Long-Term Durability of Transcatheter Aortic Valve Implantation With Self-Expandable Valve System (from a Real-World Registry)

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As transcatheter aortic valve Implantation (TAVI) moves to younger and lower risk patients with longer life expectancy, the long-term durability of TAVI is becoming an increasingly relevant issue. We sought to evaluate the long-term clinical outcome and prosthesis performance of the CoreValve self-expandable valve. Clinical registry of 182 patients consecutively treated with TAVI in a tertiary center from January 2009 to July 2017. Of these, 111 died during an average follow-up (FU) of 1,026 ± 812 days (median IQR: 745, 477 to 1,400 days; longest survival 11 years; 61% mortality at Kaplan−Meier analysis). At 1 month, functional profile improved in all survivors, with 93.9% of them achieving NYHA class I or II. At Cox analysis, the Society of Thoracic Surgeons score (HR: 1.55; p = 0.001), left ventricular ejection fraction <40% (HR: 1.65; p = 0.017) and incident acute kidney injury (HR: 1.96; p = 0.001) were independently associated with all-cause mortality. During FU, echocardiographically assessed mean transprosthetic aortic gradient remained substantially unchanged (from 9.0 ± 2.7 after TAVI to 9.0 ± 5.0 mm Hg at FU; p >0.05). Most patients had none and/or trivial (34%), or mild (58%), fewer had moderate (8%) and none had severe perivalvular leak, without significant change during FU. At 11 years, cumulative incidence of bioprosthetic valve failure and moderate structural valve deterioration (SVD) were 2.9% (95% CI 0.8% to 10%) and 9.3% (95% CI 3.3% to 26.7%), respectively. In conclusion, our registry confirmed that TAVI with the self-expandable CoreValve system was associated with favorable long-term clinical outcomes, with a reassuring low rate of significant bioprosthetic valve failure and moderate SVD. **(Am J Cardiol 2021;143:104−110)**

What is known

As TAVI moves to younger and lower risk patients having longer life expectancy than initial high risk and inoperable TAVI candidates, the long-term durability of TAVI is becoming of increasing importance. Long-term data concerning the late prosthesis performance are still limited.

What this study adds

Our registry confirmed that TAVI with the self expandable CoreValve system was associated with favorable clinical outcomes in long-term, with a reassuring low rate of significant BVF and moderate SVD. Despite our reassuring findings of TAVI in high risk and inoperable patients, data on long-term TAVI performance and durability are imperative to justify the growing implementation in low-risk patients.

In the last decade, transcatheter aortic valve implantation (TAVI) emerged as the treatment of choice for inoperable and high-risk patients with symptomatic severe aortic stenosis.[1−4] Since then, its indication was extended to intermediate-risk patients, due to the non-inferiority of TAVI compared with surgical aortic valve replacement.[5,6] Recently, 2 randomized trials demonstrated the benefit of TAVI also in low-risk populations, which were also younger[7,8] than the previous ones.[1−6] Therefore, as TAVI moves to younger and lower risk patients, who have longer life expectancy, its long-term durability is becoming an issue increasingly important. Long-term data concerning late TAVI prosthesis performance are still limited. In addition, previous studies have used different methods and criteria to assess valve durability. For this reasons, in accordance with recent recommendations from several European scientific societies,[9] we investigated over a long term follow-up the clinical outcome, the rate of bioprosthetic valve failure (BVF) and structural valve deterioration (SVD) of self-expandable CoreValve bioprosthesis implanted at our tertiary center.

METHODS

From January 2009 to July 2017, all consecutive patients with severe aortic stenosis who underwent TAVI with the CoreValve and Evolut R (Medtronic Inc., Minneapolis, Minnesota) devices in Careggi Hospital were prospectively

