Long-Term Outcomes of High-Risk or Inoperable Patients Who Underwent Transcatheter Aortic Valve Implantation

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Few studies have evaluated transcatheter aortic valve implantation (TAVI) beyond 5 years. We investigated long-term outcomes (≥5 years) and transcatheter heart valve (THV) performance in patients who had undergone TAVI at least 5 years previously, based on annual follow-up. We reviewed 114 consecutive patients who were of high surgical risk or inoperable and underwent TAVI for severe aortic stenosis from October 2009 to November 2013. There was no lost to follow-up, and median time to death or latest follow-up was 5.0 years (range: 0.1 to 8.5). Structural valve degeneration (SVD) was defined on transthoracic echocardiography (TTE) as follows: (1) mean pressure gradient ≥20 mm Hg with a >10 mm Hg increase from the post-TAVI baseline, and/or (2) moderate or severe transvalvular regurgitation. The mean patient age was 82.7 ± 6.4 years, and 37.7% of patients were men. Median Society of Thoracic Surgeons score was 7.6% (interquartile range 5.8 to 10.9). TTE ≥5 years was 76.1% complete (51 of 67 patients who survived ≥5 years postoperatively). The estimated cumulative survival rates at 1, 3, 5, and 7 years were 88.6%, 72.8%, 58.8%, and 45.3%, respectively. Albumin <3.5 g/dl was strongly associated with increased long-term mortality on multivariate analysis. Longitudinal TTE confirmed durable performance of THV up to 7 years in the majority of patients; however, 6 patients (5.3% of the total cohort) experienced SVD during the follow-up. In conclusion, this study demonstrated favorable long-term survival and stable THV performance after TAVI, although SVD was not rare. **(Am J Cardiol 2019;124:573−579)**

Transcatheter aortic valve implantation (TAVI) is widely accepted as a therapeutic option to surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis who are not considered good surgical candidates.[1,2] Technical developments have contributed to better TAVI outcomes, including decreased rates of intraprocedural complications, postprocedural aortic regurgitation, and short-term adverse events.[3,4] Several registries and clinical trials have also demonstrated favorable long-term outcomes. The Placement of Aortic Transcatheter Valves trial confirmed a comparable 5-year mortality rate of TAVI to SAVR in high-risk patients, and the superiority of TAVI in comparison to standard treatment in inoperable patients.[5,6] Stable transcatheter heart valve (THV) performance was also confirmed in these studies. Recent randomized trials for balloon-expandable or self-expanding valves demonstrated similar composite rates of death from any cause or stroke during the 2 years between TAVI and SAVR in intermediate surgical-risk patients.[7,8] More centers are applying TAVI for lower surgical-risk patients with longer life expectancy. To date, however, the number of studies investigating TAVI beyond 5 years is limited,[9,10] and data beyond 5 years are needed, including durability data of THV. Here, we investigated the long-term clinical outcomes (≥5 years) and THV performance of patients who underwent TAVI using annual follow-up data at our center.

Methods

We reviewed 114 consecutive patients who underwent TAVI for severe native aortic stenosis from October 2009 to November 2013 at our center. All patients were considered prohibitive or high risk for SAVR and underwent TAVI at least 5 years before this study. Clinical data were prospectively collected from the electronic medical record and entered into the institutional registry. Patients were routinely followed with clinical and transthoracic echocardiography (TTE) evaluation before discharge, and at 1 month, 6 months, 1 year, and yearly thereafter following TAVI. Those who did not visit our center were followed by phone or inquiry to the referring hospital. Finally, every patient had at least 5 years of follow-up without any lost to follow-up. TTE data ≥5 years postoperation were obtained in 51 of 67 patients (76.1%) who survived ≥5 years. Adverse events were judged according to the Valve Academic Research Consortium-2 criteria.[11] The study was approved by the Institutional Review Board of our institution. Written informed consent was obtained from all patients.

