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FASTTRACK CLINICAL RESEARCH

Long-term outcomes after transcatheter aortic valve implantation in failed bioprosthetic valves

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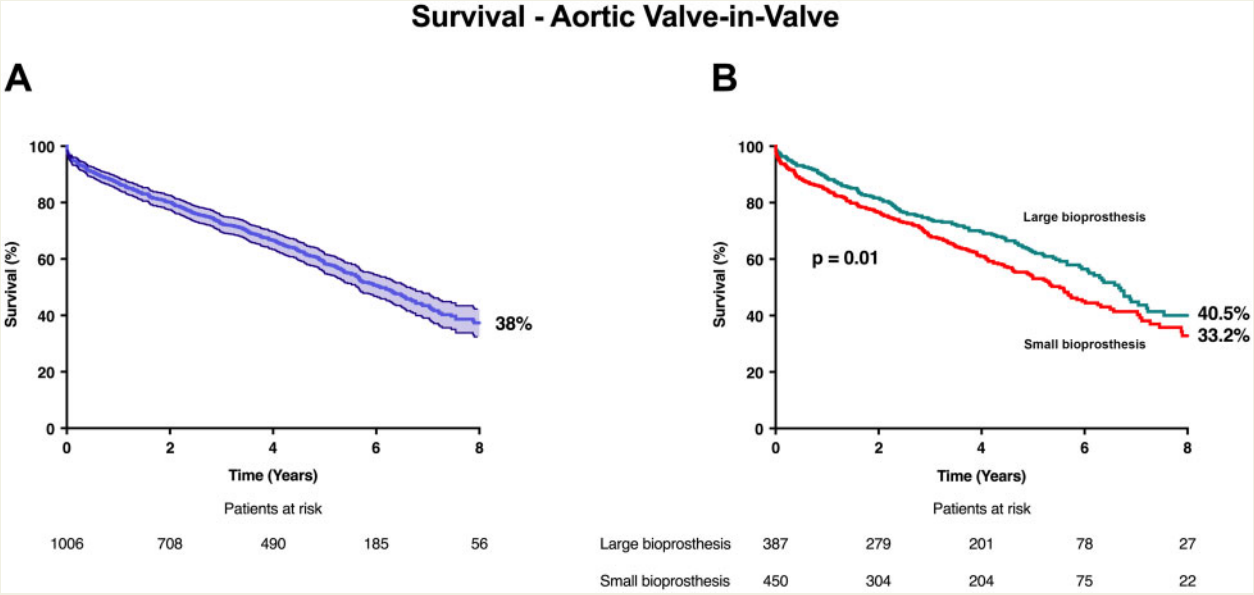
Aims Due to bioprosthetic valve degeneration, aortic valve-in-valve (ViV) procedures are increasingly performed. There are no data on long-term outcomes after aortic ViV. Our aim was to perform a large-scale assessment of long-term survival and reintervention after aortic ViV.

Methods and results A total of 1006 aortic ViV procedures performed more than 5 years ago [mean age 77.7 ± 9.7 years; 58.8% male; median STS-PROM score 7.3% (4.2–12.0)] were included in the analysis. Patients were treated with Medtronic self-expandable valves (CoreValve/Evolut, Medtronic Inc., Minneapolis, MN, USA) ($n = 523$, 52.0%), Edwards balloon-expandable valves (EBEV, SAPIEN/SAPIEN XT/SAPIEN 3, Edwards Lifesciences, Irvine, CA, USA) ($n = 435$, 43.2%), and other devices ($n = 48$, 4.8%). Survival was lower at 8 years in patients with small-failed bioprostheses [internal diameter (ID) ≤ 20 mm] compared with those with large-failed bioprostheses (ID > 20 mm) (33.2% vs. 40.5%, $P = 0.01$). Independent correlates for mortality included smaller-failed bioprosthetic valves [hazard ratio (HR) 1.07 (95% confidence interval (CI) 1.02–1.13)], age [HR 1.21 (95% CI 1.01–1.45)], and non-transfemoral access [HR 1.43 (95% CI 1.11–1.84)]. There were 40 reinterventions after ViV. Independent correlates for all-cause reintervention included pre-existing severe prosthesis–patient mismatch [subhazard ratio (SHR) 4.34 (95% CI 1.31–14.39)], device malposition [SHR 3.75 (95% CI 1.36–10.35)], EBEV [SHR 3.34 (95% CI 1.26–8.85)], and age [SHR 0.59 (95% CI 0.44–0.78)].

Conclusions The size of the original failed valve may influence long-term mortality, and the type of the transcatheter valve may influence the need for reintervention after aortic ViV.

Graphical Abstract



Keywords TAVR • Aortic valve-in-valve • Reintervention • Severe prosthesis–patient mismatch • SAPIEN valve

Introduction

An increase in the use of bioprosthetic tissue valves has been observed in the last decades.[1,2] Although bioprostheses offer the advantage of avoiding lifetime anticoagulation, their durability is limited.[3] A rapidly growing number of bioprostheses will thus require reintervention over time for the treatment of structural valve degeneration (SVD). Transcatheter aortic valve-in-valve (ViV) implantation in failed bioprosthetic valves is an effective therapy with a large worldwide experience.[4–6] Nevertheless, aortic ViV is associated with several adverse events including residual stenosis and coronary obstruction.[7–11] Long-term transcatheter aortic ViV outcome data, beyond 3 years of follow-up, are limited. The objective of this study was to perform a large-scale comprehensive assessment of long-term survival and reintervention outcomes after transcatheter aortic ViV, with the goal of identifying independent correlates for these endpoints following the procedure.