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included in this quality improvement registry that, approved by the ethic local committee, conformed the Declaration of Helsinki. Each patient signed an informed consent for data collection and analysis. Patients who underwent TAVI for a failed surgical aortic bioprosthesis were excluded. Eligibility for TAVI was based on the consensus of local Heart Team. Patient choice of TAVI size was initially made with transthoracic and/or transesophageal echocardiography (TTE, TEE) and angiography, later in time integrated with computer tomography scan, as previously described.[10] TTE was performed at baseline, 24 hours and 1 month after TAVI, and thereafter annually. The clinical follow-up was based on clinical visits or telephone interviews. CoreValve implantation procedure has been described elsewhere.[10,11] Percutaneous treatment of concomitant coronary disease, was performed before TAVI. Main end points were all-cause and cardiovascular mortality, the occurrence of SVD or BVF, and changes over time of NYHA functional class and aortic transprosthetic gradients and perivalvular leaks (PVL) measurements. Cardiovascular death and procedure complications were defined according to the Valve Academic Research Consortium-2 definitions,[12] while SVD and BVF according to European consensus statement criteria.[9] Two degrees of hemodynamic SVD were defined: (1) moderate, as (a) mean gradient ≥20 and <40 mmHg or ≥10 and <20 mm Hg increase from after-procedure (within 30 days of TAVI) and/or (b) moderate new or worsening intraprosthetic regurgitation; (2) severe, as (a) mean gradient ≥40 or ≥20 mm Hg change from after-procedure (within 30 days of TAVI) and/or (b) severe new or worsening intraprosthetic regurgitation. BVF was defined as the composite of the followings: (1) severe hemodynamic SVD; (2) aortic valve reintervention; and (3) valve-related death. Continuous and categorical variables are presented as mean ± standard deviation or as counts and percentages, respectively, and were compared by *t*-test or Mann-Whitney *U*-test, and by Chi-square or Fisher's exact test, as appropriate. Survival curves of patients with low, intermediate and high risk Society of Thoracic Surgeons (STS) score were plotted using the Kaplan−Meier analysis and compared with the log-rank test. The Cox regression analyses were applied to identify independent predictors of long-term all-cause mortality including factors with a p <0.10 at univariable analysis. Cumulative incidence functions (CIFs) for moderate or severe SVD and for late BVF were estimated accounting for the competing risk of death. In addition, mean aortic transprosthetic gradients and PVLs were presented for all time points after the procedure. Statistical analyses were performed using the SPSS 26.0 package (Armonk, New York: IBM Corp.). A 2-sided p <0.05 was considered statistically significant.

RESULTS

We implanted CoreValve or Evolute R (Medtronic Plc., Minneapolis, Minnesota) aortic prostheses in 182 patients (mean age 82.9 ± 6.0 years, 44% males; mean transvalvular aortic gradient 50.4 ± 16.0 mm Hg), in whom surgery was deemed contraindicated because of either high risk (LogEuroScore ≥10) or previous coronary artery bypass graft, porcelain aorta, chest radiotherapy or severe chronic obstructive pulmonary disease. Their baseline clinical characteristics are listed in Table 1. TAVI was accomplished via transfemoral access in 179 patients (98.3%), and transsubclavian access in 3 (1.7%) with severe peripheral artery disease. The 23-, 26-, 29- and 31-mm CoreValve ReValving systems were implanted in 17 (9%), 85 (47%), 78 (43%), and 2 (1%) patients, respectively, under local anesthesia and conscious sedation in the majority of cases (85%). All-cause and cardiovascular in-hospital mortality was 3.8% and 1.6%, respectively. A permanent pacemaker was implanted in 22.5% (n = 41), in most cases due to advanced atrio-ventricular block. Acute kidney injury (AKI) occurred in 47 patients (25.8%; class 1, 2, or 3 in 31, 8, and 8 patients, respectively), life-threatening bleeding in 11 (6%) and cerebrovascular events in 3 (1.64%). At 1 month, NYHA functional class improved in all discharged patients, with 95 (52.2%) of them achieving class I, class II (n = 76, 41.7%) or III (n = 4, 2.2%) (Figure 1). A clinical follow-up was available in all patients. Overall, 111 patients (61%) died over an average follow-up of 1,026 ± 812 days (median, IQR: 745, 477 to 1,400 days), with the longest follow-up being 3,942 days. All-cause mortality increased from 15.3% at 1 year to 61% at 11 years. Of 111 deaths, 74 (66.6%) were noncardiovascular. The overall rate of neurological events (1 case of fatal stroke) was 4.9%, with most of them occurring early after TAVI. During the follow-up, 99 patients (54.4%) were re-hospitalized: 78 (42.8%) for recurrent heart failure (considering only the first episode) and 21 (11.5%) for permanent pacemaker implantation, 2 of whom received a cardiac resynchronization therapy for symptomatic heart failure. The remarkable functional improvement observed at 1-month in the majority of patients was maintained over time (Figure 1). At Cox analysis, the STS score (HR: 1.55; 95% CI: 1.20 to 1.99; p = 0.001), left ventricular ejection fraction <40% (HR: 1.65; 95% CI: 1.09 to 2.49; p = 0.017), and AKI (HR: 1.96; 95% CI: 1.30 to 2.94; p = 0.001) were all independently associated with all-cause mortality. At STS score-stratified Kaplan-Meier analysis, survival curves diverged remarkably, early and progressively over the whole follow-up