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The TAVI procedure was performed in a hybrid operating room under general anesthesia and transesophageal echocardiographic guidance as previously described by our group.[12] Briefly, implanted THVs included balloon-expandable valves, that is, SAPIEN or SAPIEN XT (Edwards Lifesciences, Irvine, California), and self-expanding valves, that is, CoreValve (Medtronic, Minneapolis, Minnesota) or ACURATE neo (Symetis, Ecublens, Switzerland). An on-site dedicated cardiologist assessed for valve positioning and paravalvular leak (PVL) using transesophageal echocardiography, in conjunction with postimplantation aortography and hemodynamic measurements.

Based on recent proposal by Valve-in-Valve International Data (VIVD),[13] structural valve degeneration (SVD) was defined as follows on follow-up TTE assessment: (1) transvalvular mean pressure gradient (PG) ≥20 mm Hg with a >10 mm Hg increase from the post-TAVI baseline, and/or (2) moderate or severe transvalvular regurgitation. These criteria correspond to SVD Stage 2 or 3 in the VIVD definition. The post-TAVI baseline TTE was performed within 7 days after the procedure. We excluded infective endocarditis, THV thrombosis, isolated patient prosthesis mismatch, and PVL from the SVD definition. Four-dimensional computed tomography was used to rule out leaflet thrombosis by assessing for hypo-attenuating leaflet thickening or hypo-attenuation affecting motion.[14] In patients who were planned for transcatheter aortic valve (TAV) implantation inside the first TAV (TAV-in-TAV), transesophageal echocardiography was also performed to confirm the diagnosis of SVD.

Continuous variables are expressed as means ± standard deviation or median (interquartile range). Categorical variables are expressed as absolute numbers and percent values. Time-to-event curves for long-term survival based on all available follow-up data were performed using Kaplan-Meier methods. Cox proportional-hazards regression was used to adjust for the effect of pertinent variables on long-term mortality: age, gender, body mass index (BMI), Society of Thoracic Surgeons score, New York Heart Association classification, chronic dialysis, and albumin. All analyses were 2-sided, and significance was judged at $p < 0.05$. All statistical analyses were performed with JMP software (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics and echocardiographic data of 114 patients are presented in Table 1. TAVI was performed through a trans-femoral (n = 67, 58.8%), transapical (n = 41, 36.0%), trans-subclavian (n = 3, 2.6%), or direct aortic approach (n = 3, 2.6%) with predominant use of balloon-expandable valves (Table 2). THVs and their sizes were as follows: SAPIEN, n = 46 (n = 29 for 23 mm and n = 17 for 26 mm); SAPIEN XT, n = 35 (n = 6 for 20 mm, n = 23 for 23 mm, and n = 6 for 26 mm); CoreValve, n = 25 (n = 3 for 23 mm, n = 15 for 26 mm, and n = 7 for 29 mm); ACURATE neo, n = 8 (n = 4 for 23 mm, n = 3 for 25 mm, and n = 1 for 27 mm). In-hospital mortality was observed in 4 patients (3.5%). A total of 58 (50.9%) patients died during the follow-up period (median time to death or latest follow-up: 5.0 years [range: 0.1 to 8.5]) after TAVI. Of these, 2 (1.8%) deaths occurred within 30 days. The most common reason for death was infection/sepsis (n = 20, 34.5%), followed by cardiac causes (n = 11, 19.0%) and stroke (n = 7, 12.1%; Table 3). After excluding mortality occurring up to 1 year after TAVI, the order was still consistent. The estimated

Table 1
Baseline characteristics

Variable	n = 114
Age (years)	82.7 ± 6.4
Men	43 (38%)
Body mass index (kg/m^2)	22.1 ± 3.5
Society of Thoracic Surgeons score (%)	7.6 [5.8, 10.9]
New York Heart Association III or IV	66 (58%)
Chronic obstructive pulmonary disease	39 (34%)
Diabetes	29 (25%)
Previous stroke	27 (24%)
Peripheral arterial disease	33 (29%)
Chronic dialysis	7 (6.1%)
Liver cirrhosis	6 (5.3%)
Hemoglobin (g/dl)	11.1 ± 1.6
Estimated glomerular filtration rate < 60 ml/min/1.73 m^2	82 (72%)
Albumin < 3.5 g/dl	27 (24%)
Previous myocardial infarction	13 (11%)
Previous coronary artery bypass grafting	16 (14%)
Previous percutaneous coronary intervention	30 (26%)
Permanent pacemaker	7 (6.1%)
Left ventricle ejection fraction < 50%	21 (18%)
Aortic valve mean gradient (mm Hg)	58.2 ±18.8
Aortic valve area (cm^2)	0.63 ± 0.18
Aortic regurgitation ≥ moderate	14 (12%)
Mitral regurgitation ≥ moderate	10 (8.7%)