Methods

Data collection and registry

The VIVID Registry is an international multicentre collaboration including over 180 centres from the Americas, Europe, Middle East, Asia, Africa and Oceania.[4] Patient information is collected in a secure online form. All patients gave informed consent to a ViV procedure and were included in the VIVID Registry after local institutional review board approval. The study was conducted in accordance to the Declaration of Helsinki. Inconsistencies and missing information in the dataset were resolved with local investigators after direct contact from Registry personnel.

The current analysis was a retrospective cross-sectional evaluation and was designed after several investigator-directed meetings [Paris (May 2018), San Diego (September 2018), and Paris (May 2019)]. Between July and December 2019, we contacted all centres included in the VIVID Registry that performed ViV cases before 31 December 2014 (i.e. 5 years before 2019) requesting recent clinical follow-up and echocardiographic data using a dedicated case report form.

Definitions

The primary endpoint for this analysis was patient survival, and the main secondary endpoint was all-cause reintervention. All-cause reintervention was defined as all-cause repeat transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) after the index ViV procedure, regardless of the aetiology. Structural reintervention included only patients who underwent redo TAVR or SAVR for degeneration of the implanted tissue valve after excluding cases with either endocarditis and/or thrombosis. The mechanism for bioprosthetic valve failure was classified according to criteria from the American Society of Echocardiography.[12] Cases with at least a moderate degree of both stenosis and regurgitation were included in the mixed category. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate ≤60 mL/min/1.73 m^2. Edwards balloon-expandable valves (EBEV, $n = 435$) in the current analysis included the Cribier-Edwards, SAPIEN, SAPIEN XT and the SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA). Medtronic self-expandable valves (MSEV, $n = 523$) included the CoreValve and the Evolut valve (Medtronic Inc., Minneapolis, MN, USA). Other valves ($n = 48$) included Portico ($n = 19$; Abbott Vascular, Menlo

Park, CA, USA), Engager ($n = 10$; Medtronic Inc.), Symetis Acurate ($n = 9$; Boston Scientific, Marlborough, MA, USA), JenaValve ($n = 7$; JenaValve Technology Inc., Munich, Germany), Melody ($n = 2$; Medtronic Inc.), and Lotus ($n = 1$; Boston Scientific). Major clinical endpoints were assessed according to the Valve Academic Research Consortium II (VARC II) criteria.[13] Body surface area (BSA) was calculated according to the Mosteller formula.[14] Pre-existing severe prosthesis–patient mismatch (PPM) of the bioprosthetic valve was also defined according to VARC II criteria, namely: indexed effective orifice area (EOA) ≤ 0.65 cm^2/m^2 for non-obese patients (body mass index < 30 kg/m^2) and indexed EOA ≤ 0.60 cm^2/m^2 for obese patients (body mass index ≥ 30 kg/m^2). The predicted EOA of bioprosthetic valves was derived from the normal reference values for different models and sizes previously published.[15] True internal diameter (ID) for each bioprosthetic valve, when available, was derived from previous publications.[16] Malposition was operator-reported and defined as inadequate final position of the transcatheter heart valve (THV) for any cause. Small bioprosthetic valves were defined as true ID ≤ 20 mm and, conversely, large bioprosthetic valves were defined as true ID >20 mm.[17] Structural valve degeneration was defined according to current standardized definitions.[18,19]

Statistical analysis

Results are presented as mean ± standard deviation for continuous variables with normal distribution, median [interquartile range (IQR), 25th to 75th percentiles] for continuous variables without normal distribution, and number (percentage) for categorical data. Student's *t*-test was used to compare normally distributed continuous variables between two groups. When more groups were involved, one-way analysis of variance (ANOVA) was used. Tukey's honest significant difference test was used for *post hoc* evaluation of ANOVA results, as appropriate. The Mann–Whitney *U* test (two groups) and the Kruskal–Wallis test (three groups) were used for non-normally distributed variables. The χ^2 and Fisher's exact tests were used to compare categorical variables as appropriate. Time-to-event curves utilized the Kaplan–Meier method, and results were compared with the log-rank statistic. Time-to-event curves were truncated at the last time-point with ≥5% of patients still at risk. Cox regression was utilized to establish independent correlates for long-term survival. A Fine and Gray[20] cause-specific subdistribution hazards model was used for reintervention analysis, given the competing risk of mortality. The following parameters were evaluated in the univariable analyses: age, gender, New York Heart Association (NYHA) functional class IV, stented bioprosthetic valve (vs. stentless), pre-existing severe PPM, stenosis as the mechanism of bioprosthetic valve failure, diabetes mellitus (DM), permanent pacemaker at baseline, peripheral vascular disease (PVD), CKD, history of stroke, EBEV (vs. MSEV), transfemoral access, general anaesthesia, malposition, height, weight, BSA, BMI, age, true ID, baseline EOA, echocardiographic baseline peak gradient, echocardiographic baseline mean gradient, and baseline left ventricular ejection fraction (LVEF). Parameters with a *P*-value of <0.1 in the univariable analysis were included in the multivariable model with a forward likelihood ratio method. Collinearity was evaluated with variance inflation factors (VIF), and parameters with a VIF of >5 were not included in the multivariable analyses. Proportional-hazards assumption was confirmed through testing based on Schoenfeld residuals. Multivariable correlates are presented as hazard ratios (HRs), subhazard ratios (SHRs), and 95% confidence intervals (CIs). Bootstrapping was used to consider non-parametric data distribution. A two-sided *P*-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 23 (IBM Corporation, Armonk, New York, NY, USA) and Stata 14.1 (StataCorp, College Station, TX, USA) statistical software.