Table 1
Baseline clinical characteristics

Age (years)	82.9±5.95
Man	80 (44%)
BMI (Kg/m^2)	24.8±3.7
Society of Thoracic Surgeons PROM score	5.50 ± 4.13
Logistic-EuroScore	20.2 ± 13.7
NYHA III-IV class	154 (84.6%)
Diabetes mellitus	43 (24%)
Dyslipidemia	50 (27.4%)
Hypertension	113 (62%)
Smoker	12 (6.6%)
Prior stroke	7 (3.8%)
Prior myocardial infarction	24 (13%)
Prior coronary artery bypass graft	13 (7%)
Prior percutaneous coronary intervention	45 (25%)
Prior chronic kidney disease	43 (24%)
Peripheral artery disease	18 (11%)
Severe chronic obstructive pulmonary disease	34 (18%)

Values are expressed as mean ± SD or n (%).

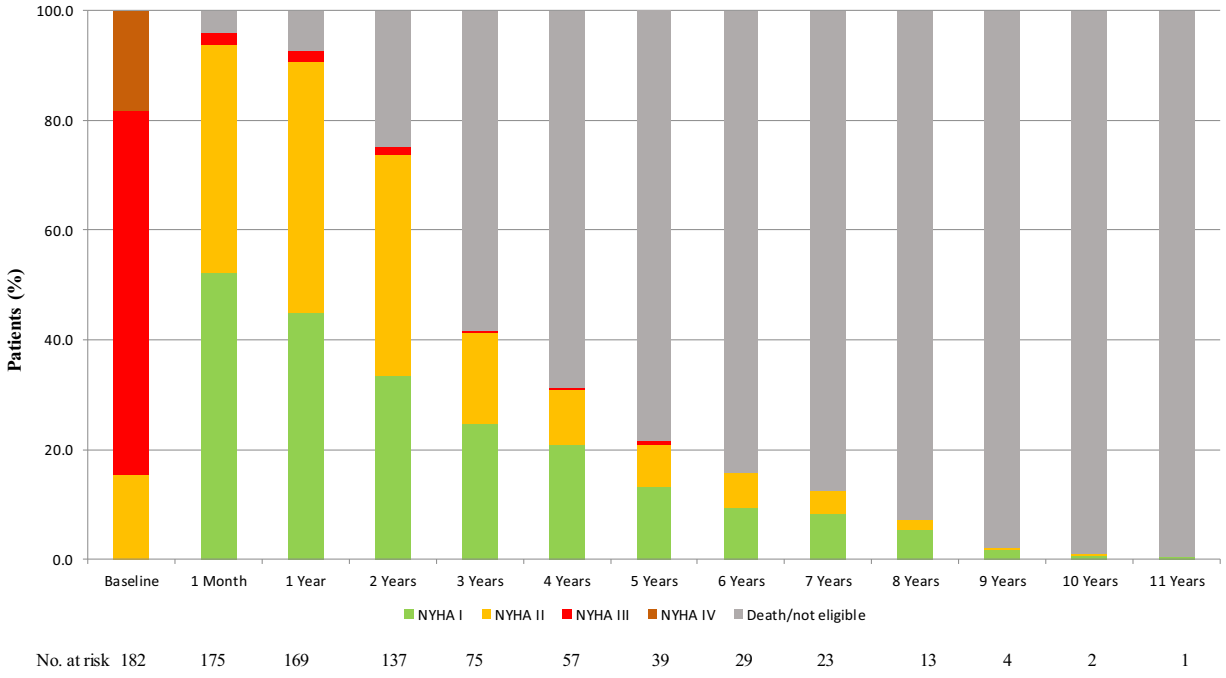

Figure 1. New York Heart Association (NYHA) class changes over time.