Table 2
Procedural and in-hospital outcomes

Variable	n = 114
Valve type	
Balloon-expandable	81 (71%)
Self-expanding	33 (29%)
Femoral access	67 (59%)
Emergent open heart surgery	2 (1.8%)
Second valve deployed	2 (1.8%)
Stroke	7 (6.1%)
Myocardial infarction	5 (4.4%)
Life-threatening or major bleeding	13 (11%)
Vascular complications	
Major	6 (5.3%)
Minor	5 (4.4%)
New permanent pacemaker implantation	20 (18%)
In-hospital mortality	4 (3.5%)

Table 3
Causes of mortality

Variable	Overall (n = 58)	≤1 year (n = 13)	>1 year (n = 45)
Infection/Sepsis	20 (35%)	4 (31%)	16 (36%)
Cardiac causes	11 (19%)	4 (31%)	7 (16%)
Stroke	7 (12%)	1 (7.7%)	6 (13%)
Cancer	6 (10%)	2 (15%)	4 (8.9%)
Renal failure	2 (3.4%)	1 (7.7%)	1 (2.2%)
Hepatic failure	2 (3.4%)	0 (0.0%)	2 (4.4%)
Others	8 (14%)	1 (7.7%)	7 (16%)
Unknown	2 (3.4%)	0 (0.0%)	2 (4.4%)

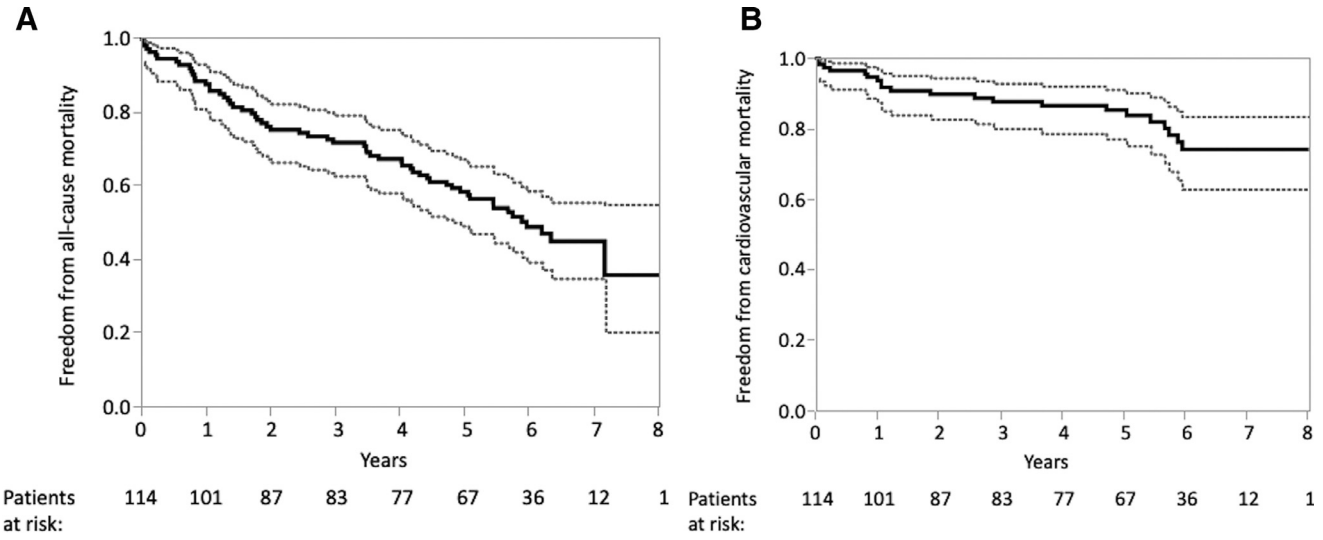

Figure 1. Kaplan-Meier curves for survival estimates. (*A*) Freedom from all-cause mortality. (*B*) Freedom from cardiovascular mortality.

cumulative survival rates at 1, 3, 5, and 7 years were 88.6%, 72.8%, 58.8%, and 45.3%, respectively, as calculated by Kaplan-Meier analysis (Figure 1). A curve for freedom from cardiovascular mortality during the follow-up period is shown in Figure 1.