Results

Baseline demographics and echocardiographic characteristics

A total of 1006 cases were included in the analysis. Cases were performed from 24 April 2007 to 29 December 2014. *Table 1* describes the baseline characteristics of this population. The patient mean age was 77.7 ± 9.7 years, and 58.8% of them were male. Patients were highly symptomatic, with 90.1% reporting NYHA class III or IV symptoms. Common comorbidities included CKD (54.5%), DM (27.3%), and PVD (22.3%). The majority of bioprosthetic valves was stented (81.3%) and mixed stenosis and regurgitation were the most common mechanisms of valve failure (44.7%). The median STS score was 7.3% (IQR 4.2–12.0). Almost half of the patients had aortic regurgitation ≥moderate-to-severe, and the baseline mean gradient was 35.5 ± 17.5 mmHg.

Baseline characteristics differed according to the THV deployed and also according to the size of the original failed bioprosthetic valve by true ID: EBEV cases were more commonly male (63.9% vs. 54.9% MSEV, $P = 0.02$) and had been more frequently utilized in stented bioprosthetic valves (85.8% vs. 77.4% MSEV, $P = 0.005$). Patients with small bioprosthetic valves were significantly older (80.3 ± 7.0 vs. 76.8 ± 9.3 years, $P < 0.001$), included predominantly stented valves (95.8% vs. 81.7%, $P < 0.001$), and had significantly more pre-existing severe PPM (10.6% vs. 0.3%, $P < 0.001$).

Procedural characteristics and early results

Table 2 details key procedural characteristics for all patients. Transfemoral technique was the most common access utilized (69.5%). Bioprosthetic valve ring fracture was not utilized in this cohort. For patients with small surgical valves (true ID ≤ 20 mm), there was no difference in age or STS score when comparing patients by THV type. However, patients with small surgical valves who underwent MSEV implantation had greater prevalence of pre-existing severe PPM (14.1% vs. 6.8% EBEV in small valves, $P = 0.022$), more transfemoral access (91.7% vs. 45.9% EBEV in small valves, $P < 0.001$), and PVD (36.1% vs. 19.3% EBEV in small valves, $P < 0.001$). After the procedure, the patients with small surgical valves in the MSEV group had larger EOA (1.51 ± 0.49 vs. 1.18 ± 0.39 cm^2 EBEV in small valves, $P < 0.001$) and lower mean gradients (16.5 ± 8.7 vs. 21.1 ± 10.4 mmHg EBEV in small valves, $P < 0.001$). There were 10 intraprocedural deaths (1.0%), with no significant difference between MSEV, EBEV, or other valves (0.8% vs. 1.4% vs. 0.0%, $P = 0.49$). The rate of coronary obstruction was similar between MSEV and EBEV or other devices (2.3% vs. 2.1% vs. 4.4%, respectively; $P = 0.61$).

Long-term follow-up and echocardiographic data

The median absolute follow-up was 3.9 years (IQR 1.5–5.4 years; total range 0–11.7 years). Clinical follow-up at 1000 days was available for 85.4% of patients. *Take home figure* depicts the Kaplan–Meier survival curve for all patients. Estimated survival at 8 years was 38.0% (95% CI 32.9–43.1%) with a median survival of 6.2 years (95% CI 5.7–6.7 years). In the multivariable analysis, smaller bioprosthetic valves [1 mm decrease in true ID, HR 1.07 (95% CI 1.02–1.13)], age [per 10-

year increase, HR 1.21 (95% CI 1.01–1.45)], lower baseline LVEF [per 10% decrease, HR 1.25 (95% CI 1.14–1.36)], CKD [HR 1.36 (95% CI 1.06–1.74)], non-transfemoral access [HR 1.43 (95% CI 1.11–1.84)], and DM [HR 1.57 (95% CI 1.22–2.03)] were independently associated with decreased patient survival (*Figure 1A* and Supplementary material online, *Table S1*). Bootstrapping did not change results substantially (Supplementary material online, *Table S2*). There was no difference in long-term survival according to post-procedural mean gradient ≥20 mmHg or residual aortic regurgitation ≥moderate (Supplementary material online, *Figure S1*). Supplementary material online, *Table S3* describes selected long-term echocardiographic data.

Reintervention

Forty patients required reintervention during follow-up. Freedom from reintervention at 8 years was 93.2% (95% CI 90.5–95.9%); 16 (40.0%) patients underwent a new TAVR and 23 (57.5%) underwent SAVR. One patient underwent balloon valvuloplasty. The most common reason for reintervention was severe transvalvular stenosis (60.0% of cases, Supplementary material online, *Table S4*). Thirty-day mortality after the reintervention was not different between procedures (9.1% TAVR vs. 4.8% SAVR, $P = 0.63$). Pre-existing severe PPM [SHR 4.34 (95% CI 1.31–14.39)], malposition [SHR 3.75 (95% CI 1.36–10.35)], EBEV [SHR 3.34 (95% CI 1.26–8.85)], and age [per 10-year increase, SHR 0.59 (95% CI 0.44–0.78)] were independent correlates for all-cause reintervention (*Figure 1B* and Supplementary material online, *Table S5*). An alternative model for structural reintervention is available in Supplementary material online, *Table S5*. *Figure 2A and B* represent all-cause reintervention cumulative incidence function curves for the type of THV and pre-existing severe PPM, respectively.