(log-rank p <0.0001) (Figure 2). The average echocardiographic follow-up was 1,011 ± 809 days (median, IQR: 743, 456 to 1,391 days). Overall, 23, 13, 2, and 1 patient completed the echo follow-up at 7, 8, 9, 10, and 11 years (29.1%, 18.0%, 5.5%, 2.8%, and 1.4% of survivors, respectively). Mean aortic pressure gradient decreased from 50.4 ± 15.9 mm Hg to 9.0 ± 2.7 mmHg at first in-hospital assessment after TAVI (p <0.001), and did not change long-term in survivors (Figure 3). First TTE after TAVI revealed moderate PVL in 15 (8%) patients, and no case of severe PVL. In the remaining patients none (n = 29, 16%), trivial (n = 32, 18%), or mild PVL (n = 105, 58%) was revealed after TAVI and no significant difference was observed in alive patients during long-term follow-up (Figure 4). Overall, 3 (1.64%) patients developed late BVF. Assuming that death is a competing risk that prevents the occurrence of BVF, actual analysis resulted in 11-year CIF of 2.9% (95% CI 0.8-10%) (Figure 5). Surgical aortic valve

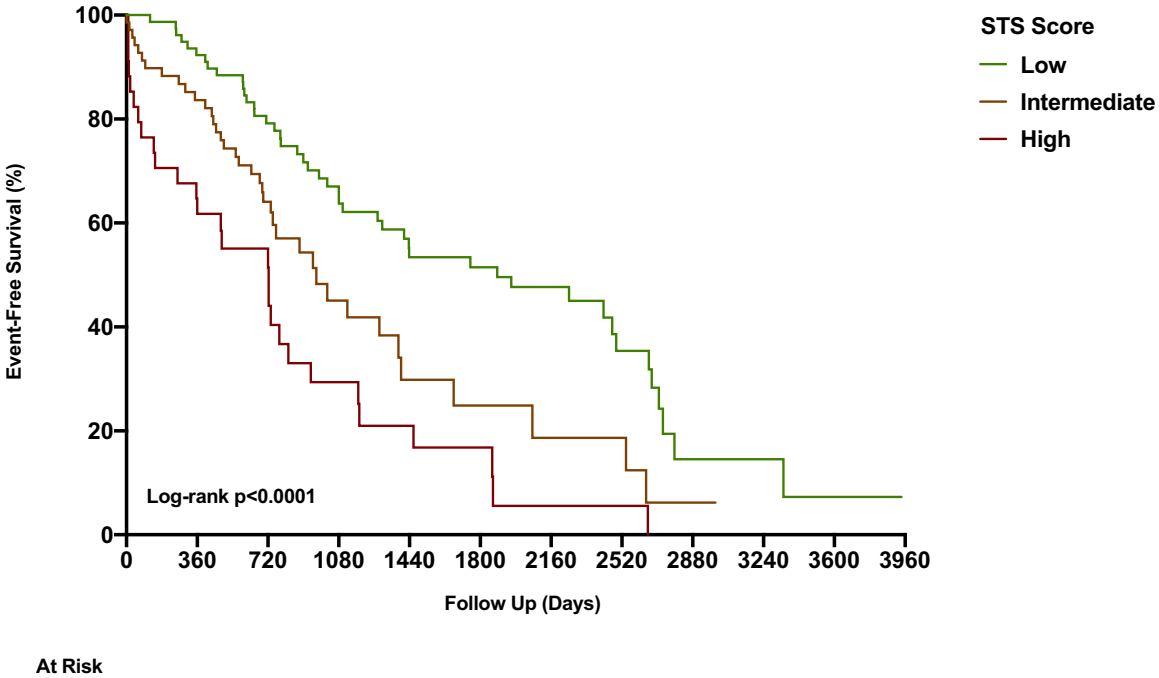

Figure 2. Survival analysis according Society of Thoracic Surgery (STS) low, intermediate and high risk score, log-rank p <0.0001.