The unadjusted and multivariate-adjusted effects of baseline or procedural variables on long-term mortality are presented in Table 4. Lower BMI and low serum albumin level (<3.5 g/dl) were significantly associated with increased mortality on univariate analysis. After adjustment using these variables and other clinically important variables such as age, gender, Society of Thoracic Surgeons score, New York Heart Association classification, and chronic dialysis, only the low serum albumin level (adjusted hazard ratio 2.44; 95% confidence interval [CI] 1.33 to 4.31; p = 0.0047) was significantly predictive of long-term mortality. Additionally, procedural outcomes such as new permanent pacemaker implantation (p = 0.24)

Table 4
Unadjusted and adjusted baseline or procedural risk factors for long-term mortality

Variable	Hazard ratio (95% confidence interval)	p value	Adjusted hazard ratio (95% confidence interval)	p value
Age (years)	1.00 (0.96−1.05)	0.84	1.01 (0.96−1.06)	0.82
Men	1.61 (0.95−2.70)	0.075	1.55 (0.87−2.73)	0.13
Body mass index (kg/m^2)	0.91 (0.84−0.99)	0.036	0.94 (0.85−1.03)	0.16
Society of Thoracic Surgeons score (%)	1.03 (1.00−1.06)	0.081	1.01 (0.97−1.05)	0.48
New York Heart Association III or IV	1.45 (0.85−2.55)	0.17	1.32 (0.75−2.39)	0.35
Chronic obstructive pulmonary disease	0.82 (0.46−1.41)	0.49		
Diabetes	1.19 (0.65−2.07)	0.57		
Previous stroke	0.95 (0.50−1.69)	0.87		
Peripheral arterial disease	1.12 (0.63−1.92)	0.70		
Chronic dialysis	2.22 (0.77−5.08)	0.13	2.45 (0.77−6.55)	0.12
Liver cirrhosis	2.05 (0.62−5.04)	0.21		
Hemoglobin (g/dl)	0.90 (0.76−1.05)	0.19		
Estimated glomerular filtration rate < 60 ml/min/1.73 m^2	1.36 (0.76−2.63)	0.32		
Albumin < 3.5 g/dl	2.60 (1.46−4.49)	0.0016	2.44 (1.33−4.31)	0.0047
Previous myocardial infarction	1.10 (0.45−2.27)	0.82		
Previous coronary artery bypass grafting	0.77 (0.32−1.59)	0.50		
Previous percutaneous coronary intervention	1.22 (0.67−2.11)	0.50		
Prior permanent pacemaker	1.89 (0.66−4.31)	0.21		
Left ventricle ejection fraction < 50%	1.52 (0.79−2.75)	0.20		
Aortic valve mean gradient (mm Hg)	1.00 (0.98−1.01)	0.56		
Aortic valve area (cm^2)	0.68 (0.16−2.61)	0.59		
Aortic regurgitation ≥ moderate	0.88 (0.36−1.81)	0.74		
Mitral regurgitation ≥ moderate	1.76 (0.72−3.64)	0.19		
Valve type (balloon-expandable)	1.59 (0.88−3.08)	0.13		
Femoral access	0.86 (0.51−1.46)	0.58		