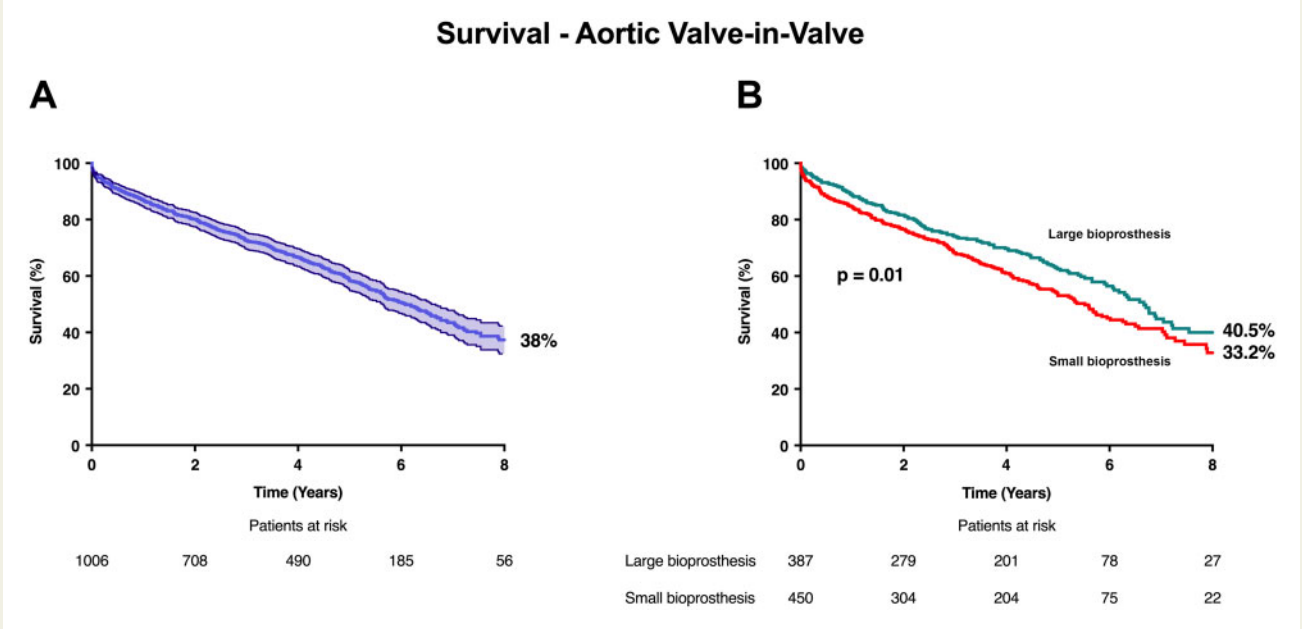
Discussion

Aortic ViV represents a significant proportion of TAVR procedures[21] and, given the increase in the use of bioprosthetic tissue valves,[2] the procedure is expected to continue to grow in numbers.[22] This is the first comprehensive long-term evaluation of aortic ViV. Our analysis shows that the size of the original failed valve may influence long-term mortality and the type of the transcatheter valve may influence the need for reintervention after aortic ViV. Hence, operator decisions during the original tissue valve implantation and/or during the ViV procedure may influence meaningful clinical outcomes.

Survival after aortic valve-in-valve

Survival after aortic ViV was recently reported in a smaller cohort of high-risk patients from the PARTNER trial.[23] Patients had a mean age of 78.9 ± 10.2 years with a mean STS score of 9.1 ± 4.7%. The estimated 3-year survival rate was 67.3%,[23] similar to the results of the present study: 73.0%. An analysis from the CoreValve US Expanded Use Study with a total of 226 extreme-risk patients was also recently published[24] and reported a 3-year survival rate of 72.3%. A small multicentre assessment of 116 aortic ViV patients (76.0 ± 11.0 years, STS score 8.0 ± 5.1%) reported a 5-year survival rate of 67.9%.[25] The current data from the VIVID Registry include a much larger number of high-risk patients ($n = 1006$) with longer follow-up and reveal an 8-year survival rate of 38.0% after ViV.

Having a small bioprosthesis represents an important risk factor for mortality after ViV procedure, both at 1 year[4] and over long-term



Take home figure Kaplan–Meier model of survival after aortic valve-in-valve. (*A*) All patients included in the analysis. (*B*) Patients with small bioprostheses (i.e. true internal diameter ≤20 mm) had worse survival at 8 years. Note that bioprosthetic valves without a known standard for internal diameter size, such as homografts, were not included.