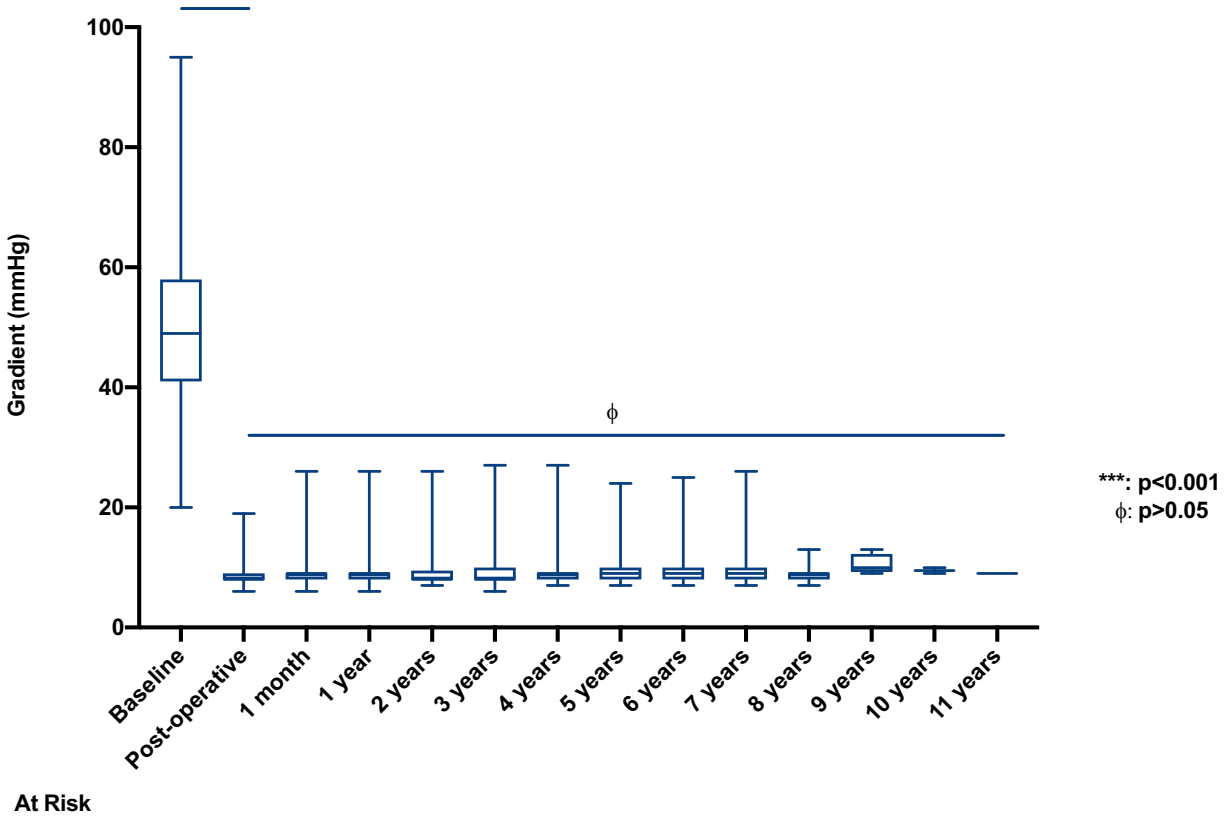

Figure 3. Time course of mean aortic gradient. Box plots indicate the distribution of the mean gradient values at the different time points based on 5 numbers summary (minimum, 25th percentile, median, 75th percentiles, and maximum) and average (rhombus). *** comparison of mean aortic gradient before and after transcatheter aortic valve replacement (TAVR), and Φ throughout the follow-up.