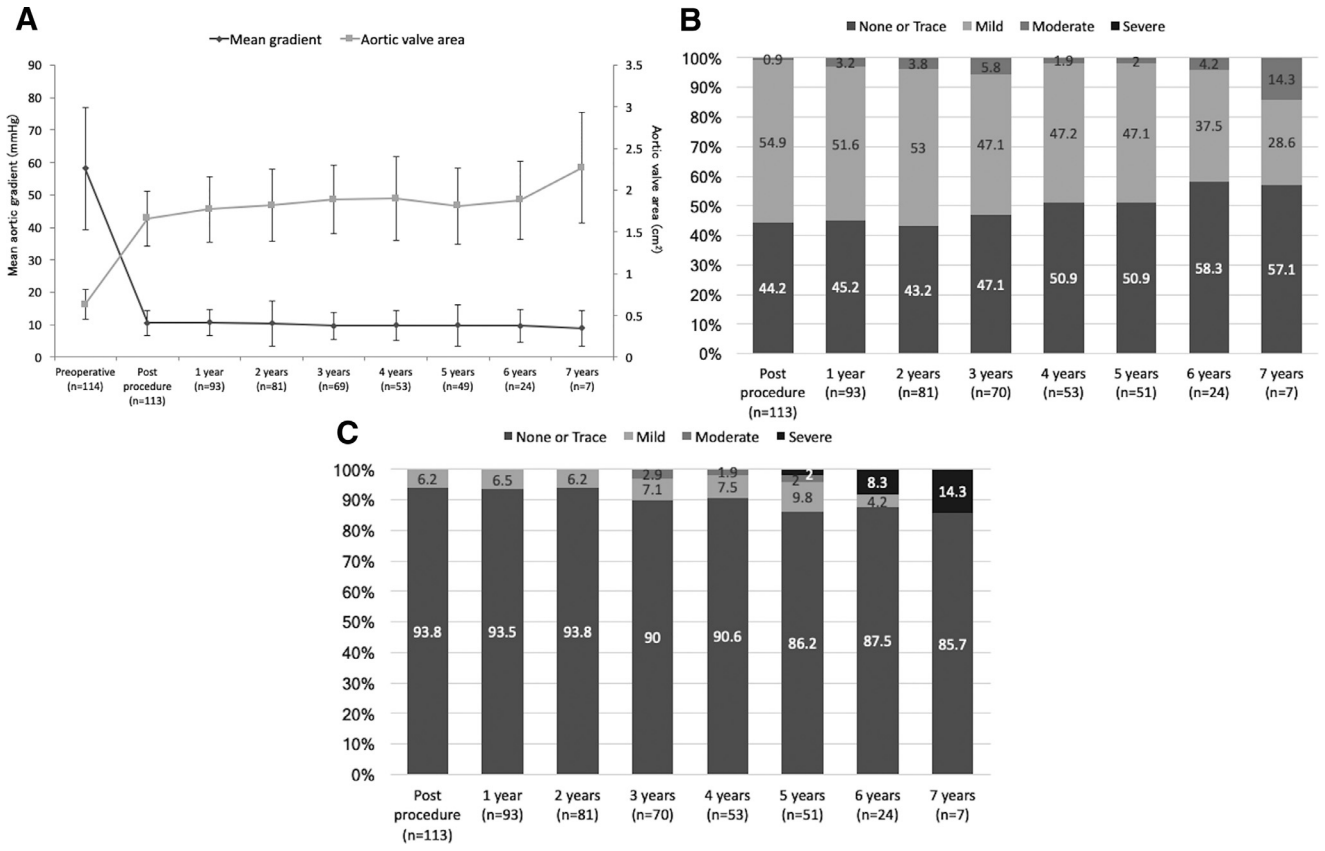

Figure 2. Transcatheter heart valve performance. (*A*) Mean aortic gradient and aortic valve area. (*B*) Paravalvular leak. (*C*) Transvalvular leak.

and PVL ≥mild (p = 0.13) were not associated with an increased hazard of mortality on univariate analysis.