Table 1 **Baseline characteristics of the aortic valve-in-valve cohort**

	Aortic ViV (*n* = 1006)	Medtronic self-expandable valves (*n* = 523)	Edwards balloon-expandable valves (*n* = 435)	Other valves (*n* = 48)	*P*-value	Large bioprosthetic valves (*n* = 387)[a]	Small bioprosthetic valves (*n* = 450)[a]	*P*-value
Age (years), mean ± SD	77.7 ± 9.7	78.2 ± 9.3	77.2 ± 10.0	76.9 ± 10.4	0.25	76.8 ± 9.3	80.3 ± 7.0	<0.001
Male gender, *n*/*N* (%)	590/1004 (58.8)	286/521 (54.9)	278/435 (63.9)	26/48 (54.2)	0.02	294/385 (76.4)	194/450 (43.1)	<0.001
Height (cm), mean ± SD	167.4 ± 9.4	166.8 ± 9.4	168.2 ± 9.5	167.5 ± 9.0	0.07	170.7 ± 9.2	164.5 ± 8.6	<0.001
Weight (kg), mean ± SD	74.8 ± 16.6	74.2 ± 16	75.4 ± 17.4	76.3 ± 15.7	0.45	79.1 ± 18.4	71.5 ± 14.5	<0.001
BSA (m^2), mean ± SD	1.86 ± 0.23	1.85 ± 0.22	1.87 ± 0.24	1.88 ± 0.22	0.30	1.93 ± 0.23	1.8 ± 0.21	<0.001
BMI (kg/m^2), mean ± SD	26.6 ± 5.6	26.7 ± 5.3	26.6 ± 6.0	27.2 ± 5.0	0.80	27.2 ± 6.7	26.3 ± 4.6	0.04
Valve type, *n*/*N* (%)					0.005			<0.001
Stented	806/992 (81.3)	398/514 (77.4)	369/430 (85.8)	39/48 (81.3)		316/387 (81.7)	431/450 (95.8)	
Stentless	186/992 (18.8)	116/514 (22.6)	61/430 (14.2)	9/48 (18.8)		71/387 (18.3)	19/450 (4.2)	
Label size (mm), mean ± SD	23.2 ± 2.2	22.9 ± 2.2[b]	23.6 ± 2.11[b]	23.3 ± 1.9	<0.001	24.9 ± 1.6	21.7 ± 1.3	<0.001
True ID (mm), mean ± SD	19.9 ± 2.4	19.7 ± 2.5[b]	20.3 ± 2.2[b]	19.8 ± 2	0.001	22.0 ± 1.6	18.1 ± 1.2	<0.001
Predicted indexed EOA (cm^2), mean ± SD	0.83 ± 0.16	0.81 ± 0.17[b]	0.85 ± 0.16[b]	0.84 ± 0.13	0.008	0.93 ± 0.17	0.75 ± 0.11	<0.001
Pre-existing severe PPM, *n*/*N* (%)	46/739 (6.2)	34/369 (9.2)	12/331 (3.6)	0/39 (0.0)	0.002	1/314 (0.3)	45/425 (10.6)	<0.001
Mechanism of bioprosthetic valve failure, *n*/*N* (%)					0.46			<0.001
Regurgitation	172/989 (17.4)	93/514 (18.1)	68/431 (15.8)	11/44 (25.0)		80/379 (21.1)	37/442 (8.4)	
Stenosis	375/989 (37.9)	197/514 (38.3)	161/431 (37.4)	17/44 (38.6)		134/379 (35.4)	190/442 (43.0)	
Mixed	442/989 (44.7)	224/514 (43.6)	202/431 (46.9)	16/44 (36.4)		165/379 (43.5)	215/442 (48.6)	
NYHA class, *n*/*N* (%)					0.81			0.24
I	12/997 (1.2)	8/523 (1.5)	4/426 (0.9)	0/48 (0.0)		2/383 (0.5)	5/449 (1.1)	
II	87/997 (8.7)	48/523 (9.2)	35/426 (8.2)	4/48 (8.3)		38/383 (9.9)	31/449 (6.9)	
III	626/997 (62.8)	322/523 (61.6)	270/426 (63.4)	34/48 (70.8)		243/383 (63.4)	279/449 (62.1)	
IV	272/997 (27.3)	145/523 (27.7)	117/426 (27.5)	10/48 (20.8)		100/383 (26.1)	134/449 (29.8)	
Diabetes mellitus, *n*/*N* (%)	274/1004 (27.3)	146/522 (28.0)	115/434 (26.5)	13/48 (27.1)	0.88	94/386 (24.4)	135/450 (30.0)	0.07
Peripheral vascular disease, *n*/*N* (%)	220/986 (22.3)	84/514 (16.3)	127/424 (30.0)	9/48 (18.8	<0.001	76/379 (20.1)	114/439 (26.0)	0.05
Chronic kidney disease, *n*/*N* (%)	537/986 (54.5)	275/507 (54.2)	237/431 (55.0)	25/48 (52.1)	0.92	186/376 (49.5)	272/447 (60.9)	0.001
History of stroke, *n*/*N* (%)	123/957 (12.9)	64/515 (12.4)	51/398 (12.8)	8/44 (18.2)	0.55	39/370 (10.5)	61/430 (14.2)	0.12
Permanent pacemaker, *n*/*N* (%)	127/892 (14.2)	77/506 (15.2)	48/359 (13.4)	2/27 (7.4)	0.44	47/348 (13.5)	61/396 (15.4)	0.46
EuroSCORE (%), median (IQR)	27.3 (17.9–40.0)	27.3 (18–38.9)	27.3 (17.8–41.5)	29.6 (18.4–37.8)	1.00	25 (16.0–36.4)	31.2 (21.5–43.5)	<0.001
EuroSCORE II (%), median (IQR)	12.7 (8.7–18.4)	13.3 (8.8–19.6)	12.4 (8.6–17.9)	11.6 (6.8–17.7)	0.14	11.3 (7.7–16.7)	14.7 (10.7–20.2)	<0.001
STS score (%), median (IQR)	7.3 (4.2–12.0)	7.8 (4.4–12.9)	7.2 (4.2–11.7)	5.5 (2.4–8.3)	0.001	6.2 (3.8–10.7)	8.6 (5.6–13.1)	<0.001
Baseline haemodynamics								

Continued

Table 1 *Continued*

	Aortic ViV ($n = 1006$)	Medtronic self-expandable valves ($n = 523$)	Edwards balloon-expandable valves ($n = 435$)	Other valves ($n = 48$)	*P*-value	Large bioprosthetic valves ($n = 387$)[a]	Small bioprosthetic valves ($n = 450$)[a]	*P*-value
LVEF (%), mean ± SD	51.8 ± 13.1	52.0 ± 13.6	51.2 ± 12.7	56.2 ± 11.8	0.06	50.7 ± 12.9	53.3 ± 12.8	0.005
EOA (cm^2), mean ± SD	0.94 ± 0.46	0.95 ± 0.48	0.92 ± 0.43	0.97 ± 0.4	0.70	1.00 ± 0.49	0.83 ± 0.36	<0.001
Peak gradient (mmHg), mean ± SD	60.8 ± 27.1	60.7 ± 27.6	61.6 ± 27	54.3 ± 21.2	0.35	60.5 ± 29	64.8 ± 24	0.04
Mean gradient (mmHg), mean ± SD	35.5 ± 17.5	34.9 ± 17.6	36.4 ± 17.7	33.3 ± 14.2	0.36	35.2 ± 18.7	37.8 ± 15.7	0.05
Aortic regurgitation, *n*/*N* (%)					0.01			0.009
None	140/961 (14.6)	91/508 (17.9)	46/411 (11.2)	3/42 (7.1)		48/363 (13.2)	71/437 (16.2)	
Mild	213/961 (22.2)	104/508 (20.5)	97/411 (23.6)	12/42 (28.6)		71/363 (19.6)	115/437 (26.3)	
Moderate	130/961 (13.5)	59/508 (11.6)	65/411 (15.8)	6/42 (14.3)		47/363 (12.9)	66/437 (15.1)	
Moderate to severe	200/961 (20.8)	99/508 (19.5)	87/411 (21.2)	14/42 (33.3)		84/363 (23.1)	92/437 (21.1)	
Severe	278/961 (28.9)	155/508 (30.5)	116/411 (28.2)	7/42 (16.7)		113/363 (31.1)	93/437 (21.3)	