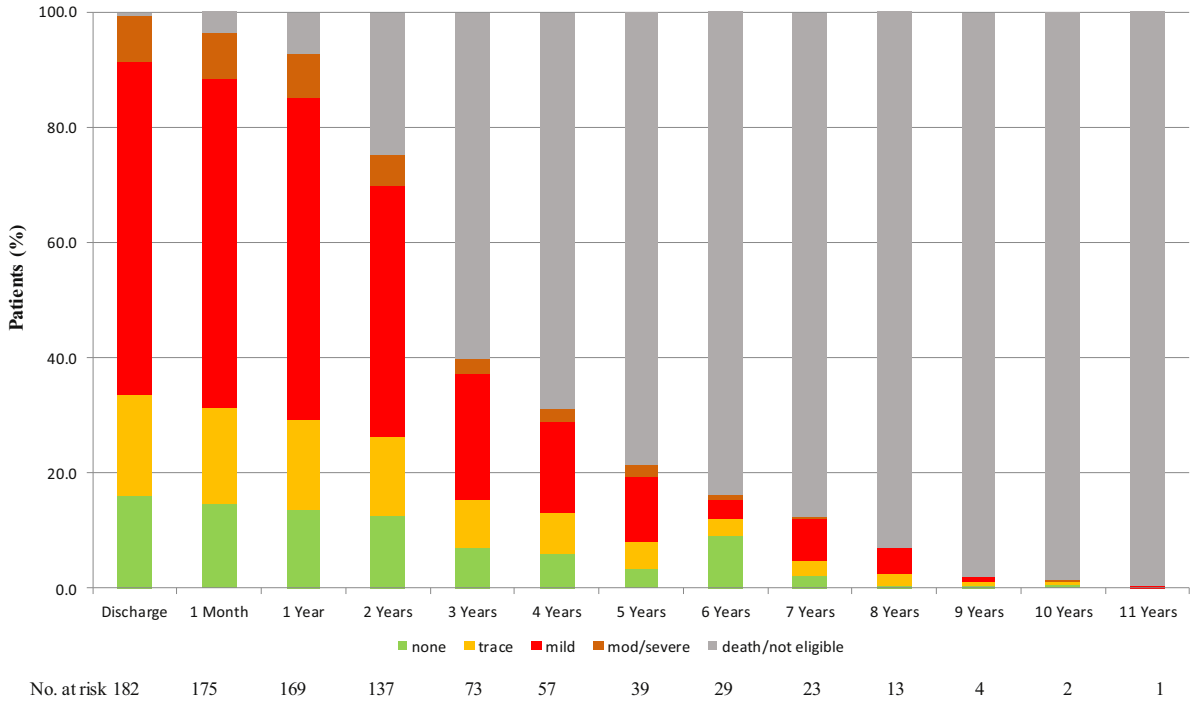

Figure 4. Time course of different degree of perivalvular leak (PVL) after transcatheter aortic valve replacement (TAVR) during follow-up.