TTE follow-up data were obtained in 51 patients ≥5 years after TAVI: 51 patients at 5 years (effective orifice area and mean PG were not available in 2 patients), 24 patients at 6 years, and 7 patients at 7 years. The chronology of changes in THV performance is shown in Figure 2. The effective orifice area and mean transvalvular PG remained unchanged throughout the follow-up period. The frequency of PVL or transvalvular regurgitation ≥moderate was very low at post-TAVI baseline (0.9% and 0.0%, respectively), and the severity remained stable. However, 2 patients underwent TAV-in-TAV due to increasing PVL and device migration 17 days and 6 months after the first TAVI, respectively. Six patients (5.3% of the total cohort) experienced SVD during the follow-up period. One patient was on chronic dialysis. Detailed TTE follow-up data in each patient are shown in Table 5. Four patients had SVD of balloon-expandable valves, which was diagnosed 2 to 5 years after the procedure, and the mode of degeneration was equally distributed for either stenosis or regurgitation. In the 2 patients with self-expanding valves, both had severe transvalvular regurgitation 6 years postoperatively. Four symptomatic patients underwent TAV-in-TAV by compassionate use. The other 2 patients with SVD were asymptomatic and treated medically. The estimated rates of SVD at 5 and 7 years were 5.6% (95% CI 2.1 to 14.2) and 11.1% (95% CI 4.7 to 24.1), respectively, using Kaplan-Meier actuarial analysis.

Discussion

This study produced 3 primary findings. First, patients who had prohibitive or high surgical risk showed favorable long-term survival rates of 58.8% for 5 years and 45.3% for 7 years after the TAVI procedure. Second, multivariate analysis in our registry demonstrated that a low serum albumin level of <3.5 g/dl was the only strong predictor of poorer long-term survival. Third, THV hemodynamics was stable up to 7 years in most patients, whereas 5.3% of patients experienced SVD with ≥moderate stenosis or regurgitation.

Our study demonstrated a higher 5-year survival rate than previous studies. For example, the studies from Italian and Canadian centers involving early TAVI patients demonstrated 35% to 45% survival at 5 years.[15,16] Seven years data are available in a few studies that reported survival rates from 23% to 35%,[9,10] which was lower than our result of 45% at 7 years. One reason for this observation may be the difference in study period. We may have applied multislice computed tomography more for TAVI planning in the most recent patients who underwent TAVI from 2009 to 2013, leading to better outcomes after the procedure. This is supported by the lower rate of significant PVL (≥moderate) in the current study than that in previous studies. Robust association between PVL presence and poorer prognosis after TAVI has been confirmed by large clinical trials and meta-analyses.[17]

Table 5
Transthoracic echocardiography follow-ups among patients with structural valve degeneration

	Age /Gender	Transcatheter aortic valve	Transthoracic echocardiography follow-up								Treatment
			Parameter	Post	1 year	2 years	3 years	4 years	5 years	6 years	7 years	
1	83	SAPIEN XT	Mean gradient (mm Hg)	16	15	10	9	9	46			TAV-in-TAV
	Female	23 mm	Transvalvular leak	None	None	None	None	None	None			
2	84	SAPIEN XT	*Peak velocity (m/s)	2.0			2.2		2.3			Medication
	Female	23 mm	Transvalvular leak	None			Severe		Severe			
3	80	CoreValve	Mean gradient (mm Hg)	10	10	13	9	8	7	13	12	Medication
	Male	29 mm	Transvalvular leak	Mild	Mild	Trace	None	None	Trace	Severe	Severe	
4	89	CoreValve	Mean gradient (mm Hg)	9	10	5	6	8	8	9		TAV-in-TAV
	Male	26 mm	Transvalvular leak	None	None	Trace	Trace	Trace	Mild	Severe		
5	86	SAPIEN	Mean gradient (mm Hg)	13	11	9	10	10	13			TAV-in-TAV
	Female	23 mm	Transvalvular leak	None	None	None	Moderate	Moderate	Severe			
6	76	SAPIEN	Mean gradient (mm Hg)	20	16	62						TAV-in-TAV
	Male	23 mm	Transvalvular leak	Trace	Mild	Mild						

* Mean pressure gradient was not available.