BMI, body mass index; BSA, body surface area; EOA, effective orifice area; ID, internal diameter; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PPM, prosthesis–patient mismatch; SD, standard deviation; ViV, valve-in-valve.

[a]Bioprosthetic valves without a known standard for ID size, such as homografts, were not included.

[b]Significant differences by *post hoc* Tukey's honest significant difference test after the analysis of variance.

Table 2 Procedural characteristics, early outcomes, and haemodynamics of the aortic valve-in-valve cohort

	Aortic ViV ($n = 1006$)	Medtronic self-expandable valves ($n = 523$)	Edwards balloon-expandable valves ($n = 435$)	Other valves ($n = 48$)	*P*-value	Large bioprosthetic valves ($n = 387$)[a]	Small bioprosthetic valves ($n = 450$)[a]	*P*-value
THV label size (mm), median (IQR)	23 (23–26)	26 (23–26)	23 (23–26)	23 (23–25)	<0.001	26 (23–26)	23 (23–26)	<0.001
Access, *n*/*N* (%)					<0.001			0.25
Transfemoral	698/1004 (69.5)	477/523 (91.2)	198/433 (45.7)	23/48 (47.9)		256/386 (66.3)	325/450 (72.2)	
Transapical	250/1004 (24.9)	0/523 (0.0)	226/433 (52.2)	24/48 (50)		111/386 (29.3)	100/450 (22.2)	
Subclavian	19/1004 (1.9)	16/523 (3.1)	3/433 (0.7)	0/48 (0.0)		7/386 (1.8)	8/450 (1.8)	
Transaortic	23/1004 (2.3)	16/523 (3.1)	6/433 (1.4)	1/48 (2.1)		10/386 (2.6)	12/450 (2.7)	
Other	14/1004 (1.4)	14/523 (2.7)	0/433 (0.0)	0/48 (0.0)		0/386 (0.0)	5/450 (1.1)	
General anaesthesia, *n*/*N* (%)	649/914 (71.0)	293/478 (61.3)	317/388 (81.7)	39/48 (81.3)	<0.001	268/356 (75.3)	271/416 (65.1)	0.002
TEE, *n*/*N* (%)	549/875 (62.7)	233/476 (48.9)	282/356 (79.2)	34/43 (79.1)	<0.001	234/339 (69.0)	216/398 (54.3)	<0.001
Pre-dilation, *n*/*N* (%)	237/947 (25)	82/518 (15.8)	138/389 (35.5)	17/40 (42.5)	<0.001	93/363 (25.6)	98/422 (23.2)	0.44
Malposition, *n*/*N* (%)	62/952 (6.5)	45/493 (9.1)	15/415 (3.6)	2/44 (4.5)	0.003	38/365 (10.4)	15/421 (3.6)	<0.001
Post-dilation, *n*/*N* (%)	128/894 (14.3)	100/475 (21.1)	18/383 (4.7)	10/36 (27.8)	<0.001	39/343 (11.4)	66/401 (16.5)	0.05
Second THV, *n*/*N* (%)	53/995 (5.3)	35/523 (6.7)	17/424 (4.0)	1/48 (2.1)	0.11	28/381 (7.3)	19/446 (4.3)	0.06
Permanent pacemaker needed, *n*/*N* (%)	63/844 (7.5)	38/427 (8.9)	23/373 (6.2)	2/44 (4.5)	0.26	20/328 (6.1)	29/374 (7.8)	0.39
Vascular complications, *n*/*N* (%)					0.001			0.07
Minor	66/972 (6.8)	49/496 (9.9)	16/428 (3.7)	1/48 (2.1)		24/373 (6.4)	38/438 (8.7)	
Major	33/972 (3.4)	19/496 (3.8)	14/428 (3.3)	0/48 (0.0)		8/373 (2.1)	20/438 (4.6)	
Major bleeding, *n*/*N* (%)	70/910 (7.7)	27/456 (5.9)	38/413 (9.2)	5/41 (12.2)	0.11	21/345 (6.1)	34/420 (8.1)	0.29
Major stroke, *n*/*N* (%)	18/954 (1.9)	10/489 (2.0)	7/419 (1.7)	1/46 (2.2)	0.91	9/368 (2.4)	5/426 (1.2)	0.17
Acute kidney injury, *n*/*N* (%)	72/918 (7.8)	38/458 (8.3)	31/415 (7.5)	3/45 (6.7)	0.86	24/351 (6.8)	36/423 (8.5)	0.39
Coronary obstruction, *n*/*N* (%)	22/957 (2.3)	11/487 (2.3)	9/425 (2.1)	2/45 (4.4)	0.61	10/370 (2.7)	9/434 (2.1)	0.56
Post-procedural haemodynamics								
LVEF (%), mean ± SD	51.6 ± 11.9	51.7 ± 12.3	51.3 ± 11.4	53.8 ± 12.0	0.45	50.7 ± 12.0	53.1 ± 11.3	0.005
EOA (cm^2), mean ± SD	1.49 ± 0.51	1.59 ± 0.50[b]	1.39 ± 0.51[b]	1.40 ± 0.57	<0.001	1.55 ± 0.47	1.38 ± 0.47	<0.001
Max. gradient (mmHg) mean ± SD	29.0 ± 14.9	27.1 ± 13.6[b]	30.8 ± 15.8[b]	34.7 ± 16.8[b]	<0.001	26.5 ± 13.0	32.3 ± 15.6	<0.001
Mean gradient (mmHg), mean ± SD	16.3 ± 9.1	14.7 ± 8.2[bb]	17.7 ± 9.5[b]	20.3 ± 10.9[b]	<0.001	14.8 ± 8	18.3 ± 9.6	<0.001
Aortic regurgitation, *n*/*N* (%)					<0.001			0.49
None	586/925 (63.4)	268/479 (55.9)	288/403 (71.5)	30/43 (69.8)		223/361 (61.8)	277/411 (67.4)	
Mild	284/925 (30.7)	169/479 (35.3)	104/403 (25.8)	11/43 (25.6)		117/361 (32.4)	116/411 (28.2)	
Moderate	41/925 (4.4)	31/479 (6.5)	8/403 (2.0)	2/43 (4.7)		17/361 (4.7)	14/411 (3.4)	
Moderate to severe	10/925 (1.1)	8/479 (1.7)	2/403 (0.5)	0/43 (0.0)		2/361 (0.6)	3/411 (0.7)	
Severe	4/925 (0.4)	3/479 (0.6)	1/403 (0.2)	0/43 (0.0)		2/361 (0.6)	1/411 (0.2)	