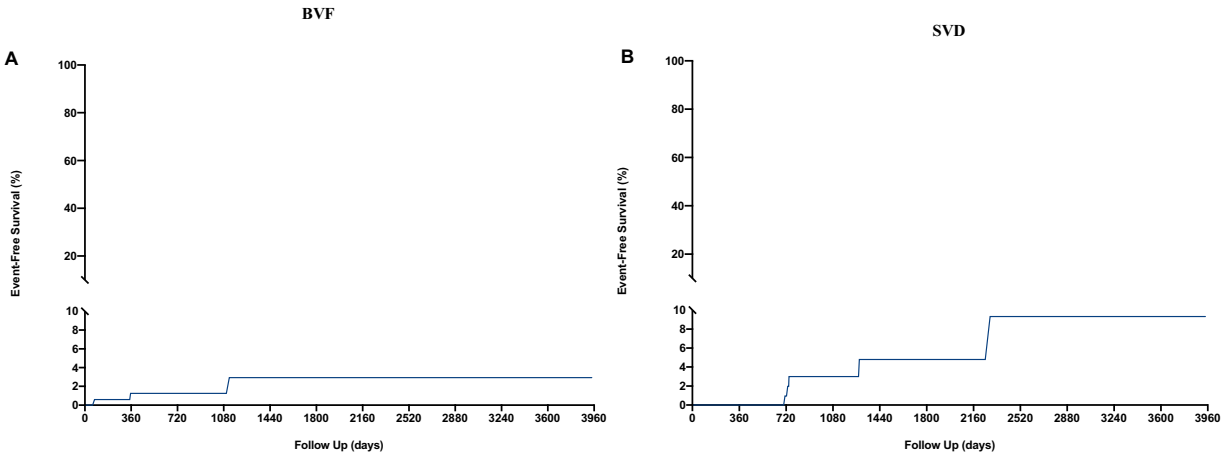

Figure 5. **(A)** Cumulative incidence function of bioprosthesis valve failure (BVF) and **(B)** moderate structural valve deterioration (SVD) according to the competing risk analysis including the risk of death.

replacement was needed in 1 decompensated BVF patient, 236 days after TAVI, due to prosthesis migration (31-mm CoreValve) determining an aortic pseudo-aneurism. This patient died 4 years after surgery. A second BVF patient was admitted to a community hospital for recurrent heart failure 65 days after TAVI. This is a case of low-flow low-gradient aortic stenosis with severe LV systolic dysfunction, dobutamine responder, successfully treated with a 26-mm CoreValve. After 1 month, the mean valvular aortic gradient, checked in our hospital, was 26 mm Hg. This patient died in hospital 95 days after TAVI and was classified as a valve-related death. The last decompensated BVF patient, was admitted to our hospital 126 days after TAVI, showing a progression from moderate to severe mitral regurgitation due to interference of aortic bioprosthesis (31-mm CoreValve) with anterior mitral leaflet. This patient died 1 year after refusing surgery. Late moderate SVD was found in 5 patients (2.7%), accounting for an 11-year CIF of 9.3% (95% CI 3.3 to 26.7%) (Figure 5). At TTE, these patients showed late stenosis with a mean transaortic gradient ranging from 20 to 40 mm Hg (at 377, 401, 749, and 1,034 days, respectively), in 1 case combined with moderate aortic regurgitation (391 days). Of them, 2 had received a 26-, 2 a 29- and the last one a 23-mm CoreValve. No patient with moderate SVD needed re-intervention. In the whole series, no prosthetic valve thrombosis or late valve embolization, nor endocarditis was observed.

DISCUSSION

In our series of 182 TAVI patients, we found that all-cause and cardiovascular mortality rates were respectively 61% and 32.7% over a median follow-up of 1,026 days. Among the major complications, bleeding and stroke occurred mainly in the earliest period after TAVI, while the high rate of early permanent pacemaker implantation continues to increase at follow-up, highlighting one of the main challenges in the TAVI field. Importantly, re-hospitalization due to cardiovascular reasons occurred in more than a half of patients, with recurrent heart failure as the most common cause. In accordance with previous observations,[13] the 30-day STS risk score extended its prognostic value also long-term, likely reflecting the fact that STS incorporates most chronic co-morbidities. Not surprisingly, in our registry baseline left ventricular systolic dysfunction was strongly associated with a poor prognosis after TAVI.[9,14] In accordance with previous observations,[10,11,15] after-procedural AKI was associated with a near 2-fold increase in all-cause mortality, reinforcing the view that any effort should be put in preventing AKI.[11] As TAVI indication moves to younger and lower risk patients with longer life expectancy, the durability of TAVI is an increasingly important issue. Notably, long-term data regarding the durability of TAVI bioprostheses are lacking and frequently hampered by the absence of standardized definitions of BVF and SVD. Gurvitch et al[16] evaluated SVD in 70 TAVI patients and confirmed a good durability of balloon-expandable bioprostheses over a 3.7-year follow-up. Moreover, the PARTNER 1 trial found an unchanged transvalvular gradient and aortic valve area over time.[17] Similarly, Toggweiler et al[18] found favorable outcomes at 5 years after TAVI in 88 patients, with 3.4 signs of moderate prosthetic valve failure. The durability of self-expandable valves has been explored by the Italian Clinical Service project, which showed a satisfactory 5-year performance with a 1.4% of significant prosthetic valve failure and 2.8% of asymptomatic degeneration with only mild stenosis.[13] More recently, the occurrence of SVD and BVF was evaluated beyond 5 years in 6 studies.[19–24] Overall, at a follow-up of 7 to 8 years, moderate SVD was reported in 3.6% to 14.9%, severe SVD in 0% to 3.8%, and BVF in 0% to 4.5% of cases. Such a wide variability can be ascribed to heterogeneity in studies design and inclusion criteria. Therefore, these observations are of limited generalizability. Our study, among the few with a follow-up extending well beyond 5 years and, most importantly, using the recommended, standardized definitions of both BVF and SVD,[9] found a good long-term performance of self-expandable CoreValve, resulting in an actual cumulative incidence of 2.9% and 9.3% for BVF and SVD, respectively. Despite these encouraging data, before TAVI indications can be routinely extended to younger patients

