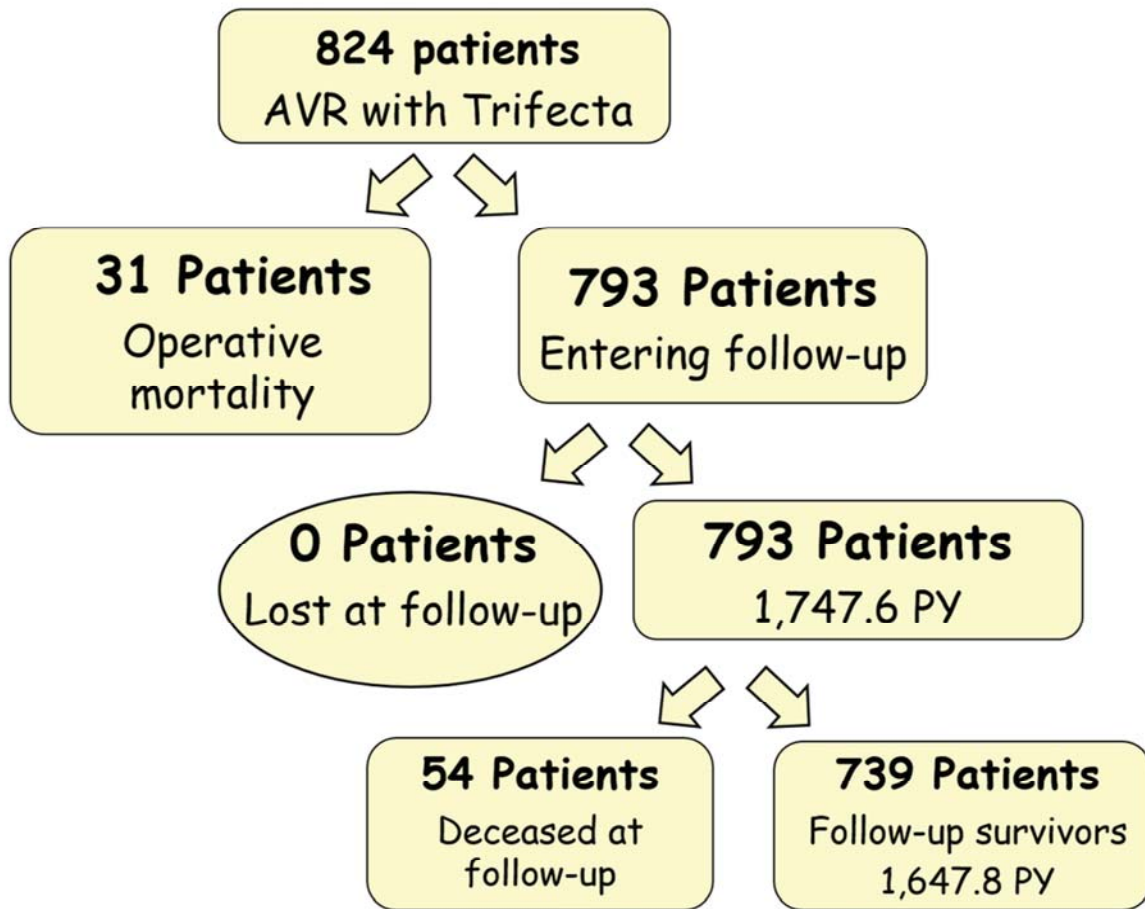


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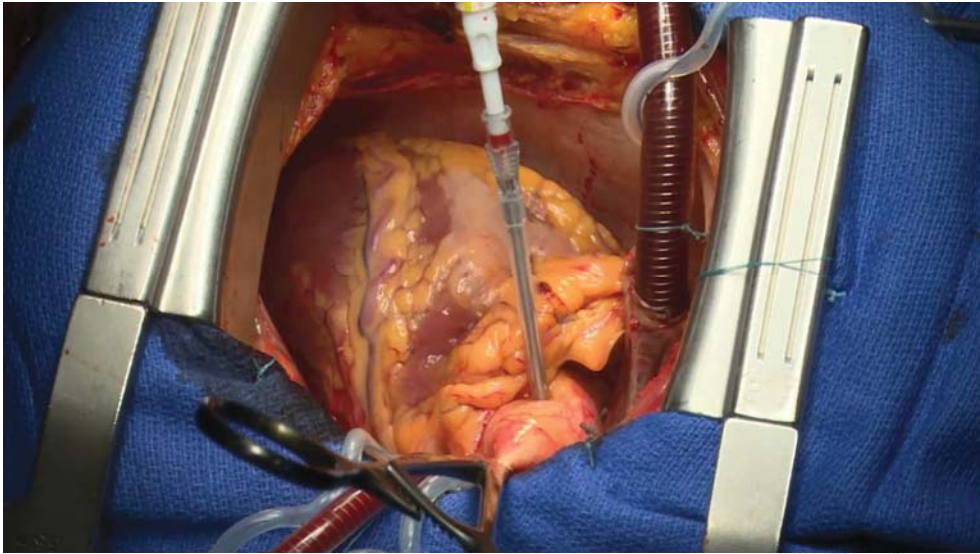


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