EOA, effective orifice area; IQR, interquartile range; LVEF, left ventricular ejection fraction; SD, standard deviation; TEE, transesophageal echocardiography; THV, transcatheter heart valve; ViV, valve-in-valve.
[a]Bioprosthetic valves without a known standard for internal diameter size, such as homografts, were not included.
[b]Significant differences by *post hoc* Tukey's honest significant difference test after the analysis of variance.

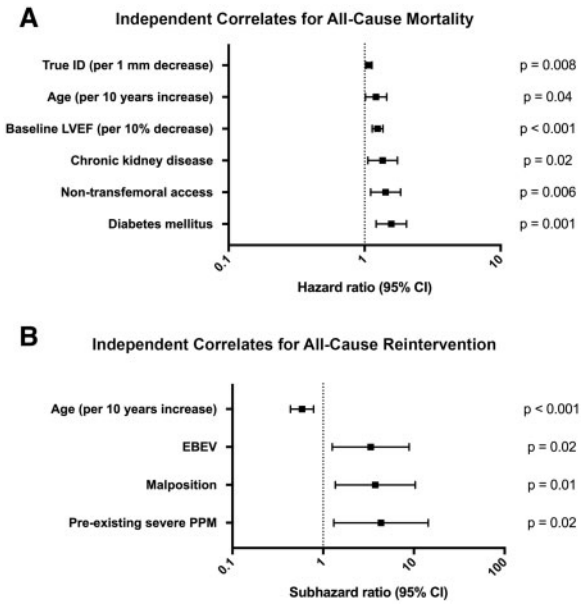


Figure 1 Independent correlates of (*A*) all-cause mortality and (*B*) all-cause reintervention in aortic valve-in-valve. Small bioprosthetic valves were independently associated with decreased survival. In addition, prosthesis–patient mismatch and balloon-expandable valves were associated with all-cause reintervention. CI, confidence interval; EBEV, Edwards balloon-expandable valves; ID, internal diameter; LVEF, left ventricular ejection fraction; PPM, prosthesis–patient mismatch.

follow-up. This is a novel finding since bioprosthetic valve size was not included in the multivariable analysis of the CoreValve US Expanded Use Study[24] and patients with label size <21 mm were excluded in the PARTNER study[23] and these studies did not report long-term outcomes beyond 3 years of follow-up. Furthermore, these studies included only one THV type, while the VIVID data allow 'real-world' analysis of the impact of different devices, including the need for reintervention.

Valve reintervention

In the present study, the 8-year reintervention rate after ViV was 6.8%, mainly for valve stenosis. Three-year reintervention rates were 4.4% in the CoreValve US Expanded Use Study[24] and 1.9% in the PARTNER ViV trial.[23] Consistent with our own findings of an almost five-fold increased risk for reintervention with the presence of pre-existing severe PPM, the authors of the CoreValve US Expanded Use Study identified a significant association between reintervention and pre-existing severe PPM (14.8% vs. 1.6% moderate PPM vs. 4.4% no PPM, $P = 0.02$).[24] As THVs may be under-expanded when implanted in small bioprosthetic valves, which may be further modified by the depth of implantation,[26] the final result may be postulated to be even worse. Severe PPM at baseline is a known independent correlate of mortality at 1-year follow-up,[8] although post-procedural PPM did not appear to affect outcomes.[27] Severe PPM has previously been associated with the increased risk of SVD following biological SAVR.[28–30] Taken together with prior findings, our study adds further evidence and insight into the fact that small bioprostheses, which frequently exhibit severe PPM, bear a high risk for worse outcomes after ViV procedures. In addition, the issue of valve thrombosis should be considered. In prior analyses, thrombosis is resolved with anticoagulation in the majority of cases without a need for reintervention.[11] In the current data, we have identified two cases requiring reintervention due to valve thrombosis. There are no specific protocols for anticoagulation in ViV patients and further evaluation is needed.