with longer life expectancy, any effort should be put to reduce the rate of BVF and SVD. In accordance with results of the TRAVEL study,[25] in our registry embolization of self-expandable bioprostheses was never observed, while the migration occurred. On the other hand, the use of self expanding or first generation valve are a well known independent predictor of migration of bioprostheses valve, as well as the presence of bicuspid aortic valve, not included in our registry.[25] Due to the inherent nature of transcatheter heart-valve interaction with the native valve apparatus and the lack of suture-based anchoring, the risk of embolization and migration will remain part of the TAVI procedure, and should be carefully monitored during follow-up echocardiography. For the same reasons, the occurrence of PVL after TAVI should be monitored, due to its uncertain prognostic significance.[26] The high 8% moderate PVL rate emerging from our registry in comparison to the 3.4% reported using new CoreValve generation (Evolute R and Evolute Pro)[27] can be explained by the non-routinely use of computed tomography scan for more precise valve sizing in the early phase of our TAVI experience, together with later technological advances, including design changes, recapturability and, more recently, the addition of an external pericardial wrap for an advanced sealing. Finally, the performance of bioprosthetic valves in our and previous studies appear reassuring and may compare favorably with the outcome of surgically implanted bioprostheses, which proved to be free of structural failure in >95% and in 60% to 90% of cases at 5[28] and 10 years,[29] respectively. However, the heterogeneous definitions of SVD deterioration and the younger age of patients included in previous surgical studies make comparisons with transcatheter valves durability inappropriate, given the well-known inverse relation between age and SVD. Recently, the 6-year outcome of NOTION trial have demonstrated similarly low BVF rates but a higher rate of SVD in surgical in comparison to transcatheter arm (24% vs 4.8%, p <0.001).[30] We recognized several limitations of our observational, single center registry. First, our results might be biased by a learning curve, as this registry started in year 2009. Second, the echocardiographic data have not been reviewed by an independent core laboratory. In addition, the number of survivors with an echocardiographic follow-up after 7-year was relatively small. However, this is a limitation inherent to whatsoever clinical registry, due to the expectedly high mortality rate of sicker and older patients receiving TAVI. To limit the bias resulting from competing risk of mortality, we calculated both actuarial and actual estimates, as recommended by the European consensus statement.[9] Finally, no thrombosis of bioprosthetic valve was detected in our study, although the sensitivity of TTE in detecting thrombosis valve is limited. Despite these limitations, our results suggest that TAVI prostheses have such a prolonged durability as to figure out that, in the near future, it may become reasonable to implant them also in younger patients with an expected longer survival. In conclusion, our real-world registry confirmed that TAVI with the self-expandable CoreValve system is associated with favorable clinical outcomes over a follow-up extended to a maximum of 11 years, with a the reassuring low rate of significant BVF and moderate SVD.

Credit Author Statement

Nazario Carrabba: Conceptualization, Validation, Writing original draft preparation, reviewing and editing; Angela Migliorini: Methodology, Investigation, Data curation, Formal analysis; Carlo Fumagalli: Methodology, Investigation, Software, Formal analysis; Matteo Vannini: Methodology, Invastigation, Software, Formal analysis; Niccolò Marchionni: Conceptualization,Writing, Reviewing and Editing; Renato Valenti: Conceptualization, Methodology, Data curation, Reviewing.

Resource Founding

None.

Disclosures

The authors have no conflicts of interest to disclose.

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