Low serum albumin has been demonstrated as a risk factor associated with poorer 30-day and 1-year survival across several studies with a cut-off value of 3.3 to 4.0 g/dl.[18–20] Frailty is currently widely used as a tool for patient selection, risk prediction, and postprocedural care under the multidisciplinary Heart Valve Team approach for TAVI. Valve Academic Research Consortium-2 considers frailty as a patient characteristic to be included in the risk models of TAVI, and serum albumin <3.5 g/dl is listed as one of the frailty criteria.[11] Multicenter registry demonstrated that hypoalbuminemia (defined as serum albumin level <3.5 g/dl) was associated with an increased risk of mortality during a median follow-up of 330 days, driven by a higher incidence of non-cardiovascular mortality than nonhypoalbuminemia.[20] Our study revealed that hypoalbuminemia remains predictive of mortality even in long-term follow-up of ≥5 years. This in turn suggests that despite a successful procedure, impaired functional recovery and a malnourished condition of frail patients continue to exert influence over a long time. These patients are thus more likely to develop infectious diseases, which were the most frequent cause of mortality in this study.

Several studies evaluating THV performance with ≥5-year follow-up were recently published.[10,21,22] The data from the Placement of Aortic Transcatheter Valves trial and its continued-access observational studies showed favorable durability of THV up to 5 years with minimal longitudinal changes in aortic valve mean gradient, effective orifice area, and Doppler velocity index in 2,482 patients.[23] Re-interventions due to SVD of THV occurred in only 5 patients. A recent meta-analysis assessing risk of SVD reported rates that ranged widely from 0 to 1.34 per 100 patient-years across 13 studies with median follow-ups from 1.6 to 5 years.[24] The pooled incidence of SVD in 8,914 patients was 28.08 per 10,000 patient-years (95% CI 2.46 to 73.44). More recently, an observational study demonstrated a 3.2% SVD rate among patients followed for up to 11 years (median, 3.1 years).[22] This inconsistency of the rates among studies may have derived from the nonuniform definitions of SVD: some studies simply used a fixed cut-off point of aortic valve mean PG, leading to a relative overdiagnosis of SVD in patients with patient prosthesis mismatch at the post-TAVI baseline, whereas others adopted an increase in mean PG >10 mm Hg from the post-TAVI baseline as a definition of SVD. Our present study utilized the recent proposal by the VIVD (SVD Stage 2 or 3) that includes both mean PG ≥20 mm Hg and >10 mm Hg increase from the post-TAVI baseline. Despite our relatively strict definition of SVD, we demonstrated a higher SVD rate (5.3%) than these previous reports. A potential explanation may be our better survival rate: more patients were alive for long-term TTE screening, and thus more SVDs could be detected. Additionally, patients in our study had lower BMI and were consequently implanted with smaller THVs than those in previous studies.[22,23] This may have also influenced the durability of THV.

Large studies have evaluated the long-term durability of recent surgical bioprosthetic valves. The Hancock II (Medtronic) porcine valve showed actuarial estimates of freedom from SVD in 1,134 patients at 5, 10, and 20 years of 99.7%, 97.6% and 63.4%, respectively.[25] In the report of

Carpentier-Edwards Perimount (Edwards Lifesciences) pericardial valve involving 2,659 patients, actuarial freedom from SVD at 15 and 20 years was 78.6% and 48.5%, respectively.[26] Only 6 cases of SVD arose within the first 5 years after the operation. These excellent durability data of recent surgical bioprostheses, together with our relatively high SVD rate, indicate that the application of TAVI should be carefully expanded to younger patients at lower surgical risk. Finally, results from larger studies, alongside ongoing clinical trials, are awaited to determine the durability of THV.

The present study is limited by its relatively small sample size. The long-term risk of SVD was assessed in a limited number of patients, although our survival rate (58.8% at 5 years) was much better than previous studies. There was no external core laboratory. Thus, implanted THV performance was evaluated by an institutional cardiologist and specialized sonographers. Most of the patients included in this study received first-generation THVs. Newer-generation devices have a different frame design and include sealing skirts to eliminate significant PVL. Thus, the results on long-term THV performance cannot be immediately interpreted into the current clinical practice. Finally, the data were from the initial TAVI experience of the physicians and Heart Valve Team at a single center. A learning curve may have influenced the outcomes, including the durability of THV.

In conclusion, this study demonstrated favorable long-term outcomes (≥5 years) in high-risk or inoperable patients who underwent TAVI. THV performance was stable in most patients, whereas SVD with ≥moderate THV stenosis or regurgitation was detected in 5.3% of patients.

Disclosures

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