The type of THV was also associated with a greater rate of all-cause reintervention. Intra-annular THV devices tend to develop higher transvalvular gradients after the ViV procedure,[4] a finding that has been replicated in the current study. The implantation of a THV with intra-annular design in a small bioprosthetic valve with severe PPM may result in leaflet pin-wheeling,[26] increased mechanical stress, and highly turbulent flow that may increase the risk of valve thrombosis and SVD.[31] There is evidence of a higher SVD rate with the SAPIEN XT beyond 5 years compared with the self-expandable CoreValve[32] and also of a higher reintervention rate in the SAPIEN XT when compared with SAVR in the PARTNER II trial.[33]

Implications for aortic valve surgery

This large-scale long-term analysis emphasizes the adverse impact of small bioprostheses and pre-existing severe PPM on mortality and reintervention rates. Surgeons should therefore aim to avoid implanting small bioprostheses whenever possible (i.e. label size <23 mm, or with predicted severe PPM). When evaluating a patient with a failing small bioprosthetic valve, patients should understand the additional surgical risk of redo open heart surgery, especially when root enlargement is performed, and also the limitations of a ViV procedure with regard to residual stenosis.

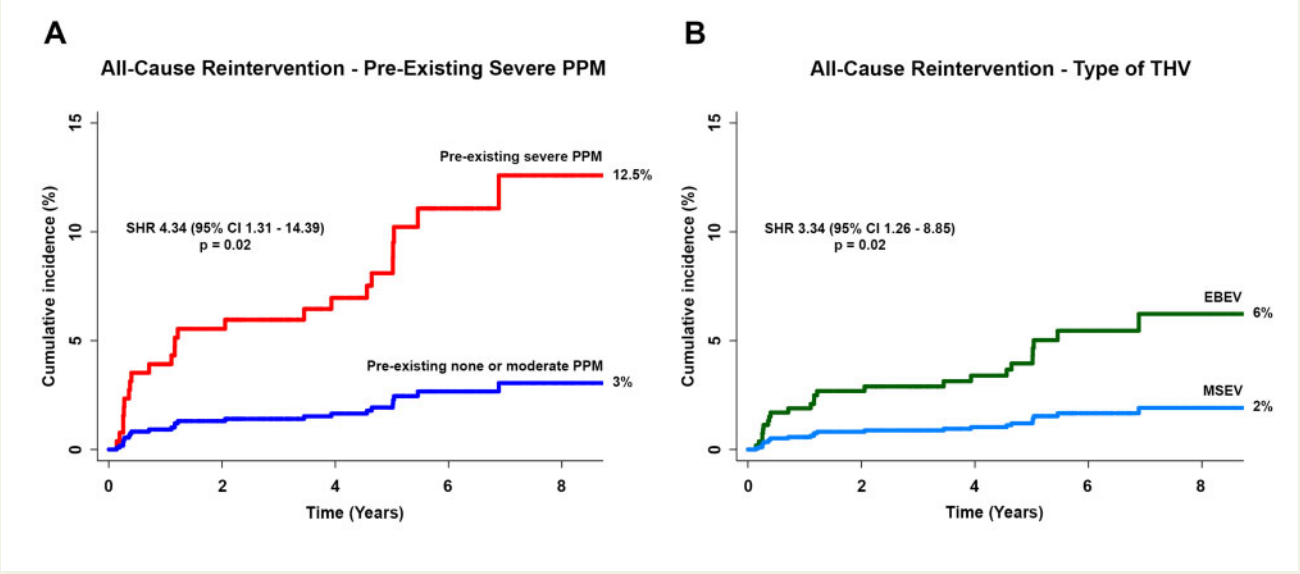


Figure 2 Fine and Gray cumulative incidence function curves showing the adjusted cumulative subhazard of all-cause reintervention. Model according to (*A*) the presence or absence of pre-existing severe prosthesis–patient mismatch and (*B*) the type of transcatheter heart valve implanted. CI, confidence interval; EBEV, Edwards balloon-expandable valves; MSEV, Medtronic self-expandable valves; PPM, prosthesis–patient mismatch; SHR, subhazard ratio; THV, transcatheter heart valve.

During ViV procedures, the operator should make every effort to avoid residual stenosis. Relevant strategies may include THV selection, precise device positioning and novel procedural techniques, such as bioprosthetic valve ring fracture.[7,9]

Limitations

Our study has several limitations. There was no control group of conventional surgery, although many patients were considered very high risk for redo open heart surgery as demonstrated by the elevated surgical scores. Echocardiographic follow-up was performed without a centralized core-lab and at the discretion of the operator. Without serial evaluations, we were unable to obtain SVD and bioprosthetic valve failure rates. However, our principal findings are based on actual reintervention events and not on echocardiographic parameters. The regression analysis regarding mortality is one of the many plausible models that likely fit the data equally as well and the individual variables selected may not be completely independent. Similarly, those not selected may not be any less important than those selected had alternative modelling taken place. As in all observational analyses, the possibility of unmeasured confounders in the models exists. The mode and methods of follow-up assessment differed among centres, as some centres routinely perform follow-up visits, while other centres performed active (through direct patient contact) or passive (through administrative or governmental data) assessment of the current health state specifically for this study. In addition, first-generation devices were most common in our population, with a lower representation of currently used valves (SAPIEN 3 and Evolut R) and the EBEV and MSEV groups differed significantly in procedural access. The EBEV group more commonly had alternative access for the TAVR procedure, which is associated with inferior early survival after TAVR procedures in comparison to transfemoral approach. Nevertheless, the clinical outcomes after EBEV ViV procedures were inferior to MSEV in several outcomes that do not seem to be related to the procedural access. EBEV cases were associated with higher post-procedural gradients and were an independent correlate of the need for reintervention. Finally, no cases of bioprosthetic valve ring fracture were included in our cohort and it is still unknown how patients with pre-existing PPM, who undergo ring fracture, will clinically perform over the long term.

Conclusions

The size of the original failed valve may influence long-term mortality, and the type of the transcatheter valve may influence the need for reintervention after aortic ViV.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Data sharing

Data sharing with qualified researchers may be considered after submission of a proposal to the board of the Institute of Valvular Research.

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